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(54) METHODS AND SYSTEMS FOR CALCULATING FREE ENERGY DIFFERENCES USING A MODIFIED BOND STRETCH POTENTIAL

VERFAHREN UND SYSTEME ZUR BERECHNUNG DER DIFFERENZEN VON FREIER ENERGIE ANHAND EINES MODIFIZIERTEN BINDUNGSDEHNUNGSPOTENZIALS

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Description

BACKGROUND

[0001] Free energy is a fundamental molecular property that plays an essential role in characterizing chemical and biological systems. An understanding of the free energy behavior of many chemical and biochemical processes, such as protein-ligand binding, can be of critical importance in endeavors such as rational drug design (which involves the design of small molecules that bind to a biomolecular target).

[0002] Computer modeling and simulations are often used in free energy studies. In most instances, evaluation of accurate absolute free energies from simulations is extremely difficult, if at all possible. Hence, the free energy difference between two well-delineated thermodynamic states, or relative free energy, are often used as a study system to provide insight to particular systems, such as a relative binding affinity of a ligand predicated on the measured affinity of a different but similar ligand (e.g., a congeneric ligand).

[0003] In the relative free energy calculations, the two thermodynamic states can be referred to as a reference system state and a target system state, which can represent respectively an initial state of a molecular system, such as a first molecule, and an ending state of the molecule after one or more transformations have taken place (such as a conformational change, topological change, or a replacement of one atom or chemical group with another (i.e., a mutation)). It is noted that such transformations may not always represent realistic physical transformations, but may involve non-physical or "alchemical" transformations. Different frameworks have been developed for calculating free energy differences, such as free energy perturbations (FEP), thermodynamic integrations (TI), and umbrella sampling.

[0004] Within the FEP framework, the free energy difference $\Delta F_{a\to b}$, between the two system states *a* and *b* can be expressed by:

$$\Delta F_{a\to b} = -\frac{1}{\beta} ln\langle exp\{-\beta[\mathcal{H}_b(x,p_x) - \mathcal{H}_a(x,p_x)]\}\rangle_a \qquad (1)$$

where $\beta^{-1} = k_B T$, whereis k_B is the Boltzmann constant, *T* is the temperature. $\mathcal{H}_a(x,p_x)$ and $\mathcal{H}_b(x,p_x)$ are the Hamiltonians characteristic of states *a* and *b* respectively. $\langle ... \rangle_a$ denotes an ensemble average over configurations representative of the initial, reference state, *a*.

[0005] In practical applications of FEP, the transformation between the two thermodynamic states is usually achieved by a series of transformations between non-physical, intermediate states along a well-delineated pathway that connects *a* to *b*. This pathway is often characterized by a general extent parameter, often referred to as a coupling parameter, λ, which varies from 0 to 1 from the reference state to the target state, and relates the Hamiltonians of the two states by:

$$\mathcal{H}(\lambda) = (1-\lambda)\mathcal{H}_a + \lambda\mathcal{H}_b \qquad (2)$$

where $\mathcal{H}(\lambda)$ is the λ -coupled or hybrid Hamiltonian of the system between the two states (including the two states, when λ takes the end values of 0 and 1). Hence, the free energy difference $\Delta F_{a\to b}$ between *a* and *b* will be:

$$\begin{aligned}\Delta F_{a\to b} &= -\frac{1}{\beta} ln\langle exp\{-\beta[\mathcal{H}(\lambda=1) - \mathcal{H}(\lambda=0)]\}\rangle_{\lambda=0} \\ &= -\frac{1}{\beta}\sum_{i=0}^{N-1} ln\langle exp\{-\beta[\mathcal{H}(x,p_x;\lambda_{i+1}) - \mathcal{H}(x,p_x;\lambda_i)]\}\rangle_i \qquad (3)\end{aligned}$$

where *N* stands for the number of "windows" between neighboring states between the reference (initial) state and the target (final) state, and λ_i is the values of the coupling parameter in the initial, intermediate, and final state.

[0006] The free energy difference between the reference system state a and the target system state b can also be calculated using thermodynamic integration method, where the free energy difference is calculated using the following formula:

$$\Delta F_{a\to b} = \int_{\lambda=0}^{\lambda=1} d\lambda \, \langle \frac{\partial\mathcal{H}(\lambda)}{\partial\lambda} \rangle_\lambda \qquad (4)$$

where λ is the coupling parameter which varies from 0 to 1 from the reference state to the target state, $\mathcal{H}(\lambda)$ is the λ -coupled or hybrid Hamiltonian of the system between the two states (including the two states, when λ takes the end values of 0 and 1), and $\frac{\partial \mathcal{H}(\lambda)}{\partial \lambda}$ is the first derivative of the coupled Hamiltonian with respect to the coupling parameter λ.

[0007] In practical applications of TI, the transformation between the reference system state and the target system state is achieved by a series transformations along a well-delineated pathway that connects *a* to *b*, and the ensemble average of $\frac{\partial \mathcal{H}(\lambda)}{\partial \lambda}$ is calculated for all the states sampled, including the reference system state, the intermediate non-physical states, and the target system state. The free energy difference between the reference system state and the target system state is then approximated by numerical integration of the above integral based on the value of the $\langle\frac{\partial \mathcal{H}(\lambda)}{\partial \lambda}\rangle_{\lambda_i}$, where λ_i is the values of the coupling parameter in the initial, intermediate, and final states.

[0008] Under conventional methods, calculating the free energy to open a ring of a molecule into a linear structure or close a linear structure of a molecule to form a ring can be difficult. In these cases, the reversible work of turning on and off a valence bond connecting two ring atoms needs to be computed. Although one possible approach might be to annihilate a whole ring and grow a corresponding linear structure from scratch, it is computationally very inefficient and sometimes impossible when the ring is very large or the ring is fused with other rings.

[0009] SMITH B. J., "A Conformational Study of 2-Oxanol: Insight into the Role of Ring Distortion on Enzyme-Catalyzed Glycosidic Bond Cleavage", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 11, 1 March 1997, pages 2699-2706, discloses free energy calculations employing molecular dynamics or Monte Carlo methods for chemical and biochemical phenomena, as well as the application of such calculations to molecular solvation, molecular association, macromolecular stability and enzyme catalysis.

SUMMARY OF THE INVENTION

[0010] The present invention is defined by the appended independent claims. Preferred embodiments are defined by the dependent claims.

[0011] In some embodiments of the method, the soft bond potential is a function of a bonded stretch component, λ_{sbs}, of the coupling parameter λ, and does not include any singular regions for all values of λ_{sbs} within [0,1] and for all values of the distance r between A_a and A_b. The soft bond potential further satisfy the following conditions: when λ_{sbs} is within (0,1), the soft bond potential is flat when the distance between A_a and A_b approaches infinity; when A_a and A_b are not valence bonded in either the reference state or the target state, the soft bond potential is flat and zero for all distances between A_a and A_b; and when A_a and A_b are valence bonded in either the target state or the reference state, the soft bond potential reverts to a harmonic potential.

[0012] The first derivative of the soft bond potential with respect to λ_{sbs} is continuous and bounded for all values of λ_{sbs} between 0 and 1 and for all values of the distance r between A_a and A_b. Both the first derivative and the second derivative of the soft bond potential with respect to the distance r between A_a and A_b are continuous and bounded for all values of λ_{sbs}, and approach zero when r approaches infinity.

[0013] In some embodiments of the method, the soft bond potential is a function of $(r - r_0)^2$, where r_0 is the equilibrium distance between A_a and A_b. In one embodiment, the soft bond potential is expressed by:

$$U_{sbs}(r, \lambda_{sbs}) = \frac{1}{2} k f(\lambda_{sbs})(r - r_0)^2 \frac{1}{1+g(\lambda_{sbs})\alpha(k,\lambda_{sbs})(r-r_0)^2}$$

where k is a constant, and the functions *f,g* and *a* are each continuous functions and satisfy the following conditions:

$$f(\lambda_{sbs} = 0) = 0,$$

$$f(\lambda_{sbs} = 1) = 1,$$

$$g(\lambda_{sbs} = 0) = 1,$$

$$g(\lambda_{sbs} = 1) = 0,$$

$$\alpha(k, \lambda_{sbs} < 1) > 0.$$

[0014] In particular embodiments, $f(\lambda_{sbs}) = \lambda_{sbs}$, $g(\lambda_{sbs}) = 1 - \lambda_{sbs}$, and $\alpha(k,\lambda_{sbs})$ is a nonnegative constant.

[0015] In some embodiments, performing molecular simulations for each of the system states comprises: if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, using a schedule of λ_{sbsA} and a corresponding soft bond potential for calculating the bonded stretch interaction energy between A_a and A_b for each of the intermediate states, wherein λ_{sbsA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, using a schedule of λ_{sbsB} and a corresponding soft bond potential for each of the intermediate states and a soft bond potential corresponding to the λ_{sbsB} for calculating the bonded stretch interaction between A_a and A_b, wherein λ_{sbsB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state.

[0016] In some embodiments of the method, performing molecular simulations for each of the system states further comprises:

(a) computing a bonded angle interaction, using applicable parameters for bonded angle interactions of a force field, between (i) a bond formed by A_a and another atom A_c, and (ii) the bond between A_a and A_b that is being broken or formed by the transformation from the reference state to the target state;
(b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, multiplying the computed bonded angle interaction obtained in (a) by a bonded angle coupling parameter λ_{baA}, wherein λ_{baA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and
if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, multiplying the computed bonded angle interaction obtained in (a) by a bonded angle coupling parameter λ_{baB}, wherein λ_{baB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state; and
(c) including the bonded angle interaction obtained in (b) into the total energy of a simulation step of the corresponding system state,

[0017] In some embodiments of the method, performing molecular simulations for each of the system states further includes:

(a) computing a dihedral angle interaction, using applicable parameters for dihedral interactions of a force field, of a group of four connected atoms $\{A_i, A_j, A_k, A_l\}$, the group including both A_a and A_b;
(b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, multiplying the computed dihedral interaction obtained in (a) by a dihedral angle coupling parameter λ_{bdA}, wherein λ_{bdA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and
if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, multiplying the computed dihedral interaction obtained in (a) by a dihedral angle coupling parameter λ_{bdB}, wherein λ_{bdB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state; and
(c) including the dihedral interaction obtained in (b) into the total energy of the simulation step of the corresponding system state.

[0018] In the above embodiments, if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, the bonded angle interaction and the bonded dihedral interaction coupling parameters λ_{baA} and λ_{bdA}, can be each selected to be 0 when λ_{sbsA} is smaller than a predefined threshold, and if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, the bonded angle interaction and the bonded dihedral interaction coupling parameters λ_{baB} and λ_{bdB} can be each selected to be 0 when λ_{sbsB} is smaller than a predefined threshold.

[0019] In some embodiments of the method, performing molecular simulations for all of the states further includes:

(a) computing nonbonded electrostatic interactions and van der Waals interactions, using applicable parameters for electrostatic interactions and van der Waals interactions of a force field, between two atoms A_i and A_j and the non-bonded exclusion status of the pair (A_i, A_j) is affected by the transformation from the reference state to the target state;

(b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are excluded in the reference state but not excluded in the target state, multiplying the nonbonded electrostatic interactions and van der Waals interactions between A_i and A_j obtained in (a) by coupling parameters $\lambda_{elecAex}$ and λ_{vdwAex}, respectively, wherein both of $\lambda_{elecAex}$ and λ_{vdwAex} are 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state;

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, and the nonbonded interactions between A; and A_j are not excluded in the reference state but excluded in the target state, multiplying the nonbonded electrostatic interactions and van der Waals interactions between A_i and A_j obtained in (a) by coupling parameters $\lambda_{elecBex}$ and λ_{vdwBex}, respectively, wherein both of $\lambda_{elecBex}$ and λ_{vdwBex} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

(c) including the calculated nonbonded electrostatic interactions and van der Waals interactions obtained in (b) into the total energy of the simulation step of the corresponding system state.

[0020] In some embodiments of the method, wherein performing molecular simulations for all of the states further includes:

if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are excluded in the reference state but not excluded in the target state, varying each of $\lambda_{elecAex}$ and λ_{vdwAex} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwAex} is smaller than 1 for an intermediate state, $\lambda_{elecAex}$ is 0 for that intermediate state; and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are not excluded in the reference state but excluded in the target state, varying each of $\lambda_{elecBex}$ and λ_{vdwBex} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwAex} is smaller than 1 for an intermediate state, $\lambda_{elecAex}$ is 0 for that intermediate state.

[0021] In some embodiments of the method, performing molecular simulations for all of the states further includes:

(a) computing nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions, using applicable parameters for electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions of a force field, between two atoms A_i and A_j which together with another two intervening atoms forms a bonded dihedral angle interaction in either the reference state or the target state;

(b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state:

if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in (a) by coupling parameters $\lambda_{elecA14}$ and λ_{vdwA14}, respectively, wherein both of $\lambda_{elecA14}$ and λ_{vdwA14} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state, and

if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in (a) by coupling parameters $\lambda_{elecB14}$ and λ_{vdwB14}, respectively, wherein both of $\lambda_{elecB14}$ and λ_{vdwB14} are 0 at the reference state, 1 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state, and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state:

if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in (a) by coupling parameters $\lambda_{elecB14}$ and λ_{vdwB14}, respectively, wherein both of $\lambda_{elecB14}$ and λ_{vdwB14} are 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state, and

if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in (a) by the coupling parameters $\lambda_{elecA14}$ and λ_{vdwA14}, respectively, wherein both of $\lambda_{elecA14}$ and λ_{vdwA14} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

(c) including the calculated electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions obtained in (b) into the total energy of the simulation step of the corresponding system state.

[0022] In some embodiments of the method, performing molecular simulations for all of the states further includes:

(a) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state,

if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, varying each of $\lambda_{elecA14}$ and λ_{vdwA14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwA14} is smaller than 1 for an intermediate state, $\lambda_{elecA14}$ is 0 for that intermediate state;

if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, varying each of $\lambda_{elecB14}$ and λ_{vdwB14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwB14} is smaller than 1 for an intermediate state, $\lambda_{elecB14}$ is 0 for that intermediate state

(b) if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state,

if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, varying each of $\lambda_{elecB14}$ and λ_{vdwB14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwB14} is smaller than 1 for an intermediate state, $\lambda_{elecB14}$ is 0 for that intermediate state,

if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, varying each of $\lambda_{elecA14}$ and λ_{vdwA14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwA14} is smaller than 1 for an intermediate state, $\lambda_{elecA14}$ is 0 for that intermediate state;

[0023] In some embodiments of the method, computing van der Waals interactions can include using a soft-core LJ interaction potential.

[0024] In some embodiments of the method, either the reference state or the target state includes a molecule having a ring structure in which the atoms A_a and A_b are bonded to each other and form a part of the ring structure.

[0025] In some embodiments of the method, calculating the free energy difference between the reference state and the target state comprises performing an analysis of the ensemble of micro-states obtained at the target state, the reference state, and the intermediate states by way of a determination and analysis of the work associated with the variation of coupling parameter λ.

[0026] In some embodiments of the method, calculating the free energy difference between the reference state and the target state comprises performing an analysis of the ensemble of micro-states obtained at the target state, the reference state, and the intermediate states by way of an analysis of the differences in a thermodynamic property of a suitable ensemble of the micro-states obtained at the target state, the reference state, and the intermediate states as the coupling parameter λ is instantaneously varied for the selected ensemble of micro-states. Performing the analysis of the differences in the thermodynamic property comprises applying an estimator selected from BAR, MBAR, WHAM, Zwanzig average estimators, or one of an FEP-family estimators. The ensemble can be, for example, an NVT ensemble, a NPT ensemble, a NVE ensemble, and a μVT ensemble.

[0027] In some embodiments of the method, calculating the free energy difference between the reference state and the target state comprises performing a thermodynamic integration analysis of the derivative of a thermodynamic property of a suitable ensemble of micro-states obtained for the target state, the reference state, and the intermediate states with respect of the coupling parameter λ. The ensemble can be, for example, an NVT ensemble, a NPT ensemble, a NVE ensemble, and a μVT ensemble.

[0028] The invention also provides an apparatus including one or more processors, a memory operably coupled to the one or more processors comprising instructions executable by the processors, the one or more processors being operable when executing the instructions to perform the various embodiments of the method as described herein. The invention further provides non-transitory computer readable media storing the instructions which when executed by one or more processors, carry out the various embodiments of the method as described herein.

[0029] Other features and advantages of the invention are apparent from the following description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The present invention will be better understood by reference to the accompanying drawings, wherein:

Figures 1a-1c are diagrams showing illustrative ring-closing transformations between a reference system state to a target system state according to some embodiments of the present invention;
Figure 2 depicts plots of a soft bond potential as a function of inter-atom distance between the two atoms involved in a bond formation or breaking transformation at different values of the coupling parameter λ according to some embodiments of the present invention;
Figure 3 depicts plots of a soft bond potential as a function of inter-atom distance between the two atoms involved in a bond formation or breaking transformation at different values of the coupling parameter λ, as well as the derivative of the potential with respect to the coupling parameter λ, and the first and second derivative of the potential with respect to the inter-particle distance according to some embodiments of the present invention;
Figure 4 is a diagram showing an illustrative ring-opening transformation occurring in a cyclic structure, the free energy change of which is amenable to the application of embodiments of the present invention;
Figure 5 is a diagram showing an illustrative bond breaking between two connected ring structures, the free energy change of which is amenable to the application of embodiments of the present invention;
Figure 6 is a depiction of a protein residue mutation transformation where a non-proline residue in the reference system is transformed into a proline residue in the target system, the free energy change of which is amenable to the application of embodiments of the present invention; and
Figure 7 is a depiction of a protein residue deletion transformation where a residue (proline) in the reference system is deleted in the target system, resulting in a direct connection between its two neighboring residues, the free energy change of which is amenable to the application of embodiments of the present invention.

DETAILED DESCRIPTION

[0031] The present application discloses computer-implemented methods and systems for computing free energy difference between a reference system state and a target system state. In particular, to address the issues in determining free energy difference arising from bond breaking in a ring structure that transforms a ring structure to a linear structure and bond formation that transforms a linear structure into a ring structure (each of which is further discussed below), the methods and systems disclosed in the present application utilize a functional form for bond stretching that allows a rigorous connection to the harmonic bond functional form to be maintained at any points in the alchemical transformation for calculating the free energy difference. Accordingly, the methods and systems of the present application can advantageously improve numerical stability and accuracy of the free energy calculations. However, it is to be recognized that the general principles of the free energy calculations using such modified bond stretching potentials disclosed herein can be applied generally in any bond formation and breaking situations, and not limited to ring closing or ring opening.

