US 20110106794A1

(19) **United States**

(12) **Patent Application Publication**

Hori et al.

(10) **Pub. No.: US 2011/0106794 A1**

(43) **Pub. Date: May 5, 2011**

(54) **SYNTHESIS PATH EVALUATION SYSTEM AND METHOD AND PROGRAM THEREOF**

(75) Inventors: **Kenji Hori**, Yamaguchi (JP); **Toru Yamaguchi**, Yamaguchi (JP)

(73) Assignee: **YAMAGUCHI UNIVERSITY**, Yamaguchi-shi, Yamaguchi (JP)

(21) Appl. No.: **13/000,759**

(22) PCT Filed: **Jun. 22, 2009**

(86) PCT No.: **PCT/JP2009/002841**

§ 371 (c)(1),
(2), (4) Date: **Dec. 22, 2010**

(30) **Foreign Application Priority Data**

Jun. 25, 2008 (JP) 2008-166649

Publication Classification

(51) **Int. Cl.**
G06F 17/30 (2006.01)

(52) **U.S. Cl.** **707/723**; 707/E17.014

(57) **ABSTRACT**

A synthetic route evaluation system extracts an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced. The synthetic route evaluation system includes an arithmetic processing device, which is composed of a quantum chemistry calculation unit, a reaction mechanism analysis unit, and a synthetic route ranking unit, and a storage device for storing data relative to the synthetic routes.