[0032] As with traditional free energy difference calculations, the atoms in the system can be categorized into different groups for evaluating the system energy in different system states. The reference state and target state both include a common set of atoms P_{AB}. The reference state further includes a set of atoms P_A, and the target state further includes a set of atoms P_B. The set of atoms P_A are present only in the reference state and not in the target state, and the set of atoms P_B are present only in the target state and not the reference state. In a ring formation scenario, P_A can be the atoms connected to the two terminal atoms to form a bond. During the course of the transformation, the atoms in P_A and in P_B interact with other atoms within their own set as well as with those in P_{AB}, but the atoms in P_A do not interact with any atoms in P_B, or vice versa. For example, for a molecule having a structure shown in Figure 1a, where a bond is about to be formed between two atoms A_1 and A_2, $P_{AB} = \{A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9\}$ (the atoms are shown as having valence of 4 for purpose of illustration only; it is understood that other atoms or groups can be represented in this structure), $P_A = \{A_{10}, A_{11}\}$, and $P_B = \varnothing$. By way of another example, for a molecule having a backbone structure A_1-A_3-A_2 shown in Figure 1b, where a molecular fragment including A_{12}, A_{13}, A_{14} is to be inserted between A_1 and A_3 to form two bonds A_1-A_{12} and A_3-A_{12}, $P_{AB} = \{A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9\}$; $P_A = \{A_{10}, A_{11}\}$, and $P_B = \{A_{12}, A_{13}, A_{14}\}$. In the latter example, the insertion of the fragment to form the two bonds can be considered as taking two steps, the first being a linear growth of the chain A_3-A_2-A_1 on A_1 (or A_3) by the fragment containing A_{12}, and the second step being the closure of the ring between A_{12}-A_3 (or A_{12}-A_1). In another example as illustrated in Figure 1c, where a molecule having a closed 4-membered ring structure is alchemically transformed into a 5-membered ring structure, $P_{AB} = \{A_1, A_2, A_3, A_4, A_5, A_6, A_7, A_8, A_9, A_{10}, A_{11}, A_{12}\}$, $P_A = \varnothing$, $P_B = \{A_{13}, A_{14}, A_{15}\}$.

[0033] As described herein, the coupling Hamiltonian $\mathcal{H}(\lambda)$ for alchemical transformation involving ring opening and closing can generally include the following terms, $\mathcal{H}_{\mathrm{bs}}(\lambda_{\mathrm{bs}})$, $\mathcal{H}_{\mathrm{ba}}(\lambda_{\mathrm{ba}})$, $\mathcal{H}_{\mathrm{bd}}(\lambda_{\mathrm{bd}})$ and $\mathcal{H}_{\mathrm{nb}}(\lambda_{\mathrm{nb}})$, corresponding to the bonded stretch terms, the bonded angle terms, the bonded dihedral angle terms, and the nonbonded exclusion and 1-4 pair interaction terms respectively. To simplify the discussion, in the following the case where a valence bond between two ring atoms is being formed (i.e., the transformation from the reference state to the target state involves ring closing) is described in detail.

[0034] As an initial step, the topology of the system is provided, including the bonded connections between the atoms in the system and the relative spatial arrangements of the atoms forming each of P_{AB}, P_A, and P_B.

[0035] One or more, e.g., a plurality of intermediate states between the reference state and the target state can be determined along a path defined by different values of the coupling parameter λ, where the increments of λ in value move the system from the reference state to the target state. While λ can be a scalar variable that varies from 0 to 1, in some embodiments of the present invention, such as those further discussed below, λ can be a vector containing different components for different types of interactions within the system. Computer molecular simulations, such as, but not limited to, molecular dynamics or Monte Carlo simulations, can be performed to obtain ensembles of the micro-states for the reference state, the target state, and each of the intermediate states. The λ values of the intermediate states can be chosen by known techniques such that between each neighboring λ windows on the "reaction pathway" from the reference state to the target state there is substantial overlap between the micro-states in the successive λ windows that are sampled by the molecular simulations.

[0036] In performing molecular simulations for all these states, the bonded stretch interaction energy between the two atoms A_a and A_b that are to form a bond (e.g., A_1 and A_3 in Figure 1a) can be defined by a soft bond potential which is modulated by λ (or the bond stretch component thereof). When $\lambda = 0$ (A_a and A_b are completely nonbonded in the reference state), the soft bond potential is a flat potential for all distances r between A_a and A_b. When $0<\lambda<1$, (the bond between A_a and A_b is being "partially formed" in the alchemical transformation), the soft bond potential levels off to a flat potential when $r \to \infty$, i.e., the partial derivative of the potential with respect to the distance r between A_a and A_b is zero when $r \to \infty$. When $\lambda = 1$ (A_a and A_b are fully valence bonded in the target state), the soft bond potential reverts to a harmonic potential. Further, the potential energy function for the bond stretch term does not have any singular regions for all values of the bonded stretch component, λ_{sbs}, of the coupling parameter λ within [0,1] and for all values of the distance *r* between Aa and Ab. The details of developing the soft bond potential and some properties of the soft bond potential are provided below.

[0037] In popular molecular mechanics force fields, such as OPLS, CHARMM, and AMBER, the bonded stretch interactions between two atoms are modeled by a harmonic bond of the following form:

$$U_{bs}(\lambda, r) = \frac{1}{2} k (r - r_0)^2 \qquad (5)$$

where *k* is the "force constant" or "Hookean constant" which defines the strength (or rigidity) of the bond of the force field used, *r* is the instantaneous distance between the two atoms and r_0 is the equilibrium distance between the two atoms. In conventional method of linear scaling of the coupling parameter between the Hamiltonians of the reference state and the target state, the bonded stretch term has the following form in the coupling Hamiltonian:

$$U_{bs}(\lambda, r) = \frac{1}{2} \lambda k (r - r_0)^2 \qquad (6)$$

Therefore,

$$\frac{\partial F(\lambda)}{\partial \lambda} = \left\langle \frac{\partial U_{bs}(\lambda, r)}{\partial \lambda} \right\rangle_{\lambda} = \left\langle \frac{1}{2} k (r - r_0)^2 \right\rangle_{\lambda} \qquad (7)$$

[0038] The integrand in the above equation approaches infinity when *r* is very large. In the limit when λ approaches 0, there is no bonded stretch interaction between the two atoms, and the distance between the two atoms can be very large, leading to singularity and numerical instability problem in the calculation of the above integral. In practice, the distance between the two atoms is limited by the size of the simulation box (a three-dimensional volume or unit cell in which the simulation is conducted and boundary conditions, such as periodic boundary conditions, can be applied), the singularity problem can be avoided. However, since the integrand in the above equation is unbounded, it can still cause numerical instability and inaccuracy problems in the free energy calculations.

[0039] Additionally, using the above conventional coupling Hamiltonian functional form, the potential is undefined for λ=0 when *r* approaches infinity. The limiting value depends on how λ approaches 0 and how *r* approaches infinity, i.e.:

$$\lim_{r\to\infty}\lim_{\lambda\to 0} U_{bs}(\lambda,r)=\lim_{r\to\infty}\lim_{\lambda\to 0}\frac{1}{2}\lambda k(r-r_0)^2 \quad \text{diverges} \tag{8}$$

[0040] In order to obtain a pathway that allows stable and efficient simulations from which reliable free energies involving the annihilation and/or formation of a bond between two atoms can be determined, the present inventors have discovered the following coupling potential (referred to herein as the soft bond potential) to connect the two physical systems where the harmonic interactions between the two atoms are fully turned on and off when the coupling parameter λ changes between 0 and 1:

$$U_{sbs}(r,\lambda)=\frac{1}{2}kf(\lambda)(r-r_0)^2\frac{1}{1+g(\lambda)\alpha(k,\lambda)(r-r_0)^2} \tag{9}$$

where the functions *f,g* and *α* are each continuous functions and simultaneously satisfy the following conditions: f(λ=0)=0; f(λ=1)=1; g(λ=0)=1; g(λ=1)=0; α(k,λ,<1)>0. It is noted that for all the discussions herein regarding the soft bond potential for the bonded stretch interactions, λ as used in the equations (from Equation 9 and onwards) refers to the bonded stretch component, λ_{sbs}, of the coupling parameter λ.

[0041] In particular example of the soft bond potential described by Eq. 9, f(λ)=λ, g(λ)=1-λ, and α(k,λ)=α=const (a constant number), i.e., the soft bond potential takes the following form:

$$U_{sbs}(r,\lambda)=\frac{1}{2}\lambda k(r-r_0)^2\frac{1}{1+\alpha(1-\lambda)(r-r_0)^2}$$

(10)

[0042] It can be seen that the soft bond interaction of Eq. 10 correctly recovers the two physical end states when λ =0 and λ =1:

$$\begin{aligned} &U_{sbs}(r,\lambda=1)=\frac{1}{2}k(r-r_0)^2\\ &U_{sbs}(r,\lambda=0)=0\\ &U_{sbs}(r\to\infty,\lambda)=\frac{k\lambda}{2\alpha(1-\lambda)} \quad \text{when } \lambda\neq 1 \end{aligned}$$

(11)

[0043] The introduction of $\alpha(1 - \lambda)(r - r_0)^2$ in the denominator of Eq. 10 changes the harmonic interaction into a soft bond interaction (the interaction is bounded when r approaches infinity) when λ is smaller than 1, and at λ =1 (the bond is formed) the function has the exact harmonic potential form.

[0044] The above functional form removes the singularity and numerical instability problems associated with the conventional harmonic potentials. In the following, some properties of the soft bond interaction functional form as exemplified by Eq. 10 are discussed.

Property 1:

[0045] The soft bond interaction functional form does not have any singular regions for all values of λ between 0 and 1 and for all values of r. From the above description, i.e.:

$$\begin{aligned} &U_{sbs}(r,\lambda=1)=\frac{1}{2}k(r-r_0)^2 \\ &U_{sbs}(r,\lambda=0)=0 \\ &U_{sbs}(r,\lambda)=\frac{1}{2}\lambda k(r-r_0)^2\frac{1}{1+\alpha(1-\lambda)(r-r_0)^2} \quad \text{for } \lambda \in (0,1) \end{aligned}$$

$$(12)$$

[0046] The soft bond potential for a model system with the force constant k = 20 $kcal \cdot mol^{-1} \cdot Å^{-2}$ and the soft bond parameter α = 1 at different values of λ are given in Figure 2. It can be seen clearly that the potential is continuous for all values of λ and r. It changes slowly from a harmonic potential at λ=1 to a soft bond potential at intermediate values of λ, and goes to 0 at λ=0.

Property 2:

[0047]

$$\frac{\partial F_{sbs}(\lambda)}{\partial\lambda}=\left\langle\frac{\partial U_{sbs}(\lambda)}{\partial\lambda}\right\rangle_{\lambda}=\left\langle\frac{1}{2}k(r-r_0)^2\frac{1+\alpha(r-r_0)^2}{(1+(1-\lambda)\alpha(r-r_0)^2)^2}\right\rangle_{\lambda}$$

$$(13)$$

[0048] As discussed in the above section, it is $\frac{\partial F(\lambda)}{\partial\lambda}$ which determines the numerical stability and accuracy of the free energy calculations. In the above formulation, when $\lambda \in [0,1)$, the thermodynamic property to be averaged in the rightmost bracket in Eq. 13 is continuous and bounded for all values of *r*. When λ =1, the soft bond potential recovers the harmonic potential, so only phase space regions where r is close to r_0 are sampled and taken into the ensemble average. In the phase space regions where r is close to r_0, the integrand in Eq. 13 is also bounded. Therefore, the quantity in the bracket of Eq. 13 is bounded for all values of λ between 0 and 1. Since $\frac{\partial F(\lambda)}{\partial\lambda}$ does not have any singular region for all values of λ between 0 and 1, accurate and reliable free energy results can be obtained using the above soft bond interaction functional form.

[0049] As an example, the derivative of the soft bond potential of Eq. 10 with respect to the coupling parameter λ at λ=0.5 for a model system with force constant k = 20 $kcal - mol^{-1} \cdot Å^{-2}$ and the soft bond parameter α = 1 is plotted in Figure 3. It can be seen that $\frac{\partial F(\lambda)}{\partial\lambda}$ does not have any singular region for all values of λ and r, allowing reliable and accurate free energy calculations.

Property 3:

[0050]

$$\frac{\partial U_{sbs}(\lambda,r)}{\partial r}=k\lambda\frac{r-r_0}{(1+(1-\lambda)\alpha(r-r_0)^2)^2}$$
$$\frac{\partial^2 U_{sbs}(\lambda,r)}{\partial r^2}=k\lambda\frac{1-3(1-\lambda)\alpha(r-r_0)^2}{(1+(1-\lambda)\alpha(r-r_0)^2)^3}$$

(14)

[0051] Both the first derivative and the second derivative of the soft bond potential of Eq. 10 with respect to the inter-particle (or inter-atom) distance *r* are continuous and bounded for all values of $\lambda \in [0,1]$ and they are short ranged and approaching 0 when $r \to \infty$. When $\lambda = 1$, the soft bond potential reverts to the harmonic potential, and only phase space regions where *r* is close to r_0 are sampled in the molecular simulations. Thus the first and the second derivatives of the potential with respect to the inter-particle distance *r* are also continuous and bounded in the physically accessible phase space regions when $\lambda = 1$. Therefore, the forces and acceleration on the atoms are always continuous and bounded for all values of λ between 0 and 1, allowing stable molecular dynamics simulations to be performed for all values of λ. As an example, the first and second derivative of the soft bond potential with respect to the inter-particle distance r at $\lambda=0.5$ for a model system with force constant $k = 20\ kcal \cdot mol^{-1} \cdot Å^{-2}$ and the soft bond parameter $\alpha = 1$ are plotted in Figure 3. It can be seen that those derivatives are continuous over the whole space, allowing stable molecular dynamics simulations.

[0052] It is clear from the above description that the soft bond potential removes the singularity and numerical instability problems associated with the traditional methods, and it allows stable molecular dynamics simulations and more convergent Monte Carlo to be performed for all system states, including the reference system state, the intermediate system states, and the target system state. Using the soft bond potential described herein, the free energy difference between the reference system state and the target system state involving breaking and form valance bond can be accurately and reliable calculated. The free energy calculations utilizing such a soft bond potential are particularly advantageous for alchemical transformations involving ring opening, ring closing, or ring rearrangement, where the computational efficiency and convergence of the free energy calculations can be significantly improved over the conventional methods.

[0053] As described in above section, in the conventional coupling Hamiltonian, the limit does not exist for the initial state where $\lambda=0$ when *r* approaches infinity, while in the soft bond potential the limit exists for all values of r. The conventional coupling Hamiltonian is a special case of the soft bond potential where $\alpha = 0$. While the conventional coupling Hamiltonian and the soft bond potential reach the same end state when $\lambda=1$, the initial states when $\lambda=0$ are different depending on the value of the soft bond parameter α. In the following, it is shown that the free energy of the initial state does not depend on the soft bond parameter α.

[0054] Consider a Hamiltonian with the following potential energy term (i.e., Eq. 10 where $\lambda = 0$):

$$U(r,\alpha,\lambda)=\frac{1}{2}k\lambda(r-r_0)^2\frac{1}{1+\alpha(r-r_0)^2}$$

(15)

[0055] When $\alpha=0$, it becomes the conventional harmonic potential, and when $\alpha \neq 0$ it becomes the soft bond potential. We need to prove that

$$F(\alpha=0,\lambda=0)=F(\alpha=\alpha'>0,\lambda=0)$$

(16)

Note that

$$F(\alpha=\alpha'>0,\lambda=0)-F(\alpha=0,\lambda=0)=\int_0^{\alpha'}d\alpha\lim_{\lambda\to 0}\frac{\partial F(\alpha,\lambda)}{\partial\alpha}$$

(17)

where

$$\frac{\partial F(\alpha,\lambda)}{\partial \alpha} = \left\langle \frac{\partial U(r,\alpha,\lambda)}{\partial \alpha} \right\rangle_{\alpha} = \left\langle \frac{k\lambda(r-r_0)^4}{2(1+\alpha(r-r_0)^2)^2} \right\rangle_{\alpha} = \lambda \left\langle \frac{k(r-r_0)^4}{2(1+\alpha(r-r_0)^2)^2} \right\rangle_{\alpha} = \lambda I(\alpha)$$

(18)

[0056] The ensemble average $I(\alpha)$ is a finite number since

$$\begin{aligned} I(\alpha) = \left\langle \frac{k(r-r_0)^4}{2(1+\alpha(r-r_0)^2)^2} \right\rangle_{\alpha} &= \int_0^{r_{\max}} dr \frac{k(r-r_0)^4}{2(1+\alpha(r-r_0)^2)^2} \frac{\exp(-\beta U(r,\alpha,\lambda))}{\int_0^{r_{\max}} dr \exp(-\beta U(r,\alpha,\lambda))} \\ &\leq \int_0^{r_{\max}} dr\, k(r-r_0)^4 \frac{1}{\exp(-\beta U(r_{\max},\alpha,\lambda))V} \\ &\leq \frac{k r_{\max}^4}{\exp(-\beta U(r_{\max},\alpha,\lambda))V} \end{aligned}$$

(19)

[0057] Therefore,

$$\begin{gathered} \lim_{\lambda \to 0} \frac{\partial F(\alpha,\lambda)}{\partial \alpha} = \lim_{\lambda \to 0} \lambda I(\alpha) = 0 \\ F(\alpha = \alpha' > 0, \lambda = 0) - F(\alpha = 0, \lambda = 0) = 0 \end{gathered}$$

(20)

[0058] In view of the above, the initial state for the conventional coupling Hamiltonian and soft bond potential when $\lambda=0$ have the same free energy.

[0059] In free energy calculations, the convergence of the free energy can be affected by the overlap of phase space regions between neighboring or successive λwindows. Empirically, a suitable path from the initial state to the final state can be achieved when the change of the free energy as a function of λ is continuous and smooth for all values of λ, i.e.:

$$\frac{\partial F_{sbs}(\lambda)}{\partial \lambda} = \left\langle \frac{\partial U_{sbs}(\lambda)}{\partial \lambda} \right\rangle_{\lambda} = \left\langle \frac{1}{2} k(r-r_0)^2 \frac{1+\alpha(r-r_0)^2}{(1+(1-\lambda)\alpha(r-r_0)^2)^2} \right\rangle_{\lambda} \approx const \quad (21)$$

[0060] Thus, in preferred embodiments, the value of the soft bond parameter α can be obtained when Eq. 21 is satisfied.

[0061] As mentioned above, in ring opening and closing free energy calculations, in addition to the bonded stretch interactions, there can be other interaction energy terms which are different in the initial and final states, including the bonded angle terms, the bonded dihedral angle terms, and the nonbonded interactions. These different types of interactions can be treated differently during the transformation process. As described herein, in some embodiments, the coupling parameter λ can take a vector form which includes components for different types of interactions. For example, the coupling vector λ can include the following components for interactions affected by the formation (or the breaking) of the valence bond between the reference state and the target state: a component λ_{sbs} for bonded stretch energy term; a component λ_{ba} for the bonded angle energy term; a component λ_{bd} for bonded dihedral angle energy term; components λ_{vdw} and λ_{elec} for the van de Waals and electrostatic energy terms of the nonbonded exclusion and 1-4 pair interaction, respectively. The coupling vector λ can further include components λ_{other} for other interactions not affected by the formation and/or breaking of the valence bond between the reference state and the target state. Each component of the coupling vector λ belongs to [0, 1]. During the course of the alchemical transformation from the reference state to the target state, the interactions unique in the reference state can be turned off according to a first set of schedules for different λ components, and the interactions unique in the target state can be turned on according to a second set of schedules for different λ components, as will be further described below.

[0062] In popular molecular mechanics force fields, the bonded angle and bonded dihedral angle interactions usually have the following potential energy form:

$$U_{ba}(\theta)=k_{\theta}(\theta-\theta_{0})^{2} \qquad (22)$$

$$U_{bd}(\phi)=k_{\phi}\sum_{n}f(\cos(n\phi)) \qquad (23)$$

where θ is the bond angle, θ_0 is the equilibrium bond angle, k_θ is the angle force constant (both θ_0 and k_θ depend on the atoms forming the bond angle); ϕ is the dihedral angle, k_ϕ is the dihedral angle force constant (which depends on the atoms forming the dihedrals). With the opening or closing of a ring, the bonded angle and dihedral angle terms that are affected by the breaking or forming of the bond can be modulated by components λ_{ba} and λ_{bd} of the coupling parameter λ, respectively. Although the bonded angle and dihedral interaction terms are bounded for all λ values, the absolute values of these terms can be very large if the molecule is in a very twisted geometry. To improve the accuracy of the free energy calculation, in some embodiments, the bonded stretch interaction can be first turned on to a significant degree (e.g., $\lambda_{sbs} = 0.5$) before turning on the bonded angle and bonded dihedral angle interaction (during bond formation). In this way, the bonded stretch interaction will steer the molecule clear from a severely twisted geometry, improving the inaccuracy problem caused by the bonded angle and bonded dihedral angle interactions in the free energy calculations.

[0063] The nonbonded electrostatic and van der Waals interactions between two atoms are usually modeled by the following potential energy form in popular molecular mechanics force fields:

$$U_{elec}(r)=C\frac{q_1q_2}{r} \qquad (24)$$

$$U_{vdw}(r)=4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12}-\left(\frac{\sigma}{r}\right)^{6}\right] \qquad (25)$$

where in Eqs. 24 and 25, r is the inter-atom distance, q_1 and q_2 are the charges of the two atoms, C is a constant, ε is the depth of the potential well of $U_{vdw}(r)$, and σ is the finite distance at which the inter-atom potential $U_{vdw}(r)$ is zero.

[0064] Many force fields, including OPLS, CHARM, AMBER, exclude or modify the nonbonded interactions between atoms separated by one, two, or three bonds. In particular, when two atoms are separated by three bonds (e.g., the two atoms A_1 and A_8 shown in Figure 1a), the conventional non-bonded electrostatic and van der Waals interactions as described in Eq. 24 between the two atoms are not calculated (i.e., excluded); instead, they are substituted by electrostatic 1-4 pair and van der Waals 1-4 pair interactions.

[0065] With the opening or closing of a ring, the nonbonded electrostatic and van der Waals interactions for atoms that span the bond that is broken or forming can be modulated for by components λ_{elec} and λ_{vdw}, respectively, which will be further discussed below. As used herein, in some embodiments of the invention, the van der Waals and/or the electrostatic interaction can be described by a soft-core Lennard Jones (LJ) and/or soft-core Coulomb potential that keeps pairwise interaction energies finite for all configurations. By way of example, a soft-core LJ potential may take the following functional form:

$$U_{LJ}(r,\lambda)=4\varepsilon\lambda\left(\frac{1}{(\alpha_{LJ}(1-\lambda)^{n}+(r/\sigma)^{6})^{2}}-\frac{1}{\alpha_{LJ}(1-\lambda)^{n}+(r/\sigma)^{6}}\right)$$
(26)

where it a_{LJ} is the soft core parameter, ε and σ are the standard Lennard Jones interaction parameters, n is the order parameter which usually takes values between 1 and 6. See Beutler et al., "Avoiding singularities and numerical instabilities in free energy calculations based on molecular simulations," Chem. Phys. Lett., 222 (1994) 529-539. The soft-core LJ interaction recovers the standard Lennard Jones interactions when λ = 1 and it becomes 0 when λ = 0.

[0066] In some embodiments, for ring opening and closing free energy calculations, a λ schedule for all the system states can be used to treat the bonded stretch, bonded angle, bonded dihedral angle, nonbonded exclusion and 1-4 pair interactions, that are affected by the formation and/or annihilation of a bond that results in the opening or the closing of a ring structure. The coupling parameter λ for those interactions affected by the bond formation or breaking may include seven components for bond breaking transformation and seven components for bond formation transformation from the reference state to the target state.

[0067] The seven components of the coupling parameter λ applicable for the bond breaking transformation include the following terms: λ_{sbsA}, which modulates the bonded stretch interactions, respectively, that are present in the initial state (the bond is present and yet to be broken) but not in the final state (the bond is broken); λ_{baA} and λ_{bdA}, which modulate the bonded angle and bonded dihedral angle interactions that are present in the initial state but not in the final state; $\lambda_{elecA_{ex}}$ and $\lambda_{vdwA_{ex}}$, which modulate the nonbonded electrostatic interactions and van der Waals interactions present in the final state but excluded (nonbonded exclusions) in the initial state due to the breaking of a bond present in the initial state during the transformation from the initial state to the final state, and $\lambda_{elecA_{14}}$ and $\lambda_{vdwA_{14}}$ which modulate the electrostatic 1-4 pair and van der Waals 1-4 pair interactions present in the initial state but not included in the final state due to the breaking or formation of the bond during the transformation from the initial state to the final state.

[0068] Similarly, the seven components for bond formation transformation include the following terms: λ_{sbsB}, which modulates the bonded stretch interactions that are present in the final state (the bond is formed) but not in the initial state (the bond is yet to be formed), λ_{baB} *and* λ_{bdB}, which modulate the bonded angle and bonded dihedral angle interactions that are present in the final state but not in the initial state, respectively, $\lambda_{elecB_{ex}}$ and $\lambda_{vdwB_{ex}}$, which modulate the nonbonded electrostatic and van der Waals interactions present in the initial state but excluded in the final state due to the formation of a bond in the final state, and $\lambda_{elecB14}$ and λ_{vdwB14}, which modulate the electrostatic 1-4 pair and van der Waals 1-4 pair interactions present in the final state but excluded in the initial state due to the formation or breaking of the bond during the transformation from the initial state to the final state .

[0069] As used herein, the term "modulate" when used in connection with a component of the coupling parameter λ means that the interaction energy for that particular component is calculated using parameters of a conventional force field and the corresponding component coupling parameter. To be specific, for bonded stretch interaction and the LJ interaction, (or the electrostatic interaction) where the soft-core potentials are used, the interaction energies are calculated according to equations 9 and 26 respectively, while for other types of the interactions, the interaction energy is calculated using parameters of a conventional force field multiplied by the corresponding component coupling parameter λ.

[0070] One example of λ schedules discussed above is shown in Scheme 1 below, in which the superscript (0, 1, ..., m, m+1, ..., n) indicate the indexes of the reference system state, the intermediate states, and the target system state, and λ^{i}_{comp} is the respective λ component value for state with index "i" and component "comp".

$$\begin{aligned}
\lambda_{sbsA} &= [\lambda^{0}_{sbsA} = 1,\ \lambda^{1}_{sbsA} \ \dots\ \lambda^{m}_{sbsA} = 0.5,\ \lambda^{m+1}_{sbsA} \ \dots\ \lambda^{n}_{sbsA} = 0] \\
\lambda_{baA} &= [\lambda^{0}_{baA} = 1,\ \lambda^{1}_{baA} \ \dots\ \lambda^{m}_{baA} = 0,\ \lambda^{m+1}_{baA} = 0 \ \dots\ \lambda^{n}_{baA} = 0] \\
\lambda_{bdA} &= [\lambda^{0}_{bdA} = 1,\ \lambda^{1}_{bdA} \ \dots\ \lambda^{m}_{bdA} = 0,\ \lambda^{m+1}_{bdA} = 0 \ \dots\ \lambda^{n}_{bdA} = 0] \\
\lambda_{elecA_{ex}} &= [\lambda^{0}_{elecA_{ex}} = 0,\ \lambda^{1}_{elecA_{ex}} = 0 \ \dots\ \lambda^{m}_{elecA_{ex}} = 0,\ \lambda^{m+1}_{elecA_{ex}} \ \dots\ \lambda^{n}_{elecA_{ex}} = 1] \\
\lambda_{vdwA_{ex}} &= [\lambda^{0}_{vdwA_{ex}} = 0,\ \lambda^{1}_{vdwA_{ex}} \ \dots\ \lambda^{m}_{vdwA_{ex}} = 1,\ \lambda^{m+1}_{vdwA_{ex}} = 1 \ \dots\ \lambda^{n}_{vdwA_{ex}} = 1] \\
\lambda_{elecA_{14}} &= [\lambda^{0}_{elecA_{14}} = 1,\ \lambda^{1}_{elecA_{14}} \ \dots\ \lambda^{m}_{elecA_{14}} = 0,\ \lambda^{m+1}_{elecA_{14}} = 0 \dots\ \lambda^{n}_{elecA_{14}} = 0] \\
\lambda_{vdwA_{14}} &= [\lambda^{0}_{vdwA_{14}} = 1,\ \lambda^{1}_{vdwA_{14}} \ \dots\ \lambda^{m}_{vdwA_{14}} = 1,\ \lambda^{m+1}_{vdwA_{14}} \ \dots\ \lambda^{n}_{vdwA_{14}} = 0] \\
\lambda_{sbsB} &= [\lambda^{0}_{sbsB} = 0,\ \lambda^{1}_{sbsB} \ \dots\ \lambda^{m}_{sbsB} = 0.5,\ \lambda^{m+1}_{sbsB} \ \dots\ \lambda^{n}_{sbsB} = 1] \\
\lambda_{baB} &= [\lambda^{0}_{baB} = 0,\ \lambda^{1}_{baB} = 0 \ \dots\ \lambda^{m}_{baB} = 0,\ \lambda^{m+1}_{baB} \ \dots\ \lambda^{n}_{baB} = 1] \\
\lambda_{bdB} &= [\lambda^{0}_{bdB} = 0,\ \lambda^{1}_{bdB} = 0 \ \dots\ \lambda^{m}_{bdB} = 0,\ \lambda^{m+1}_{bdB} \ \dots\ \lambda^{n}_{bdB} = 1] \\
\lambda_{elecB_{ex}} &= [\lambda^{0}_{elecB_{ex}} = 1,\ \lambda^{1}_{elecB_{ex}} \ \dots\ \lambda^{m}_{elecB_{ex}} = 0,\ \lambda^{m+1}_{elecB_{ex}} \ \dots\ \lambda^{n}_{elecB_{ex}} = 0] \\
\lambda_{vdwB_{ex}} &= [\lambda^{0}_{vdwB_{ex}} = 1,\ \lambda^{1}_{vdwB_{ex}} = 1 \ \dots\ \lambda^{m}_{vdwB_{ex}} = 1,\ \lambda^{m+1}_{vdwB_{ex}} \ \dots\ \lambda^{n}_{vdwB_{ex}} = 0] \\
\lambda_{elecB_{14}} &= [\lambda^{0}_{elecB_{14}} = 0,\ \lambda^{1}_{elecB_{14}} = 0 \ \dots\ \lambda^{m}_{elecB_{14}} = 0,\ \lambda^{m+1}_{elecB_{14}} \ \dots\ \lambda^{n}_{elecB_{14}} = 1] \\
\lambda_{vdwB_{14}} &= [\lambda^{0}_{vdwB_{14}} = 0,\ \lambda^{1}_{vdwB_{ex}} \ \dots\ \lambda^{m}_{vdwB_{ex}} = 1,\ \lambda^{m+1}_{vdwB_{ex}} = 1 \dots\ \lambda^{n}_{vdwB_{ex}} = 1]
\end{aligned}$$

Scheme 1

[0071] λ_{sbsA} as shown in Scheme 1 can be varied from 1 to 0 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of λ_{sbsA} can be linear and/or monotonic over the transformation. In other embodiments, the variation of λ_{sbsA} can be non-linear and/or non-monotonic over the transformation. Although it is shown that $\lambda_{sbsA} = 0.5$ at the intermediate system state indexed by m, this schedule for λ_{sbsA} is merely illustrative and non-limiting (e.g., other values smaller or greater than 0.5 can also be used for the intermediate system state indexed by m).

[0072] λ_{baA} as shown in Scheme 1 can be varied from 1 to 0 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of λ_{baA} can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of λ_{baA} can be non-linear and/or non-monotonic over the transformation or a portion of the transformation.

[0073] λ_{bdA} as shown in Scheme 1 can be varied from 1 to 0 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of λ_{bdA} can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of λ_{bdA} can be non-linear and/or non-monotonic over the transformation or a portion of the transformation.

[0074] Further, in certain embodiments, for improved sampling efficiency in the molecular simulations, the bonded angle and bonded dihedral interactions between two atoms can be turned off more quickly to 0 before the bonded stretch interactions are turned off during the bond breaking transformation (conversely, the bonded angle and bonded dihedral interactions can be turned on only after the bonded stretch interactions are turned on to a predetermined degree). Although it is shown that λ_{baA} / λ_{bdA} can be decreased to 0 at the intermediate system state indexed by m (meaning that λ_{baA} / λ_{bdA} can be varied from 1 at the initial state to 0 at this intermediate state by a more rapid decrease than that of λ_{sbsA}), the schedule for λ_{baA} / λ_{bdA} are merely illustrative and non-limiting (e.g., λ_{baA} / λ_{bdA} can be decreased to 0 more rapidly or slowly from the initial state). Also, the λ_{baA} and λ_{bdA} can be varied separately according to their own respective schedules and do not need to be synchronized.

[0075] $\lambda_{elecA_{ex}}$ as shown in Scheme 1 can be varied from 0 to 1 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of $\lambda_{elecA_{ex}}$ can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of $\lambda_{elecA_{ex}}$ can be non-linear and/or non-monotonic over the transformation or a portion of the transformation. Although it is shown that $\lambda_{elecA_{ex}} = 0$ at the intermediate system state indexed by m (i.e., $\lambda_{elecA_{ex}}$ can be 0 from the initial state through the intermediate state indexed by m, and increased from this intermediate state to the final state), this schedule is merely illustrative and non-limiting (e.g., $\lambda_{elecA_{ex}}$ can be kept at 0 until an intermediate state that precedes or subsequent to the intermediate state indexed by m).

[0076] $\lambda_{vdwA_{ex}}$ as shown in Scheme 1 can be varied from 0 to 1 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of $\lambda_{vdwA_{ex}}$ can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of $\lambda_{vdwA_{ex}}$ can be non-linear and/or non-monotonic over the transformation or a portion of the transformation. Although it is shown that $\lambda_{vdwA_{ex}} = 1$ at the intermediate system state indexed by m ($\lambda_{vdwA_{ex}}$ can be increased from the initial state at the value of 0 to the intermediate state indexed by m at the value of 1, and stay at 1 thereon until the final state), this schedule is merely illustrative and non-limiting (e.g., $\lambda_{vdwA_{ex}}$ can be increased to 1 at an intermediate state that precedes or follows the intermediate state indexed by m). Further, in certain embodiments, for improved sampling efficiency in the molecular simulations, the van der Waals interaction between two atoms can be fully turned on before the electrostatic interactions are turned on during the transformation. This is illustrated in Schedule 1, where the schedules of $\lambda_{elecA_{ex}}$ and $\lambda_{vdwA_{ex}}$ are coordinated such that when $\lambda_{vdwA_{ex}}$ is smaller than 1 for an intermediate state, $\lambda_{elecA_{ex}}$ is 0 for that intermediate state.

[0077] $\lambda_{elecA_{14}}$ as shown in Scheme 1 can be varied from 1 to 0 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of $\lambda_{elecA_{14}}$ can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of $\lambda_{elecA_{14}}$ can be non-linear and/or non-monotonic over the transformation or a portion of the transformation. Although it is shown that $\lambda_{elecA_{14}} = 0$ at the intermediate system state indexed by m (i.e., $\lambda_{elecA_{14}}$ can be varied from 1 at the initial state to 0 at this intermediate state by a more rapid decrease than that of λ_{sbsA}), this schedule is merely illustrative and non-limiting (e.g., $\lambda_{elecA_{14}}$ can be decreased to 0 more rapidly or slowly from the initial state).

[0078] $\lambda_{vdwA_{14}}$ as shown in Scheme 1 can be varied from 1 to 0 over the bond breaking (e.g., a ring opening) transformation. In some embodiments, the variation of $\lambda_{vdwA_{14}}$ can be linear and/or monotonic over the transformation or a portion of the transformation. In other embodiments, the variation of $\lambda_{vdwA_{14}}$ can be non-linear and/or non-monotonic over the transformation or a portion of the transformation. Although it is shown that $\lambda_{vdwA_{14}} = 1$ at the intermediate system state indexed by m ($\lambda_{vdwA_{14}}$ can be kept at 1 from the initial state through the intermediate state indexed by m, and then decreased to 0 from that intermediate state to the final state), this schedule is merely illustrative and non-limiting (e.g., $\lambda_{vdwA_{14}}$ can be kept to 1 from the initial state through an intermediate state that precedes or follows the intermediate state indexed by m, and then decreased to 0 from that intermediate state to the final state). Further, in certain embodiments, for improved sampling efficiency in the molecular simulations, the van der Waals interactions between two atoms are turned off only after the electrostatic interactions are fully turned off during the transformation. This is illustrated in Schedule 1, where the schedules of $\lambda_{elecA_{14}}$ and $\lambda_{vdwA_{14}}$ are coordinated such that when $\lambda_{vdwA_{14}}$ is smaller than 1 for an intermediate state, $\lambda_{elecA_{14}}$ is 0 for that intermediate state.

[0079] The schedules of the λ components for the bond formation transformation, λ_{sbsB}, λ_{baB} *and* λ_{bdB}, $\lambda_{elecB_{ex}}$ and $\lambda_{vdwB_{ex}}$, $\lambda_{elecB_{14}}$ and $\lambda_{vdwB_{14}}$ can be readily understood by a person of ordinary skill in the art in view of the above description of the λ schedule for the bond breaking transformation, as the two transformation processes are essentially reverse to each other. It is noted, however, that although the values of a λ component in the bond formation and the corresponding λ component in the bond breaking transformation (e.g., λ_{sbsA} and λ_{sbsB}) appear to sum up to 1, this is merely illustrative. For any given system, a bond cannot be both forming and breaking simultaneously in the same alchemical transformation considered in this application. Thus, the λ component schedules in a bond breaking transformation do not need to coordinate with those in bond formation transformation. As an example, λ_{sbsB} can follow a schedule of increasing from 0 to 1 in a non-linear manner while λ_{sbsA} follows a schedule of decreasing from 1 to 0 in a linear manner. Further, as shown in Figure 1c, this application contemplates the breaking of one bond (e.g., the bond between A_1 and A_4) and the simultaneous formation of another bond (or bonds) (e.g., the bond between A_1 and A_{13} and the bond between A_4 and A_{13}). In this case, the λ component schedules for the bond breaking transformation and the λ component schedules for the bond formation transformation can be selected separately and not dependent upon each other.

[0080] In the following, energy calculations in a molecular simulation of the transformation shown in Figure 1a are illustrated in connection with certain embodiments of the above-described λ schedule.

- Bonded stretch interactions that are affected by the bond formation between A_1 and A_3 in Figure 1a: (A_1,A_3)
- Bonded angle interactions that are affected by the bond formation between A_1 and A_3 in Figure 1a:

  (i) Bonded angle interactions only appearing in the initial state and not in the final state: (A_2,A_1,A_{10}), (A_4,A_1,A_{10}), (A_5,A_1,A_{10}), (A_2,A_3,A_{11}), (A_8,A_3,A_{11}), (A_9,A_3,A_{11});

  (ii) Bonded angle interactions only appearing in the final state and not in the initial state: (A_2,A_1,A_3), (A_4,A_1,A_3), (A_5,A_1A_3), (A_1,A_3,A_2), (A_1,A_3,A_8), (A_1,A_3,A_9).

- Bonded dihedral interactions that are affected by the bond formation between A_1 and A_3 in Figure 1a:

  (i) Bonded dihedral angle interactions involving atoms only appearing in the initial state and not in the final state: (A_{10},A_1,A_2,A_3), (A_{10},A_1,A_2,A_6), (A_{10},A_1,A_2,A_7), (A_1,A_2,A_3,A_{11}), (A_6,A_2,A_3,A_{11}), (A_7,A_2,A_3,A_{11});

  (ii) Bonded dihedral angle interactions involving atoms only appearing in the final state and not in the initial state: (A_3,A_1,A_2,A_6), (A_3,A_1,A_2,A_7), (A_2,A_1,A_3,A_8), (A_2,A_1,A_3,A_9), (A_4,A_1,A_3,A_2), (A_4,A_1,A_3,A_8), (A_4,A_1,A_3,A_9),

(A_5,A_1,A_3,A_2), (A_5,A_1,A_3,A_8), (A_5,A_1A_3,A_9), (A_6,A_2,A_3,A_1), (A_7,A_2,A_3,A_1).

- Atom pairs excluded for the calculation of nonbonded interactions in the initial state but not excluded in the final state in Figure 1a: (A_1,A_{10}), (A_1,A_{11}), (A_2,A_{10}), (A_2,A_{11}), (A_3,A_{10}), (A_3,A_{11}), (A_4,A_{10}), (A_5,A_{10}), (A_6,A_{10}), (A_6,A_{11}), (A_7,A_{10}), (A_7,A_{11}), (A_8,A_{11}), (A_9,A_{11}).
- Atom pairs excluded for the calculation of nonbonded interactions in the final state but not excluded in the initial state in Figure 1a: (A_4,A_8), (A_4,A_9), (A_5,A_8), (A_5,A_9).
- 1-4 atom pairs included in the initial state but not included in the final state in Figure 1a: (A_1,A_8), (A_1,A_9), (A_3,A_4), (A_3,A_5).
- 1-4 atom pairs included in the final state but not included in the initial state in Figure 1a: (A_4,A_8), (A_4,A_9), (A_5,A_8), (A_5,A_9).

[0081] The other bonded and nonbonded interactions that are not affected by the formation and annihilation of bonds for the ring opening or closing transformation can be modulated by a regular λ schedule as in conventional free energy perturbations not involving ring opening and closing (e.g., incrementing λ_{other} from the initial state to the final state, where the interactions between P_{AB} and P_A is scaled by $1-\lambda_{other}$, and the interactions between P_{AB} and P_B is scaled by λ_{other}). Further, all the interactions involving atoms that only appear in the initial state but missing from the final state (i.e., those atoms that become "dummy" atoms in the final state) will also be treated by a normal λ schedule. Conversely, for the reverse (bond formation) transformation, all the interactions involving atoms that appear only in the final state and are missing from the initial state (e.g., A_{11} and A_{12} in Figure 1a) will also be treated by the normal λ schedule. The remaining interactions, i.e., those affected by the formation and annihilation of bonds for the ring opening or closing transformation that do not involve atoms that only appear in the initial state or only appear in the final state can be modulated by a "special" λ schedule similar to what is described in Schedule 1, that is, for the ring closing transformation depicted in Figure 1a:

- Bonded stretch interaction included in the initial state but not in the final state is modulated by λ_{sbsA} using a soft bond interaction potential described herein (in this example, no interaction belongs to this category);
- Bonded stretch interaction not included in the initial state but included in the final state is modulated by λ_{sbsB} using a soft bond interaction potential described herein (in this example, the bonded stretch interaction between atoms A_1 and A_3 belong to this category);
- Bonded angle interactions included in the initial state but not in the final state are modulated by λ_{baA} (in this example, no interaction belongs to this category);
- Bonded angle interactions included in the final state but not in the initial state are modulated by λ_{baB} (in this example, the bonded angle interactions between atoms (A_2,A_1,A_3), (A_4,A_1,A_3), (A_5,A_1,A_3), (A_1,A_3,A_2), (A_1,A_3,A_8), (A_1,A_3,A_9) belong to this category);
- Bonded dihedral angle interactions included in the initial state but not in the final state are modulated by λ_{bdA} (in this example, no interaction belongs to this category);
- Bonded dihedral angle interactions included in the final state but not in the initial state are modulated by λ_{bdB} (in this example, the bonded dihedral angle interactions between atoms (A_3,A_1,A_2,A_6), (A_3,A_1,A_2,A_7), (A_2,A_1,A_3,A_8), (A_2,A_1,A_3,A_9), (A_4,A_1,A_3,A_2), (A_4,A_1,A_3,A_8), (A_4,A_1,A_3,A_9), (A_5,A_1,A_3,A_2), (A_5,A_1,A_3,A_8), (A_5,A_1,A_3,A_9), (A_6,A_2,A_3,A_1), (A_7,A_2,A_3,A_1) belong to this category);
- Interactions excluded in the initial state but not excluded in the final state are modulated by $\lambda_{elecAex}$ and λ_{vdwAex} (in this example, no interaction belongs to this category);
- Interactions excluded in the final state but not excluded in the initial state are modulated by $\lambda_{elecBex}$ and λ_{vdwBex} (in this example, the interactions excluded in the final state for pairs (A_4,A_8), (A_4,A_9), (A_5,A_8), (A_5,A_9) belong to this category);
- 1-4 pair interactions included in the initial state but not in the final state are modulated by $\lambda_{elecA14}$ and λ_{vdwA14} (in this example, the 1-4 pair interactions for pairs (A_1,A_8), (A_1A_9), (A_3,A_4), (A_3,A_5) belong to this category); and
- 1-4 pair interactions included in the final state but not in the initial state are modulated by $\lambda_{elecB14}$ and λ_{vdwB14} (in this example, the 1-4 pair interactions for pairs (A_4,A_8), (A_4,A_9), (A_5,A_8), (A_5,A_9) belong to this category).

[0082] With the energy terms defined by a suitable λ schedule (such as the one depicted in Scheme 1) for all the system states in the transformation from the initial state to the final state, molecular simulations can be run to sample the ensembles of micro-states obtained at the reference state, the target state, and the intermediate states according to the λ schedule. For each λ window, the free energy difference can be calculated between all the neighboring lambda windows $\Delta F_{\lambda i \rightarrow \lambda i+1}$ and/or between any pair of lambda windows $\Delta F_{i \rightarrow j}$, including between the reference state and the target state. The total free energy difference between the reference state and the target state can be obtained by adding the free energy differences between each two successive state along the transformation path defined by the λ schedule or directly obtained by analyzing the data from all the sampled states.

[0083] The free energy difference between neighboring λ windows or generally between any pair of states including initial state and the final state can be calculated by a variety of ways. For example, e.g., by the use of internal energy difference (FEP NVT ensemble), the enthalpy difference (FEP NPT ensemble), or other related thermodynamic property difference (FEP other ensembles, such as the NVE ensemble), of a suitable ensemble of the micro-states obtained at the target state, the reference state, and the intermediate states as coupling parameter λ is instantaneously varied for the selected ensemble of micro-states. The analysis can be further performed, for example, by way of Bannet Acceptance Ratio (BAR), Multistate Bannet Acceptance Ratio (MBAR), Weighted Histogram Analysis Method (WHAM), Zwanzig averaging, or other similar FEP-family estimators. Alternatively, the free energy difference between neighboring λ windows or generally between any pairs of states including the initial state and the final state can be calculated by way of an analysis the derivative of the energy with respect of the coupling vector λ (TI NVT ensemble), the derivative of the enthalpy with respect to the coupling vector λ (TI NPT ensemble), or the derivative of other related thermodynamic properties with respect to the coupling vector λ (TI other ensembles, such as the TI NVE ensemble), for each microscopic state obtained. In other embodiments, the free energy difference of each λ window can be calculated by way of an analysis of the potential of mean force (PMF) associated with sampling of the coupling vector λ as a dynamical variable that can dynamically transition between the reference state, the target state and intermediate states for example and without loss of generality via the λ-dynamics, the principle of which is generally described in Knight et al., λ-dynamics free energy simulation methods, J. Comput. Chem., 2009, 30: 1692-1700. λ-dynamics based sampling methods include, but are not limited to, λ-Monte Carlo, λ-metadynamics, λ-OSRW, and other λ PMF sampling family methods.

[0084] The methods for free energy difference calculations described herein can be applied to a number of highly useful applications, which include, for example:

- Relative protein-ligand binding affinity and/or relative solvation free energy calculations between congeneric ligands with ring opening or closing (see Figure 4);
- Relative protein-ligand binding affinity and/or relative solvation free energy calculations between congeneric ligands that differ by a macrocyclization (see Figure 5);
- The calculation of the effect of a non-proline to proline or proline to non-proline residue mutation to protein thermodynamic stability, protein-ligand binding affinity, or protein-protein binding affinity (see Figure 6); and
- The calculation of the effect of a residue insertion or residue deletion to protein thermodynamic stability, protein-ligand binding affinity, or protein-protein binding affinity (see Figure 7, which schematically shows a transformation of the illustrative protein segment structure depicted on the left by losing a residue numbered 129, resulting in the structure depicted on the right).

[0085] Embodiments of the method for the free energy calculations of the disclosed subject matter can be implemented in a computer program, which can take the form of a software component of a suitable hardware platform, for example, a standalone computer, a networked computer, a network server computer, a handheld device, or the like. Different aspects of the disclosed methods may be implemented in different software modules and executed by one processor or different processors, sequentially or in parallel, depending on how the software is designed. The apparatus on which the program can be executed can include one or more processors, one or more memory devices (such as ROM, RAM, flash memory, hard drive, optical drive, etc.), input/output devices, network interfaces, and other peripheral devices. A computer readable non-transitory media storing the program is also provided.

[0086] The disclosed subject matter is not to be limited in scope by the specific embodiments described herein.

Claims

1. A computer-implemented method for computing a free energy difference between a reference state and a target state which represent respectively an initial state of a molecular system and an ending state of the molecular system after one or more transformations, wherein the reference state and target state each include a common set of atoms P_{AB}, and wherein the reference state further includes a set of atoms P_A, the target state further includes a set of atoms P_B, the set P_A being present only in the reference state and not in the target state, and the set P_B being present only in the target state and not the reference state, where there exist at least two atoms A_a and A_b, A_a and A_b being either: 1) not valence-bonded to each other in the reference state and valence-bonded in the target state, or 2) valence-bonded to each other in reference state and not valence-bonded to each other in the target state, the method comprising:

    a) providing a topology, including the bonded connections between the atoms and the relative spatial arrangements of the atoms, for all the atoms in P_A, P_B, and P_{AB};

b) determining one or more intermediate system states along a transformation path between the reference state and the target state, the transformation path defined by a coupling parameter λ that modulates the energies arising from inter-atom interactions for each system state, the coupling parameter λ including a plurality of components each having a value belonging to [0,1] and modulating a different type of interaction energy;
c) performing, using at least one computer processor, molecular simulations to obtain ensembles of micro-states for the reference state, the target state, and the intermediate states, wherein performing molecular simulations for each of the system states includes calculating a bonded stretch interaction energy between the atoms A_a and A_b, the bonded stretch interaction energy being defined by a soft bond potential,
wherein the soft bond potential is a function of a bonded stretch component, λ_{sbs}, of the coupling parameter λ, and does not include any singular regions for all values of λ_{sbs} within [0,1] and for all values of the distance r between A_a and A_b, wherein both the first derivative and the second derivative of the soft bond potential with respect to the distance r between A_a and A_b are continuous and bounded for all values of λ_{sbs}, and approach zero when r approaches infinity, and wherein the soft bond potential further satisfies the following conditions:

when λ_{sbs} is within (0,1), the soft bond potential is flat when the distance between A_a and A_b approaches infinity;
when A_a and A_b are not valence bonded in the reference state, the soft bond potential is flat and zero for all distances between A_a and A_b;
when A_a and A_b are not valence bonded in the target state, the soft bond potential is flat and zero for all distances between A_a and A_b; and
when A_a and A_b are valence bonded in either the target state or the reference state, the soft bond potential reverts to a harmonic potential; and

d) calculating, using at least one computer processor, the free energy difference between the reference state and the target state, by way of an analysis of the ensembles of micro-states obtained at the target state, the reference state, and the intermediate states, wherein the molecular simulations include for example at least one of molecular dynamic simulations and Monte Carlo simulations.

2. The method of claim 1, wherein the soft bond potential is a function of $(r - r_0)^2$, where r_0 is the equilibrium distance between A_a and A_b, and optionally wherein the soft bond potential is expressed by:

$$U_{sbs}(r,\lambda_{sbs}) = \frac{1}{2}kf(\lambda_{sbs})(r-r_0)^2\frac{1}{1+g(\lambda_{sbs})\alpha(k,\lambda_{sbs})(r-r_0)^2}$$

where k is a constant, and the functions *f,g* and α are each continuous functions and satisfy the following conditions:

$$f(\lambda_{sbs}=0)=0,$$

$$f(\lambda_{sbs}=1)=1,$$

$$g(\lambda_{sbs}=0)=1,$$

$$g(\lambda_{sbs}=1)=0,$$

$$\alpha(k,\lambda_{sbs}<1)>0\;,$$

for example, wherein

$$f(\lambda_{sbs})=\lambda_{sbs},\; g(\lambda_{sbs})=1-\lambda_{sbs},\; \text{and}\quad \alpha(k,\lambda_{sbs})=const.$$

3. The method of claim 1, wherein performing molecular simulations for each of the system states comprises:

if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, using a schedule of λ_{sbsA} and a corresponding soft bond potential for calculating the bonded stretch interaction energy between A_a and A_b for each of the intermediate states, wherein λ_{sbsA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state;

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, using a schedule of λ_{sbsB} and a corresponding soft bond potential for each of the intermediate states and a soft bond potential corresponding to the λ_{sbsB} for calculating the bonded stretch interaction between A_a and A_b, wherein λ_{sbsB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state.

4. The method of claim 3, wherein performing molecular simulations for each of the system states further comprises:

a) computing a bonded angle interaction, using applicable parameters for bonded angle interactions of a force field, between i) a bond formed by A_a and another atom A_c, and ii) the bond between A_a and A_b that is being broken or formed by the transformation from the reference state to the target state;

b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, multiplying the computed bonded angle interaction obtained in a) by a bonded angle coupling parameter λ_{baA}, wherein λ_{baA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, multiplying the computed bonded angle interaction obtained in a) by a bonded angle coupling parameter λ_{baB}, wherein λ_{baB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state; and

c) including the bonded angle interaction obtained in b) into the total energy of a simulation step of the corresponding system state,

5. The method of claim 4, wherein performing molecular simulations for each of the system states further includes:

a) computing a dihedral angle interaction, using applicable parameters for dihedral interactions of a force field, of a group of four connected atoms $\{A_i, A_j, A_k, A_l\}$, the group including both A_a and A_b;

b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, multiplying the computed dihedral interaction obtained in a) by a dihedral angle coupling parameter λ_{bdA}, wherein λ_{bdA} is 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, multiplying the computed dihedral interaction obtained in a) by a dihedral angle coupling parameter λ_{bdB}, wherein λ_{bdB} is 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state; and

c) including the dihedral interaction obtained in b) into the total energy of the simulation step of the corresponding system state.

6. The method of claim 5, wherein:

if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded to each other in the target state, a bonded angle interaction parameter λ_{baA} and a bonded dihedral interaction coupling parameter λ_{bdA}, are each selected to be 0 when λ_{sbsA} is smaller than a predefined threshold, and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded to each other in the target state, the bonded angle interaction parameter λ_{baA} and the bonded dihedral interaction coupling parameter λ_{bdB} are each selected to be 0 when λ_{sbsB} is smaller than a predefined threshold, wherein the bonded angle interaction parameter λ_{baA} and the bonded dihedral interaction coupling parameter λ_{bdB} are components of the coupling parameter λ.

7. The method of claim 5, wherein performing molecular simulations for all of the states further includes:

a) computing nonbonded electrostatic interactions and van der Waals interactions, using applicable parameters for electrostatic interactions and van der Waals of a force field, between two atoms A_i and A_j and the nonbonded exclusion status of the pair (Ai, A_j) is affected by the transformation from the reference state to the target state;

b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are excluded in the reference state but not excluded in the target state, multiplying the nonbonded electrostatic interactions and van der Waals interactions between A_i and A_j obtained in a) by coupling parameters $\lambda_{elecAex}$ and λ_{vdwAex}, respectively, wherein both of $\lambda_{elecAex}$ and λ_{vdwAex} are 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state;

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are not excluded in the reference state but excluded in the target state, multiplying the nonbonded electrostatic interactions and van der Waals interactions between A_i and A_j obtained in a) by coupling parameters $\lambda_{elecBex}$ and λ_{vdwBex}, respectively, wherein both of $\lambda_{elecBex}$ and λ_{vdwBex} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

c) including the calculated nonbonded electrostatic interactions and van der Waals interactions obtained in b) into the total energy of the simulation step of the corresponding system state.

8. The method of claim 7, wherein performing molecular simulations for all of the states further includes:

if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state, and the nonbonded interactions between A_i and A_j are excluded in the reference state but not excluded in the target state, varying each of $\lambda_{elecAex}$ and λ_{vdwAex} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwAex} is smaller than 1 for an intermediate state, $\lambda_{elecAex}$ is 0 for that intermediate state; and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state, and the nonbonded interactions between A_i and A_i are not excluded in the reference state but excluded in the target state, varying each of $\lambda_{elecBex}$ and λ_{vdwBex} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwAex} is smaller than 1 for an intermediate state, $\lambda_{elecAex}$ is 0 for that intermediate state.

9. The method of claim 7, wherein performing molecular simulations for all of the states further includes:

a) computing nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions, using applicable parameters for electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions of a force field, between two atoms A_i and A_j which together with another two intervening atoms forms a bonded dihedral angle interaction in either the reference state or the target state;

b) if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state:

> if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in a) by coupling parameters $\lambda_{elecA14}$ and λ_{vdwA14}, respectively, wherein both of $\lambda_{elecA14}$ and λ_{vdwA14} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state, and
>
> if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in a) by coupling parameters $\lambda_{elecB14}$ and λ_{vdwB14}, respectively, wherein both of $\lambda_{elecB14}$ and λ_{vdwB14} are 0 at the reference state, 1 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state, and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state:

> if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in a) by coupling parameters $\lambda_{elecB14}$ and λ_{vdwB14}, respectively, wherein both of $\lambda_{elecB14}$ and λ_{vdwB14} are 0 at the reference state, 1 at the target state, and varied from 0 to 1 at each intermediate state along the transformation from the reference state to the target state, and
>
> if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, multiplying the nonbonded electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions between A_i and A_j obtained in a) by the coupling parameters $\lambda_{elecA14}$ and λ_{vdwA14}, respectively,

wherein both of $\lambda_{elecA14}$ and λ_{vdwA14} are 1 at the reference state, 0 at the target state, and varied from 1 to 0 at each intermediate state along the transformation from the reference state to the target state; and

c) including the calculated electrostatic 1-4 pair interactions and van der Waals 1-4 pair interactions obtained in b) into the total energy of the simulation step of the corresponding system state, and optionally wherein performing molecular simulations for all of the states further includes:

if A_a and A_b are valence-bonded to each other in the reference state and not valence-bonded in the target state,

if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, varying each of $\lambda_{elecA14}$ and λ_{vdwA14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwA14} is smaller than 1 for an intermediate state, $\lambda_{elecA14}$ is 0 for that intermediate state;
if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, varying each of $\lambda_{elecB14}$ and λ_{vdwB14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwB14} is smaller than 1 for an intermediate state, $\lambda_{elecB14}$ is 0 for that intermediate state; and

if A_a and A_b are not valence-bonded to each other in the reference state and valence-bonded in the target state,

if the nonbonded 1-4 pair interactions between A_i and A_j are not included in the reference state but included in the target state, varying each of $\lambda_{elecB14}$ and λ_{vdwB14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwB14} is smaller than 1 for an intermediate state, $\lambda_{elecB14}$ is 0 for that intermediate state;
if the nonbonded 1-4 pair interactions between A_i and A_j are included in the reference state but not included in the target state, varying each of $\lambda_{elecA14}$ and λ_{vdwA14} according to a schedule for each of the intermediate states along the transformation from the reference state to the target state such that when λ_{vdwA14} is smaller than 1 for an intermediate state, $\lambda_{elecA14}$ is 0 for that intermediate state.

10. The method of any of claims 7-9, wherein at least one of the computing of the van der Waals interactions includes using a soft-core LJ interaction potential.

11. The method of claim 1, wherein at least one of the reference state and the target state includes a molecule having a ring structure in which the atoms A_a and A_b are bonded to each other and form a part of the ring structure.

12. The method of claim 1, wherein calculating the free energy difference between the reference state and the target state comprises performing an analysis of the ensembles of micro-states obtained at the target state, the reference state, and the intermediate states by way of a determination and analysis of the work associated with the variation of coupling parameter λ.

13. The method of claim 1, wherein calculating the free energy difference between the reference state and the target state comprises performing an analysis of the ensembles of micro-states obtained at the target state, the reference state, and the intermediate states by way of an analysis of the differences in a thermodynamic property of an ensemble of the micro-states obtained at the target state, the reference state, and the intermediate states as coupling parameter λ is instantaneously varied for the selected ensemble of micro-states, and optionally wherein one of a), b), and c), wherein:

a) the ensemble is selected from an NVT ensemble, a NPT ensemble, a NVE ensemble, and a μVT ensemble;
b) performing the analysis of the differences in a thermodynamic property comprises applying an estimator selected from BAR, MBAR, WHAM, Zwanzig average estimators; and
c) performing the analysis of the differences in a thermodynamic property comprises applying one of an FEP-family estimators.

14. The method of claim 1, wherein calculating the free energy difference between the reference state and the target state comprises performing a thermodynamic integration analysis of the derivative of a thermodynamic property of an ensemble of micro-states obtained for the target state, the reference state, and the intermediate states with respect of the coupling parameter λ, and optionally wherein the ensemble is selected from an NVT ensemble, a NPT ensemble, a NVE ensemble, and a μVT ensemble,

15. The method of claim 1, wherein at least one of P_A and P_B is null.

16. A nontransitory computer readable medium, storing the instructions which when executed by one or more processors, carry out the method for computing the free energy difference of any one of claims 1 to 15.

Patentansprüche

1. Computerimplementiertes Verfahren zum Berechnen einer freien Energiedifferenz zwischen einem Referenzzustand und einem Zielzustand, die einen Anfangszustand eines molekularen Systems beziehungsweise einen Endzustand des molekularen Systems nach einer oder mehreren Transformationen repräsentieren, wobei der Referenzzustand und der Zielzustand jeweils einen gemeinsamen Satz von Atomen P_{AB} einschließen, und wobei der Referenzzustand des Weiteren einen Satz von Atomen P_A einschließt, der Zielzustand des Weiteren einen Satz von Atomen P_B einschließt, wobei der Satz P_A nur im Referenzzustand und nicht im Zielzustand vorhanden ist, und der Satz P_B nur im Zielzustand und nicht im Referenzzustand vorhanden ist, wobei mindestens zwei Atome A_a und A_b vorhanden sind, wobei A_a und A_b eines der folgenden sind, entweder: 1) im Referenzzustand nicht aneinander valenzgebunden und im Zielzustand aneinander valenzgebunden, oder 2) im Referenzzustand aneinander valenzgebunden und im Zielzustand nicht aneinander valenzgebunden, wobei das Verfahren umfasst:

a) Bereitstellen einer Topologie, die die gebundenen Verbindungen zwischen den Atomen und die relativen räumlichen Anordnungen der Atome für alle der Atome in P_A, P_B und P_{AB} einschließt;
b) Bestimmen von einem oder mehreren intermediären Systemzuständen entlang eines Transformationspfads zwischen dem Referenzzustand und dem Zielzustand, wobei der Transformationspfad durch einen Kopplungsparameter λ definiert ist, der die Energien moduliert, die aus Wechselwirkungen zwischen den Atomen (Interatomwechselwirkungen) für jeden Systemzustand entstehen, wobei der Kopplungsparameter λ eine Vielzahl von Komponenten einschließt, die jeweils einen Wert haben, der zu [0,1] gehört, und einen anderen Typ von Wechselwirkungsenergie moduliert;
c) Durchführen von molekularen Simulationen unter Verwendung von mindestens einem Computerprozessor, um Ensembles von Mikrozuständen für den Referenzzustand, den Zielzustand und die intermediären Zustände zu erhalten, wobei das Durchführen von molekularen Simulationen für jeden der Systemzustände Berechnen einer gebundenen Dehnungswechselwirkungsenergie zwischen den Atomen A_a und A_b einschließt, wobei die gebundene Dehnungswechselwirkungsenergie durch ein weiches Bindungspotential definiert ist,
wobei das weiche Bindungspotential eine Funktion einer gebundenen Dehnungskomponente, λ_{sbs}, des Kopplungsparameters λ ist und keinerlei singuläre Regionen für alle Werte von λ_{sbs} innerhalb von [0,1] und für alle Werte des Abstands r zwischen A_a und A_b einschließt, wobei sowohl die erste Ableitung als auch die zweite Ableitung des weichen Bindungspotentials nach dem Abstand r zwischen A_a und A_b stetig sind und für alle Werte von λ_{sbs} beschränkt sind und sich null nähern, wenn sich r unendlich nähert, und wobei das weiche Bindungspotential des Weiteren die folgenden Bedingungen erfüllt:

wenn λ_{sbs} innerhalb von (0,1) liegt, ist das weiche Bindungspotential eben, wenn der Abstand zwischen A_a und A_b sich unendlich nähert;
wenn A_a und A_b im Referenzzustand nicht valenzgebunden sind, ist das weiche Bindungspotential eben und null für alle Abstände zwischen A_a und A_b;
wenn A_a und A_b im Zielzustand nicht valenzgebunden sind, ist das weiche Bindungspotential eben und null für alle Abstände zwischen A_a und A_b; und
wenn A_a und A_b in entweder dem Zielzustand oder dem Referenzzustand valenzgebunden sind, kehrt das weiche Bindungspotential zu einem harmonischen Potential zurück; und

d) Berechnen der freien Energiedifferenz zwischen dem Referenzzustand und dem Zielzustand unter Verwendung von mindestens einem Computerprozessor mittels einer Analyse der Ensembles von Mikrozuständen, die an dem Zielzustand, dem Referenzzustand und den intermediären Zuständen erhalten werden, wobei die molekularen Simulationen beispielsweise mindestens eine von Molekulardynamik-Simulationen und Monte-Carlo-Simulationen einschließen.

2. Verfahren nach Anspruch 1, wobei das weiche Bindungspotential eine Funktion von $(r - r_0)^2$ ist, wobei r_0 der Gleichgewichtsabstand zwischen A_a und A_b ist, und wobei gegebenenfalls das weiche Bindungspotential ausgedrückt wird durch:

$$U_{sbs}(r,\lambda_{sbs}) = \frac{1}{2}\,kf(\lambda_{sbs})(r-r_0)^2\frac{1}{1+g(\lambda_{sbs})\alpha(k,\lambda_{sbs})}$$

wobei k eine Konstante ist, und die Funktionen *f,* g und α jeweils stetige Funktionen sind und die folgenden Bedingungen erfüllen:

$f(\lambda_{sbs} = 0) = 0$,
$f(\lambda_{sbs} = 1) = 1$,
$g(\lambda_{sbs} = 0) = 1$,
$g(\lambda_{sbs} = 1) = 0$,

beispielsweise $\alpha(k, \lambda_{sbs} < 1) > 0$, wobei

$$f(\lambda_{sbs}) = \lambda_{sbs},\ g(\lambda_{sbs}) = 1 - \lambda_{sbs}, \text{ und } \alpha(k,\lambda_{sbs}) = \text{konstant.}$$

3. Verfahren nach Anspruch 1, wobei Durchführen von molekularen Simulationen für jeden der Systemzustände umfasst:

falls A_a und A_b in dem Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht valenzgebunden sind, Verwenden eines Schemas von λ_{sbsA} und eines entsprechenden weichen Bindungspotentials zum Berechnen der gebundenen Dehnungswechselwirkungsenergie zwischen A_a und A_b für jeden der intermediären Zustände, wobei λ_{sbsA} im Referenzzustand 1 ist, im Zielzustand 0 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variiert;
falls A_a und A_b in dem Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand valenzgebunden sind, Verwenden eines Schemas von λ_{sbsB} und eines entsprechenden weichen Bindungspotentials für jeden der intermediären Zustände und eines weichen Bindungspotentials, das λ_{sbsB} entspricht, zum Berechnen der gebundenen Dehnungswechselwirkung zwischen A_a und A_b, wobei λ_{sbsB} im Referenzzustand 0 ist, im Zielzustand 1 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 0 bis 1 variiert.

4. Verfahren nach Anspruch 3, wobei Durchführen von molekularen Simulationen für jeden der Systemzustände des Weiteren umfasst:

a) Berechnen einer gebundenen Winkelwechselwirkung unter Verwendung von anwendbaren Parametern für gebundene Winkelwechselwirkungen eines Kraftfelds zwischen i) einer Bindung, die durch A_a und ein anderes Atom A_c gebildet ist, und ii) der Bindung zwischen A_a und A_b, die durch die Transformation von dem Referenzzustand zu dem Zielzustand gebrochen oder gebildet wird;
b) falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht aneinander valenzgebunden sind, Multiplizieren der in a) erhaltenen berechneten gebundenen Winkelwechselwirkung mit einem gebundenen Winkelkopplungsparameter λ_{baA}, wobei λ_{baA} im Referenzzustand 1 ist, im Zielzustand 0 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variiert; und
falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand aneinander valenzgebunden sind, Multiplizieren der in a) erhaltenen berechneten gebundenen Winkelwechselwirkung mit einem gebundenen Winkelkopplungsparameter λ_{baB}, wobei λ_{baB} im Referenzzustand 0 ist, im Zielzustand 1 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 0 bis 1 variiert; und
c) Einschließen der in b) erhaltenen gebundenen Winkelwechselwirkung in die Gesamtenergie eines Simulationsschritts des entsprechenden Systemzustands.

5. Verfahren nach Anspruch 4, wobei Durchführen von molekularen Simulationen für jeden der Systemzustände des Weiteren einschließt:

a) Berechnen einer dihedralen Winkelwechselwirkung unter Verwendung von anwendbaren Parametern für dihedrale Wechselwirkungen eines Kraftfelds von einer Gruppe von vier verbundenen Atomen $\{A_i, A_j, A_k, A_l\}$, wobei die Gruppe sowohl A_a als auch A_b einschließt;

b) falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht aneinander valenzgebunden sind, Multiplizieren der in a) erhaltenen berechneten dihedralen Wechselwirkung mit einem dihedralen Winkelkopplungsparameter λ_{bdA}, wobei λ_{bdA} im Referenzzustand 1 ist, im Zielzustand 0 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variiert; und

falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand aneinander valenzgebunden sind, Multiplizieren der in a) erhaltenen berechneten dihedralen Wechselwirkung mit einem dihedralen Winkelkopplungsparameter λ_{bdB}, wobei λ_{baB} im Referenzzustand 0 ist, im Zielzustand 1 ist, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 0 bis 1 variiert; und

c) Einschließen der in b) erhaltenen dihedralen Wechselwirkung in die Gesamtenergie des Simulationsschritts des entsprechenden Systemzustands.

6. Verfahren nach Anspruch 5, wobei:

falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht aneinander valenzgebunden sind, werden ein gebundener Winkelwechselwirkungsparameter λ_{baA} und ein gebundener dihedraler Wechselwirkungskopplungsparameter λ_{baA} jeweils so ausgewählt, dass sie 0 sind, wenn λ_{bdA} kleiner als ein vordefinierter Schwellenwert ist, und

falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand aneinander valenzgebunden sind, der gebundene Winkelwechselwirkungsparameter λ_{baA} und der gebundene dihedrale Wechselwirkungskopplungsparameter λ_{bdB} jeweils so gewählt werden, dass sie 0 sind, wenn λ_{sbsB} kleiner als ein vordefinierter Schwellenwert ist, wobei der gebundene Winkelwechselwirkungsparameter λ_{baA} und der gebundene dihedrale Wechselwirkungskopplungsparameter λ_{bdB} Komponenten des Kopplungsparameters λ sind.

7. Verfahren nach Anspruch 5, wobei Durchführen von molekularen Simulationen für alle der Zustände des Weiteren einschließt:

a) Berechnen von ungebundenen elektrostatischen Wechselwirkungen und van der Waals-Wechselwirkungen unter Verwendung von anwendbaren Parametern für elektrostatische Wechselwirkungen und van der Waals-Wechselwirkungen eines Kraftfelds zwischen zwei Atomen A_i und A_j und wobei der ungebundene Ausschlussstatus des Paares (A_i, A_j) durch die Transformation von dem Referenzzustand zu dem Zielzustand beeinflusst wird;

b) falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht valenzgebunden sind, und die ungebundenen Wechselwirkungen zwischen A_i und A_j im Referenzzustand ausgeschlossen sind, im Zielzustand jedoch nicht ausgeschlossen sind, Multiplizieren der ungebundenen elektrostatischen Wechselwirkungen und van der Waals-Wechselwirkungen zwischen A_i und A_j, die in a) erhalten werden, mit Kopplungsparametern $\lambda_{elekAex}$ beziehungsweise λ_{vdwAex}, wobei sowohl $\lambda_{elekAex}$ als auch λ_{vdwAex} im Referenzzustand 0 sind, im Zielzustand 1 sind, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 0 bis 1 variieren;

falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand valenzgebunden sind, und die ungebundenen Wechselwirkungen zwischen A_i und A_j im Referenzzustand nicht ausgeschlossen sind, im Zielzustand jedoch ausgeschlossen sind, Multiplizieren der ungebundenen elektrostatischen Wechselwirkungen und van der Waals-Wechselwirkungen zwischen A_i und A_j, die in a) erhalten wurden, mit Kopplungsparametern $\lambda_{elekBex}$ beziehungsweise λ_{vdwBex}, wobei sowohl $\lambda_{elekBex}$ als auch λ_{vdwBex} im Referenzzustand 1 sind, im Zielzustand 0 sind, und an jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variieren; und

c) Einschließen der berechneten ungebundenen elektrostatischen Wechselwirkungen und van der Waals-Wechselwirkungen, die in b) erhalten wurden, in die Gesamtenergie des Simulationsschritts des entsprechenden Systemzustands.

8. Verfahren nach Anspruch 7, wobei Durchführen von molekularen Simulationen für alle der Zustände des Weiteren einschließt:

falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht valenzgebunden sind, und die ungebundenen Wechselwirkungen zwischen A_i und A_j im Referenzzustand ausgeschlossen sind, im Zielzustand jedoch nicht ausgeschlossen sind, Variieren von jedem von $\lambda_{elekAex}$ und λ_{vdwAex} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwAex} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekAex}$ für diesen intermediären Zustand 0 ist; und

falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand valenzgebunden sind, und die ungebundenen Wechselwirkungen zwischen A_i und A_j im Referenzzustand nicht ausgeschlossen sind, im Zielzustand jedoch ausgeschlossen sind, Variieren von jedem von $\lambda_{elekBex}$ und λ_{vdwBex} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwAex} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekAex}$ für diesen intermediären Zustand 0 ist.

9. Verfahren nach Anspruch 7, wobei Durchführen von molekularen Simulationen für alle der Zustände des Weiteren einschließt:

a) Berechnen von ungebundenen elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen unter Verwendung von anwendbaren Parametern für elektrostatische 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen eines Kraftfelds zwischen zwei Atomen A_i und A_j, die zusammen mit weiteren zwei dazwischen befindlichen Atomen eine gebundene dihedrale Winkelwechselwirkung in entweder dem Referenzzustand oder dem Zielzustand bilden;

b) falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht valenzgebunden sind:

falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j in den Referenzzustand eingeschlossen sind, jedoch nicht in den Zielzustand eingeschlossen sind, Multiplizieren der ungebundenen elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen zwischen A_i und A_j, die in a) erhalten wurden, mit Kopplungsparametern $\lambda_{elekA14}$ beziehungsweise λ_{vdwA14}, wobei sowohl $\lambda_{elekA14}$ als auch λ_{vdwA14} im Referenzzustand 1 sind, im Zielzustand 0 sind, und in jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variieren, und

falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j nicht in den Referenzzustand eingeschlossen sind, jedoch in den Zielzustand eingeschlossen sind, Multiplizieren der ungebundenen elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen zwischen A_i und A_j, die in a) erhalten wurden, mit Kopplungsparametern $\lambda_{elekB14}$ beziehungsweise λ_{vdwB14}, wobei sowohl $\lambda_{elekB14}$ als auch λ_{vdwB14} im Referenzzustand 0 sind, im Zielzustand 1 sind, und in jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variieren, und

falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand valenzgebunden sind:

falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j nicht in den Referenzzustand eingeschlossen sind, jedoch in den Zielzustand eingeschlossen sind, Multiplizieren der ungebundenen elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen zwischen A_i und A_j, die in a) erhalten wurden, mit Kopplungsparametern $\lambda_{elekB14}$ beziehungsweise λ_{vdwB14}, wobei sowohl $\lambda_{elekB14}$ als auch λ_{vdwB14} im Referenzzustand 0 sind, im Zielzustand 1 sind, und in jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 0 bis 1 variieren, und

falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j in den Referenzzustand eingeschlossen sind, jedoch nicht in den Zielzustand eingeschlossen sind, Multiplizieren der ungebundenen elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Paarwechselwirkungen zwischen A_i und A_j, die in a) erhalten wurden, mit den Kopplungsparametern $\lambda_{elekA14}$ beziehungsweise λ_{vdwA14}, wobei sowohl $\lambda_{elekA14}$ als auch λ_{vdwA14} im Referenzzustand 1 sind, im Zielzustand 0 sind, und in jedem intermediären Zustand entlang der Transformation von dem Referenzzustand zu dem Zielzustand von 1 bis 0 variieren; und

c) Einschließen der berechneten elektrostatischen 1-4-Paarwechselwirkungen und van der Waals-1-4-Wechselwirkungen, die in b) erhalten wurden, in die Gesamtenergie des Simulationsschritts des entsprechenden Systemzustands, und wobei gegebenenfalls Durchführen von molekularen Simulationen für alle der Zustände weiter einschließt:

falls A_a und A_b im Referenzzustand aneinander valenzgebunden sind und im Zielzustand nicht valenzgebunden sind,
falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j in den Referenzzustand eingeschlossen sind, jedoch nicht in den Zielzustand eingeschlossen sind, Variieren von jedem von $\lambda_{elekA14}$ und λ_{vdwA14} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwA14} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekA14}$ für jenen intermediären Zustand 0 ist;
falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j nicht in den Referenzzustand eingeschlossen sind, jedoch in den Zielzustand eingeschlossen sind, Variieren von jedem von $\lambda_{elekB14}$ und λ_{vdwB14} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwB14} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekB14}$ für jenen intermediären Zustand 0 ist; und
falls A_a und A_b im Referenzzustand nicht aneinander valenzgebunden sind und im Zielzustand valenzgebunden sind,
falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j nicht in den Referenzzustand eingeschlossen sind, jedoch in den Zielzustand eingeschlossen sind, Variieren von jedem von $\lambda_{elekB14}$ und λ_{vdwB14} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwB14} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekB14}$ für jenen intermediären Zustand 0 ist; und
falls die ungebundenen 1-4-Paarwechselwirkungen zwischen A_i und A_j in den Referenzzustand eingeschlossen sind, jedoch nicht in den Zielzustand eingeschlossen sind, Variieren von jedem von $\lambda_{elekA14}$ und λ_{vdwA14} gemäß einem Schema für jeden der intermediären Zustände entlang der Transformation von dem Referenzzustand zu dem Zielzustand, so dass, wenn λ_{vdwA14} für einen intermediären Zustand kleiner als 1 ist, $\lambda_{elekA14}$ für jenen intermediären Zustand 0 ist.

10. Verfahren nach einem der Ansprüche 7 bis 9, wobei mindestens eine von dem Berechnen der van der Waals-Wechselwirkungen ein Weichkem-LJ-Wechselwirkungspotential einschließt.

11. Verfahren nach Anspruch 1, wobei mindestens einer von dem Referenzzustand und dem Zielzustand ein Molekül mit einer Ringstruktur einschließen, worin die Atome A_a und A_b aneinander gebunden sind und einen Teil der Ringstruktur bilden.

12. Verfahren nach Anspruch 1, wobei Berechnen der freien Energiedifferenz zwischen dem Referenzzustand und dem Zielzustand Durchführen einer Analyse der Ensembles der Mikrozustände, die an dem Zielzustand, dem Referenzzustand und den intermediären Zuständen erhalten wurden, mittels einer Bestimmung und Analyse der Arbeit umfasst, die mit der Variation des Kopplungsparameters λ assoziiert ist.

13. Verfahren nach Anspruch 1, wobei Berechnen der freien Energiedifferenz zwischen dem Referenzzustand und dem Zielzustand Durchführen einer Analyse der Ensembles der Mikrozustände, die an dem Zielzustand, dem Referenzzustand und den intermediären Zuständen erhalten wurden, mittels einer Analyse der Differenzen in einer thermodynamischen Eigenschaft eines Ensembles der Mikrozustände umfasst, die an dem Zielzustand, dem Referenzzustand und den intermediären Zuständen erhalten wurden, wenn Kopplungsparameter λ verzögerungsfrei für das ausgewählte Ensemble der Mikrozustände variiert wird, und wobei gegebenenfalls eines von a), b, und c) gilt, wobei:

a) das Ensemble ausgewählt ist aus einem NVT-Ensemble, einem NPT-Ensemble, einem NVE-Ensemble und einem μVT-Ensemble;
b) Durchführen der Analyse der Differenzen in einer thermodynamischen Eigenschaft Anwenden eines Estimators ausgewählt aus BAR-, MBAR-, WHAM-, Zwanzig-Mittelwert-Estimatoren umfasst; und
c) Durchführen der Analyse der Differenzen in einer thermodynamischen Eigenschaft Anwenden von einem der Estimatoren einer FEP-Familie umfasst.

14. Verfahren nach Anspruch 1, wobei Berechnen der freien Energiedifferenz zwischen dem Referenzzustand und dem Zielzustand Durchführen einer thermodynamischen Integrationsanalyse der Ableitung einer thermodynamischen Eigenschaft eines Ensembles von Mikrozuständen, die für den Zielzustand, den Referenzzustand und die intermediären Zustände erhalten wird, in Bezug auf den Kopplungsparameter λ umfasst, und wobei das Ensemble gegebenenfalls ausgewählt ist aus einem NVT-Ensemble, einem NPT-Ensemble, einem NVE-Ensemble und einem μVT-

Ensemble.

15. Verfahren nach Anspruch 1, wobei mindestens einer von P_A und P_B null ist.

16. Nicht-flüchtiges computerlesbares Medium, das die Anweisungen speichert, die bei Ausführung durch einen oder mehrere Prozessoren das Verfahren zum Berechnen der freien Energiedifferenz gemäß einem der Ansprüche 1 bis 15 durchführen.

Revendications

1. Procédé mis en oeuvre par ordinateur pour calculer une différence d'énergie libre entre un état de référence et un état cible qui représentent respectivement un état initial d'un système moléculaire et un état final du système moléculaire après une ou plusieurs transformations, l'état de référence et l'état cible comprenant chacun un ensemble commun d'atomes P_{AB}, et l'état de référence comprenant en outre un ensemble d'atomes P_A, l'état cible comprenant en outre un ensemble d'atomes P_B, l'ensemble P_A étant présent uniquement dans l'état de référence et non dans l'état cible, et l'ensemble P_B étant présent uniquement dans l'état cible et non dans l'état de référence, où il existe au moins deux atomes A_a et A_b, A_a et A_b étant soit : 1) non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible, ou 2) liés par valence l'un à l'autre dans l'état de référence et non liés par valence l'un à l'autre dans l'état cible, le procédé comprenant :

a) la fourniture d'une topologie, comprenant les liaisons entre les atomes et les agencements spatiaux relatifs des atomes, pour tous les atomes dans P_A, P_B et PAB ;
b) la détermination d'un ou plusieurs états intermédiaires du système le long d'un chemin de transformation entre l'état de référence et l'état cible, le chemin de transformation étant défini par un paramètre de couplage λ qui module les énergies résultant des interactions interatomiques pour chaque état du système, le paramètre de couplage λ comprenant plusieurs composants ayant chacun une valeur appartenant à [0, 1] et modulant un type différent d'énergie d'interaction ;
c) la réalisation, à l'aide d'au moins un processeur informatique, de simulations moléculaires afin d'obtenir des ensembles de micro-états pour l'état de référence, l'état cible et les états intermédiaires, la réalisation de simulations moléculaires pour chacun des états du système comprenant le calcul d'une énergie d'interaction d'étirement liée entre les atomes A_a et A_b, l'énergie d'interaction d'étirement liée étant définie par un potentiel de liaison souple,
le potentiel de liaison souple étant une fonction d'une composante d'étirement liée, λ_{sbs}, du paramètre de couplage λ, et n'incluant aucune région singulière pour toutes les valeurs de λ_{sbs} comprises dans [0, 1] et pour toutes les valeurs de la distance r entre A_a et A_b, la dérivée première et la dérivée seconde du potentiel de liaison souple par rapport à la distance r entre A_a et A_b étant continues et limitées pour toutes les valeurs de λ_{sbs}, et s'approchant de zéro lorsque r s'approche de l'infini, et le potentiel de liaison souple satisfaisant en outre aux conditions suivantes :

lorsque λ_{sbs} est compris entre (0,1), le potentiel de liaison souple est plat lorsque la distance entre A_a et A_b s'approche de l'infini ;
lorsque A_a et A_b sont non liés par valence dans l'état de référence, le potentiel de liaison souple est plat et nul pour toutes les distances entre A_a et A_b ;
lorsque A_a et A_b sont non liés par valence dans l'état cible, le potentiel de liaison souple est plat et nul pour toutes les distances entre A_a et A_b ; et
lorsque A_a et A_b sont liés par valence dans l'état cible ou l'état de référence, le potentiel de liaison souple redevient un potentiel harmonique ; et

d) le calcul, à l'aide d'au moins un processeur informatique, de la différence d'énergie libre entre l'état de référence et l'état cible, au moyen d'une analyse des ensembles de micro-états obtenus à l'état cible, à l'état de référence et aux états intermédiaires, les simulations moléculaires comprenant par exemple au moins l'une des simulations de dynamique moléculaire et des simulations de Monte Carlo.

2. Procédé selon la revendication 1, le potentiel de liaison souple étant une fonction de $(r - r_0)^2$, r_0 étant la distance d'équilibre entre A_a et A_b, et éventuellement le potentiel de liaison souple étant exprimé par :

$$U_{sbs}(r,\lambda_{sbs}) = \frac{1}{2}\,kf(\lambda_{sbs})(r-r_0)^2\frac{1}{1+g(\lambda_{sbs})\alpha(k,\lambda_{sbs})(r-r_0)^2}$$

k étant une constante, et les fonctions *f*, g et α étant des fonctions continues et satisfaisant aux conditions suivantes :

$$f(\lambda_{sbs} = 0) = 0,$$

$$f(\lambda_{sbs} = 1) = 1,$$

$$g(\lambda_{sbs} = 0) = 1,$$

$$g(\lambda_{sbs} = 1) = 0,$$

$$\alpha(k, \lambda_{sbs} < 1) > 0,$$

par exemple,

$$f(\lambda_{sbs}) = \lambda_{sbs},\ g(\lambda_{sbs}) = 1 - \lambda_{sbs} \text{ et } \alpha(k, \lambda_{sbs}) = const.$$

3. Procédé selon la revendication 1, la réalisation de simulations moléculaires pour chacun des états du système comprenant :

si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence dans l'état cible, l'utilisation d'un programme de λ_{sbsA} et d'un potentiel de liaison souple correspondant pour calculer l'énergie d'interaction d'étirement liée entre A_a et A_b pour chacun des états intermédiaires, λ_{sbsA} étant 1 à l'état de référence, 0 à l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ;
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible, l'utilisation d'un programme de λ_{sbsB} et d'un potentiel de liaison souple correspondant pour chacun des états intermédiaires et d'un potentiel de liaison souple correspondant au λ_{sbsB} pour calculer l'interaction d'étirement liée entre A_a et A_b, λ_{sbsB} étant égal à 0 à l'état de référence, à 1 à l'état cible et variant de 0 à 1 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible.

4. Procédé selon la revendication 3, la réalisation de simulations moléculaires pour chacun des états du système comprenant en outre :

a) le calcul d'une interaction angulaire liée, à l'aide de paramètres applicables aux interactions angulaire liées d'un champ de force, entre i) une liaison formée par A_a et un autre atome A_c, et ii) la liaison entre A_a et A_b qui est rompue ou formée par la transformation de l'état de référence à l'état cible ;
b) si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence l'un à l'autre dans l'état cible, la multiplication de l'interaction angulaire liée calculée obtenue en a) par un paramètre de couplage d'angle lié λ_{baA}, λ_{baA} étant égal à 1 dans l'état de référence, à 0 dans l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et

> si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence l'un à l'autre dans l'état cible, la multiplication de l'interaction angulaire liée calculée obtenue en a) par un paramètre de couplage d'angle lié λ_{baB},
> λ_{baB} étant égal à 0 à l'état de référence, à 1 à l'état cible, et variant de 0 à 1 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et

c) l'inclusion de l'interaction angulaire liée obtenue en b) dans l'énergie totale d'une étape de simulation de l'état du système correspondant,

5. Procédé selon la revendication 4, la réalisation de simulations moléculaires pour chacun des états du système comprenant en outre :

a) le calcul d'une interaction angulaire dièdre, à l'aide de paramètres applicables aux interactions dièdres d'un champ de force, d'un groupe de quatre atomes connectés {Ai, A_j, A_k, Ai}, le groupe comprenant à la fois A_a et A_b ;
b) si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence l'un à l'autre dans l'état cible, la multiplication de l'interaction dièdre calculée obtenue en a) par un paramètre de couplage d'angle dièdre λ_{bdA}, λ_{bdA} étant égal à 1 dans l'état de référence, à 0 dans l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence l'un à l'autre dans l'état cible, la multiplication de l'interaction dièdre calculée obtenue en a) par un paramètre de couplage d'angle dièdre λ_{bdB}, λ_{bdB} étant égal à 0 à l'état de référence, à 1 à l'état cible, et variant de 0 à 1 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et
c) l'inclusion de l'interaction dièdre obtenue en b) dans l'énergie totale de l'étape de simulation de l'état du système correspondant.

6. Procédé selon la revendication 5,

si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence l'un à l'autre dans l'état cible, un paramètre d'interaction angulaire liée λ_{baA} et un paramètre de couplage d'interaction dièdre liée λ_{bdA} étant chacun sélectionnés pour être 0 lorsque λ_{sbsA} est plus petit qu'un seuil prédéfini, et
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence l'un à l'autre dans l'état cible, le paramètre d'interaction angulaire liée λ_{baA} et le paramètre de couplage d'interaction dièdre liée λ_{bdB} étant chacun sélectionnés pour être égaux à 0 lorsque λ_{sbsB} est inférieur à un seuil prédéfini, le paramètre d'interaction angulaire liée λ_{baA} et le paramètre de couplage d'interaction dièdre liée λ_{bdB} étant des composantes du paramètre de couplage λ.

7. Procédé selon la revendication 5, la réalisation de simulations moléculaires pour tous les états comprenant en outre :

a) le calcul des interactions électrostatiques non liées et des interactions de van der Waals, à l'aide de paramètres applicables aux interactions électrostatiques et de van der Waals d'un champ de force, entre deux atomes A_i et A_j et le statut d'exclusion non lié de la paire (A_i, A_j) étant affecté par la transformation de l'état de référence à l'état cible ;
b) si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence dans l'état cible, et si les interactions non liées entre A_i et A_j sont exclues dans l'état de référence mais ne sont pas exclues dans l'état cible, la multiplication des interactions électrostatiques non liées et des interactions de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecAex}$ et λ_{vdwAex}, respectivement, $\lambda_{elecAex}$ et λ_{vdwAex} étant tous deux égaux à 0 à l'état de référence, à 1 à l'état cible et variant de 0 à 1 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ;
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible, et si les interactions non liées entre A_i et A_j ne sont pas exclues dans l'état de référence mais exclues dans l'état cible, la multiplication des interactions électrostatiques non liées et des interactions de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecBex}$ et λ_{vdwBex}, respectivement, $\lambda_{elecBex}$ et λ_{vdwBex} étant tous deux égaux à 1 à l'état de référence, à 0 à l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et
c) l'inclusion des interactions électrostatiques non liées et des interactions de van der Waals calculées obtenues en b) dans l'énergie totale de l'étape de simulation de l'état du système correspondant.

8. Procédé selon la revendication 7, la réalisation de simulations moléculaires pour tous les états comprenant en outre :

si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence dans l'état cible, et si les interactions non liées entre A_i et A_j sont exclues dans l'état de référence mais ne sont pas exclues dans l'état cible, le fait de faire varier $\lambda_{elecAex}$ et λ_{vdwAex} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible, de sorte que lorsque λ_{vdwAex} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecAex}$ est égal à 0 pour cet état intermédiaire ; et
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible,

et si les interactions non liées entre A_i et A_j ne sont pas exclues dans l'état de référence mais exclues dans l'état cible, le fait de faire varier $\lambda_{elecBex}$ et λ_{vdwBex} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible, de telle sorte que lorsque λ_{vdwAex} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecAex}$ est égal à 0 pour cet état intermédiaire.

9. Procédé selon la revendication 7, la réalisation de simulations moléculaires pour tous les états comprenant en outre :

a) le calcul des interactions par paires 1-4 électrostatiques non liées et des interactions par paires 1-4 de van der Waals, à l'aide de paramètres applicables aux interactions par paires 1-4 électrostatiques et aux interactions par paires 1-4 de van der Waals d'un champ de force, entre deux atomes A_i et A_j qui, avec deux autres atomes intermédiaires, forment une interaction angulaire dièdre liée dans l'état de référence ou dans l'état cible ;
b) si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence dans l'état cible :

si les interactions par paires 1-4 non liées entre A_i et A_j sont incluses dans l'état de référence mais non incluses dans l'état cible, la multiplication des interactions par paires 1-4 électrostatiques non liées et des interactions par paires 1-4 de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecA14}$ et λ_{vdwA14}, respectivement, $\lambda_{elecA14}$ et λ_{vdwA14} étant tous deux égaux à 1 à l'état de référence, à 0 à l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible, et
si les interactions par paires 1-4 non liées entre A_i et A_j ne sont pas incluses dans l'état de référence mais incluses dans l'état cible, la multiplication des interactions par paires 1-4 électrostatiques non liées et des interactions par paires 1-4 de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecB14}$ et λ_{vdwB14}, respectivement, $\lambda_{elecB14}$ et λ_{vdwB14} étant tous deux égaux à 0 à l'état de référence, à 1 à l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible, et
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible :

si les interactions par paires 1-4 non liées entre A_i et A_j ne sont pas incluses dans l'état de référence mais incluses dans l'état cible, la multiplication des interactions par paires 1-4 électrostatiques non liées et des interactions par paires 1-4 de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecB14}$ et λ_{vdwB14}, respectivement, $\lambda_{elecB14}$ et λ_{vdwB14} étant tous deux égaux à 0 à l'état de référence, à 1 à l'état cible, et variant de 0 à 1 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible, et
si les interactions par paires 1-4 non liées entre A_i et A_j sont incluses dans l'état de référence mais pas dans l'état cible, la multiplication des interactions par paires 1-4 électrostatiques non liées et des interactions par paires 1-4 de van der Waals entre A_i et A_j obtenues en a) par les paramètres de couplage $\lambda_{elecA14}$ et λ_{vdwA14}, respectivement, $\lambda_{elecA14}$ et λ_{vdwA14} étant tous deux égaux à 1 à l'état de référence, à 0 à l'état cible, et variant de 1 à 0 à chaque état intermédiaire le long de la transformation de l'état de référence à l'état cible ; et

c) l'inclusion des interactions par paires 1-4 électrostatiques et des interactions par paires 1-4 de van der Waals calculées obtenues en b) dans l'énergie totale de l'étape de simulation de l'état du système correspondant, et éventuellement, la réalisation de simulations moléculaires pour tous les états comprenant en outre :

si A_a et A_b sont liés par valence l'un à l'autre dans l'état de référence et non liés par valence dans l'état cible,
si les interactions par paires 1-4 non liées entre A_i et A_j sont incluses dans l'état de référence mais pas dans l'état cible, le fait de faire varier $\lambda_{elecA14}$ et λ_{vdwA14} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible de telle sorte que lorsque λ_{vdwA14} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecA14}$ est égal à 0 pour cet état intermédiaire ;
si les interactions par paires 1-4 non liées entre A_i et A_j ne sont pas incluses dans l'état de référence mais incluses dans l'état cible, le fait de faire varier $\lambda_{elecB14}$ et λ_{vdwB14} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible, de sorte que lorsque λ_{vdwB14} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecB14}$ est égal à 0 pour cet état intermédiaire ; et
si A_a et A_b sont non liés par valence l'un à l'autre dans l'état de référence et liés par valence dans l'état cible,
si les interactions par paires 1-4 non liées entre A_i et A_j ne sont pas incluses dans l'état de référence mais incluses dans l'état cible, le fait de faire varier $\lambda_{elecB14}$ et λ_{vdwB14} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible, de sorte que lorsque λ_{vdwB14} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecB14}$ est égal à 0 pour cet état intermédiaire ;

si les interactions par paires 1-4 non liées entre A_i et A_j sont incluses dans l'état de référence mais non incluses dans l'état cible, le fait de faire varier $\lambda_{elecA14}$ et λ_{vdwA14} selon un programme pour chacun des états intermédiaires le long de la transformation de l'état de référence à l'état cible, de sorte que lorsque λ_{vdwA14} est inférieur à 1 pour un état intermédiaire, $\lambda_{elecA14}$ est égal à 0 pour cet état intermédiaire.

10. Procédé selon l'une quelconque des revendications 7 à 9, au moins l'un des calculs des interactions de van der Waals comprenant l'utilisation d'un potentiel d'interaction LJ à noyau souple.

11. Procédé selon la revendication 1, au moins l'un de l'état de référence et de l'état cible comprenant une molécule ayant une structure en anneau dans laquelle les atomes A_a et A_b sont liés l'un à l'autre et forment une partie de la structure en anneau.

12. Procédé selon la revendication 1, le calcul de la différence d'énergie libre entre l'état de référence et l'état cible comprenant la réalisation d'une analyse des ensembles de micro-états obtenus à l'état cible, à l'état de référence et aux états intermédiaires au moyen d'une détermination et d'une analyse du travail associé à la variation du paramètre de couplage λ.

13. Procédé selon la revendication 1, le calcul de la différence d'énergie libre entre l'état de référence et l'état cible comprenant la réalisation d'une analyse des ensembles de micro-états obtenus à l'état cible, à l'état de référence et aux états intermédiaires au moyen d'une analyse des différences dans une propriété thermodynamique d'un ensemble des micro-états obtenus à l'état cible, à l'état de référence, et aux états intermédiaires lorsque le paramètre de couplage λ varie instantanément pour l'ensemble sélectionné de micro-états, et éventuellement l'un de a), b), et c),

a) l'ensemble étant choisi parmi un ensemble NVT, un ensemble NPT, un ensemble NVE et un ensemble μVT ;
b) la réalisation de l'analyse des différences dans une propriété thermodynamique comprenant l'application d'un estimateur choisi parmi les estimateurs BAR, MBAR, WHAM et les estimateurs moyens de Zwanzig ; et
c) la réalisation de l'analyse des différences dans une propriété thermodynamique comprenant l'application de l'un des estimateurs de la famille FEP.

14. Procédé selon la revendication 1, le calcul de la différence d'énergie libre entre l'état de référence et l'état cible comprenant la réalisation d'une analyse d'intégration thermodynamique de la dérivée d'une propriété thermodynamique d'un ensemble de micro-états obtenus pour l'état cible, l'état de référence et les états intermédiaires par rapport au paramètre de couplage λ, et éventuellement l'ensemble étant choisi parmi un ensemble NVT, un ensemble NPT, un ensemble NVE et un ensemble μVT.

15. Procédé selon la revendication 1, au moins l'un des paramètres P_A et P_B étant nul.

16. Support non transitoire lisible par ordinateur, stockant les instructions qui, lorsqu'elles sont exécutées par un ou plusieurs processeurs, mettent en oeuvre le procédé de calcul de la différence d'énergie libre selon l'une quelconque des revendications 1 à 15.

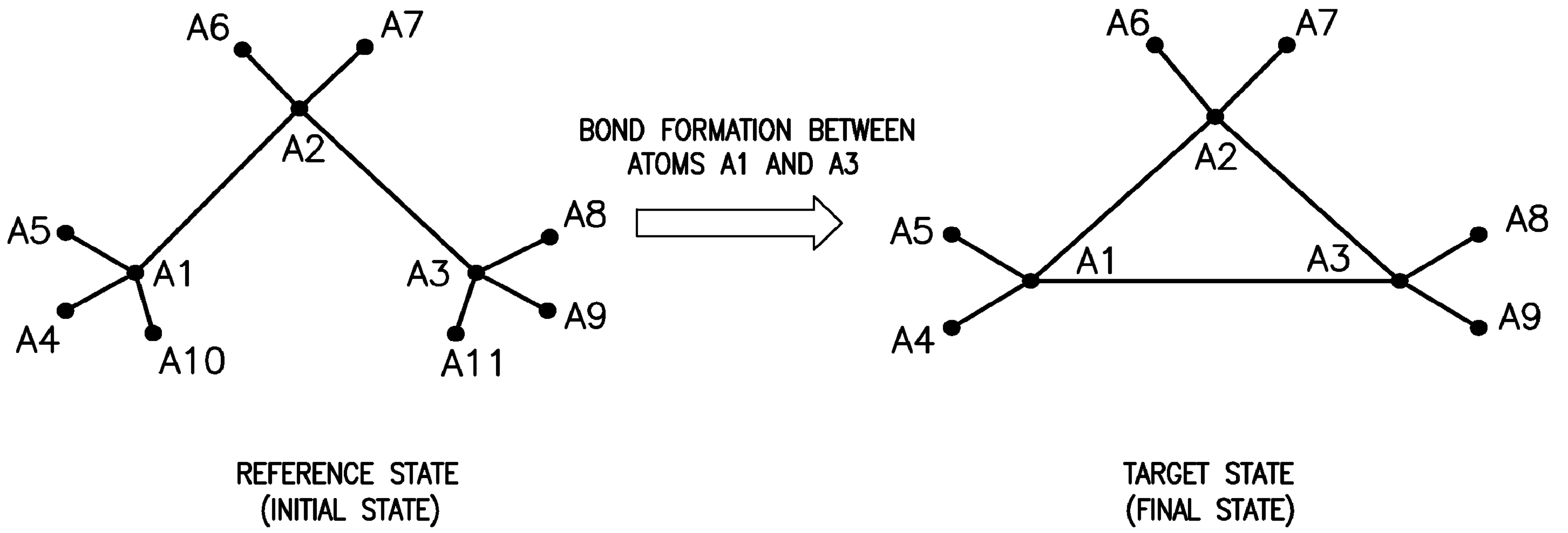
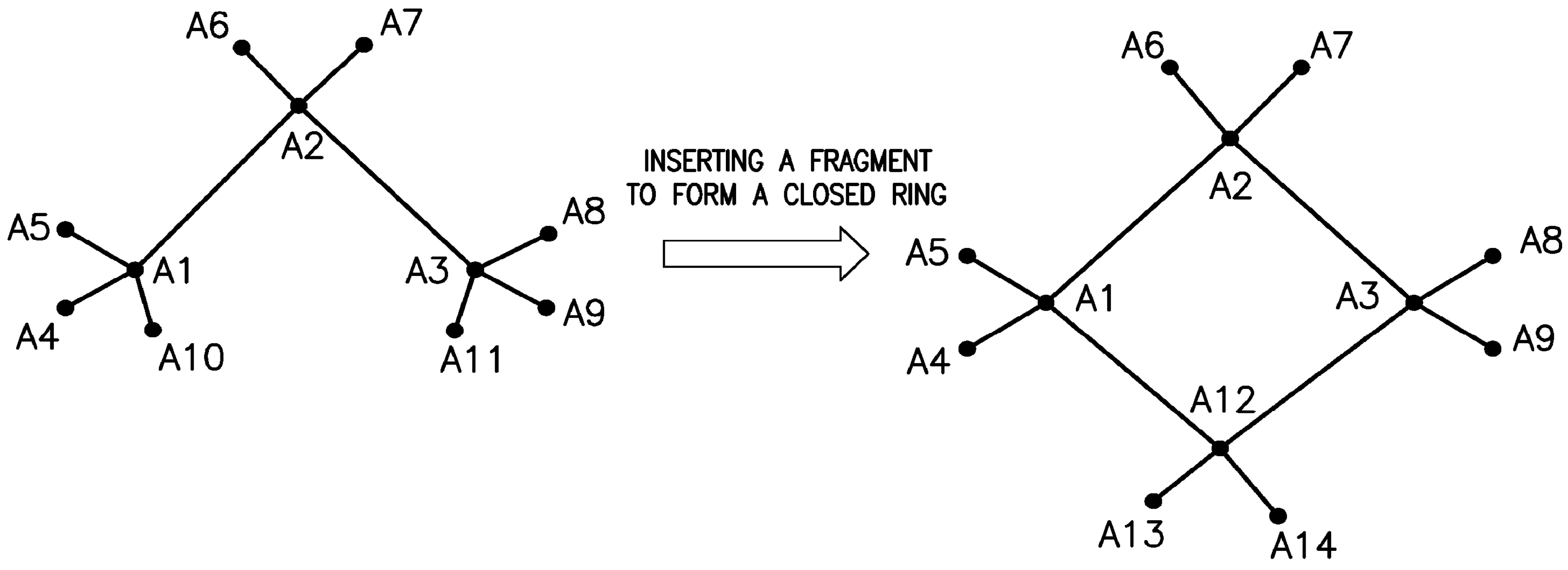

A6
A7
A2
A5
A1
A4
A10
A3
A8
A9
A11
BOND FORMATION BETWEEN ATOMS A1 AND A3
A6
A7
A2
A5
A1
A3
A8
A4
A9
REFERENCE STATE (INITIAL STATE)
TARGET STATE (FINAL STATE)

FIG.1a



REFERENCE STATE
(INITIAL STATE)

TARGET STATE
(FINAL STATE)

FIG.1b

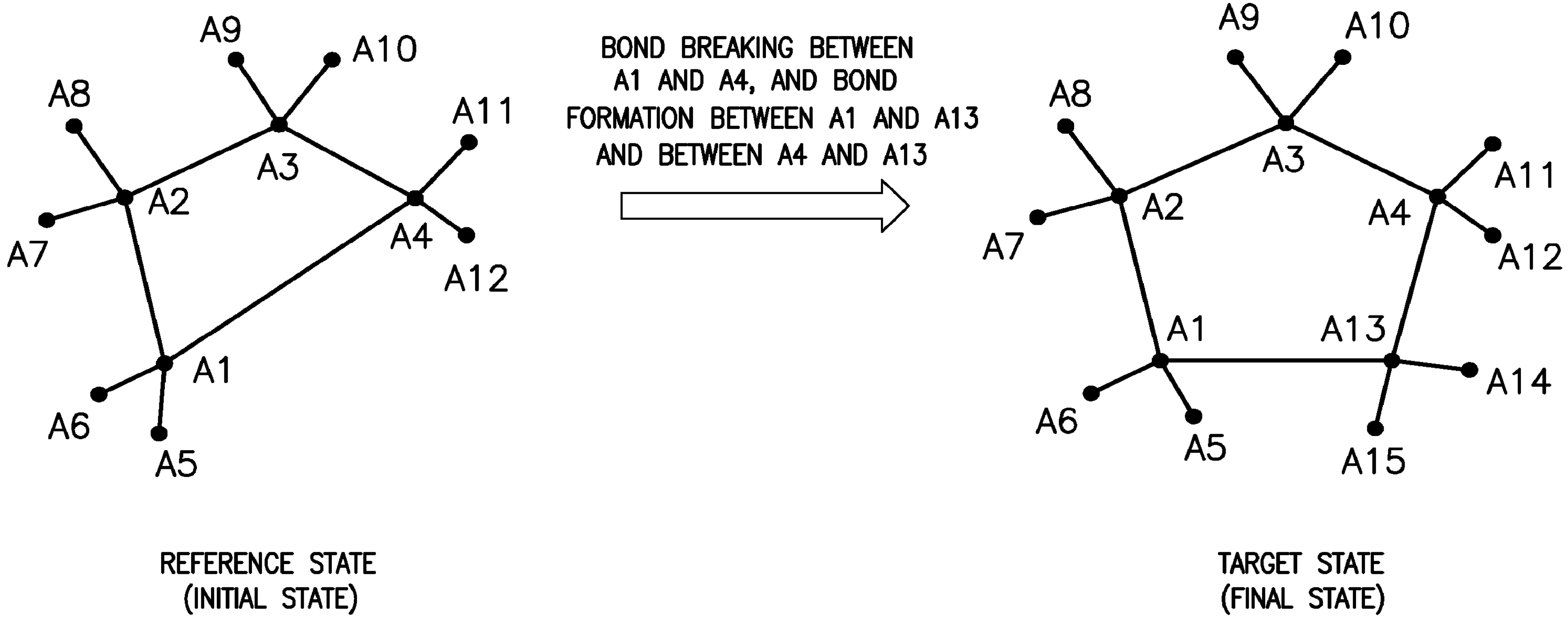
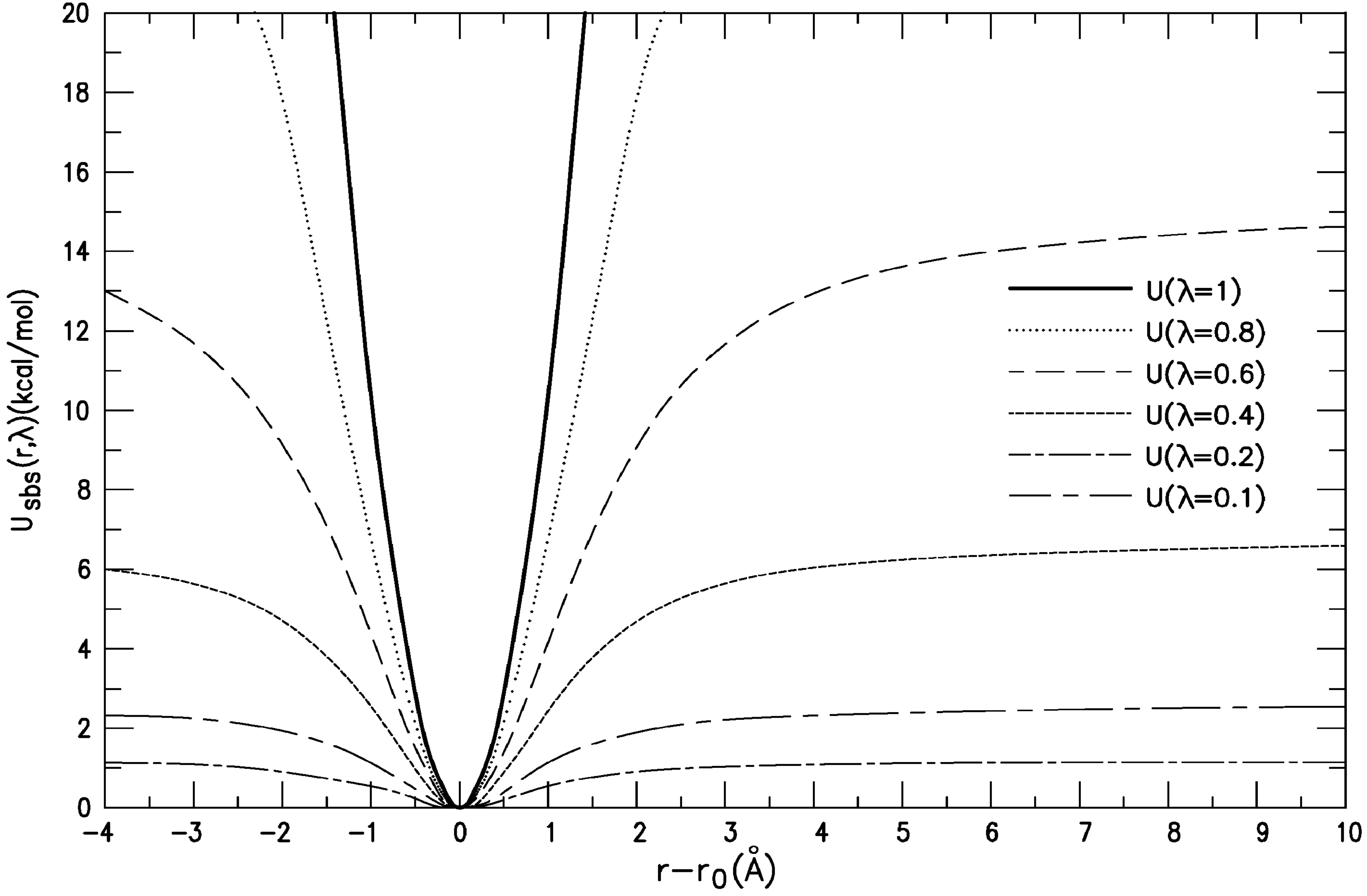

A9
A10
A8
A11
A3
A2
A7
A4
A12
A1
A6
A5
BOND BREAKING BETWEEN A1 AND A4, AND BOND FORMATION BETWEEN A1 AND A13 AND BETWEEN A4 AND A13
A9
A10
A8
A3
A11
A2
A4
A7
A12
A1
A13
A14
A6
A5
A15
REFERENCE STATE (INITIAL STATE)
TARGET STATE (FINAL STATE)

FIG.1c



20
18
16
14
12
10
8
6
4
2
0
$U_{sbs}(r,\lambda)$(kcal/mol)
−4
−3
−2
−1
0
1
2
3
4
5
6
7
8
9
10
$r-r_0$(Å)
U(λ=1)
U(λ=0.8)
U(λ=0.6)
U(λ=0.4)
U(λ=0.2)
U(λ=0.1)

FIG.2

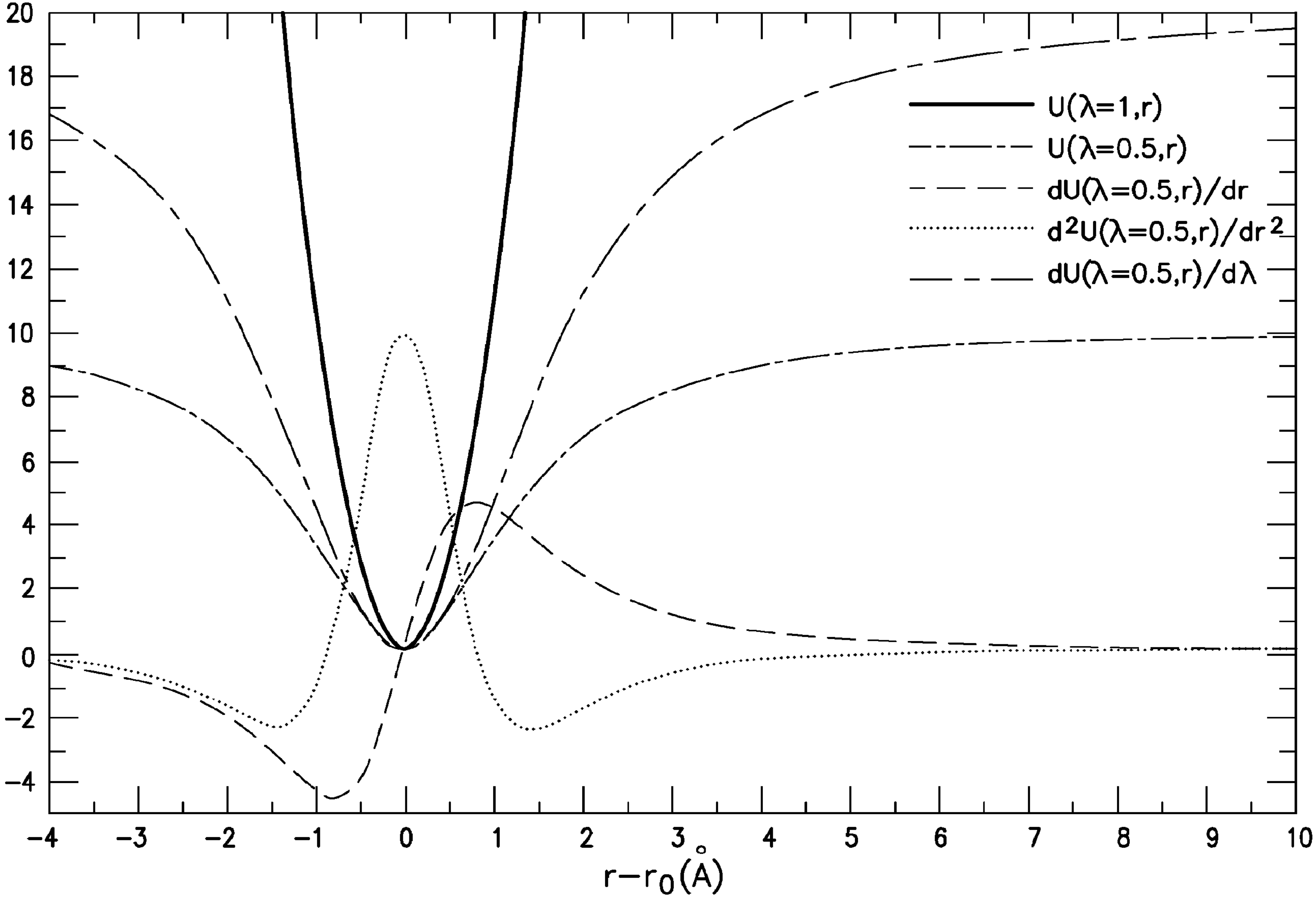

U(λ=1,r)
U(λ=0.5,r)
dU(λ=0.5,r)/dr
d2U(λ=0.5,r)/dr2
dU(λ=0.5,r)/dλ
20
18
16
14
12
10
8
6
4
2
0
−2
−4
−4
−3
−2
−1
0
1
2
3
4
5
6
7
8
9
10
r−r0(Å)

FIG.3

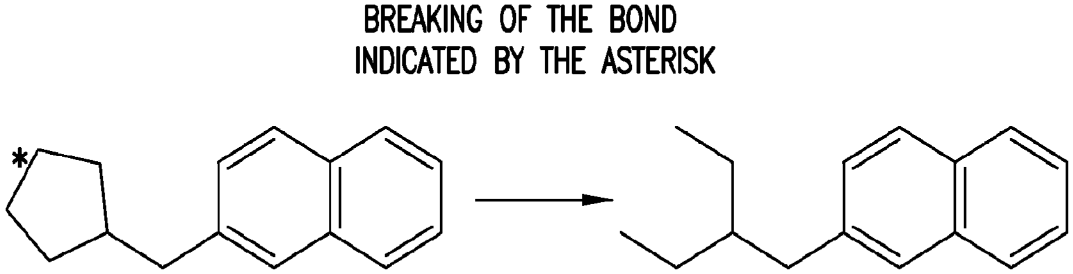

BREAKING OF THE BOND
INDICATED BY THE ASTERISK
*

FIG.4

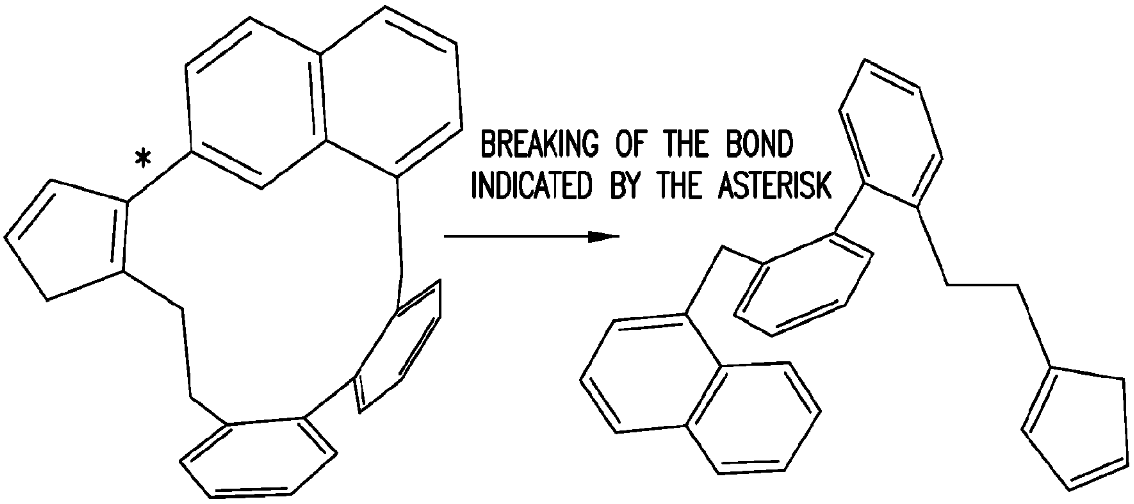

*
BREAKING OF THE BOND
INDICATED BY THE ASTERISK

FIG.5

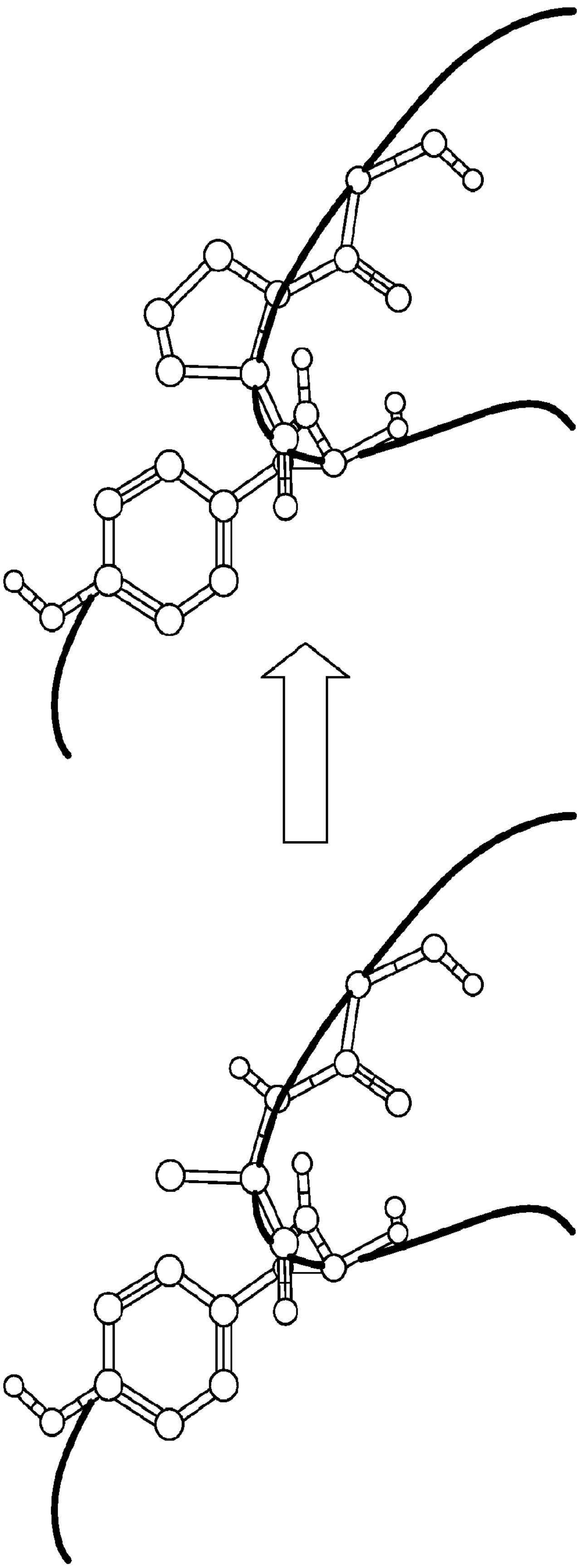


FIG.6

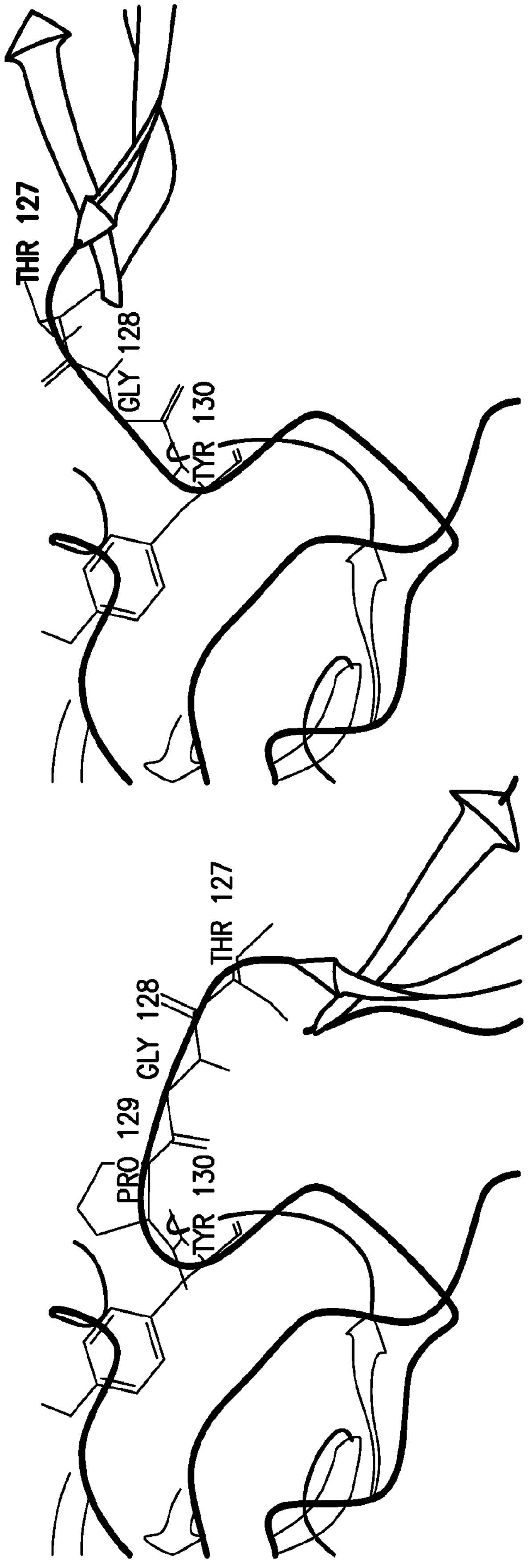


FIG.7

REFERENCES CITED IN THE DESCRIPTION

Non-patent literature cited in the description

- **SMITH B. J.** A Conformational Study of 2-Oxanol: Insight into the Role of Ring Distortion on Enzyme-Catalyzed Glycosidic Bond Cleavage. *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,* 01 March 1997, vol. 119 (11), 2699-2706 **[0009]**
- **BEUTLER et al.** Avoiding singularities and numerical instabilities in free energy calculations based on molecular simulations. *Chem. Phys. Lett.,* 1994, vol. 222, 529-539 **[0065]**
- **KNIGHT et al.** λ-dynamics free energy simulation methods. *J. Comput. Chem.,* 2009, vol. 30, 1692-1700 **[0083]**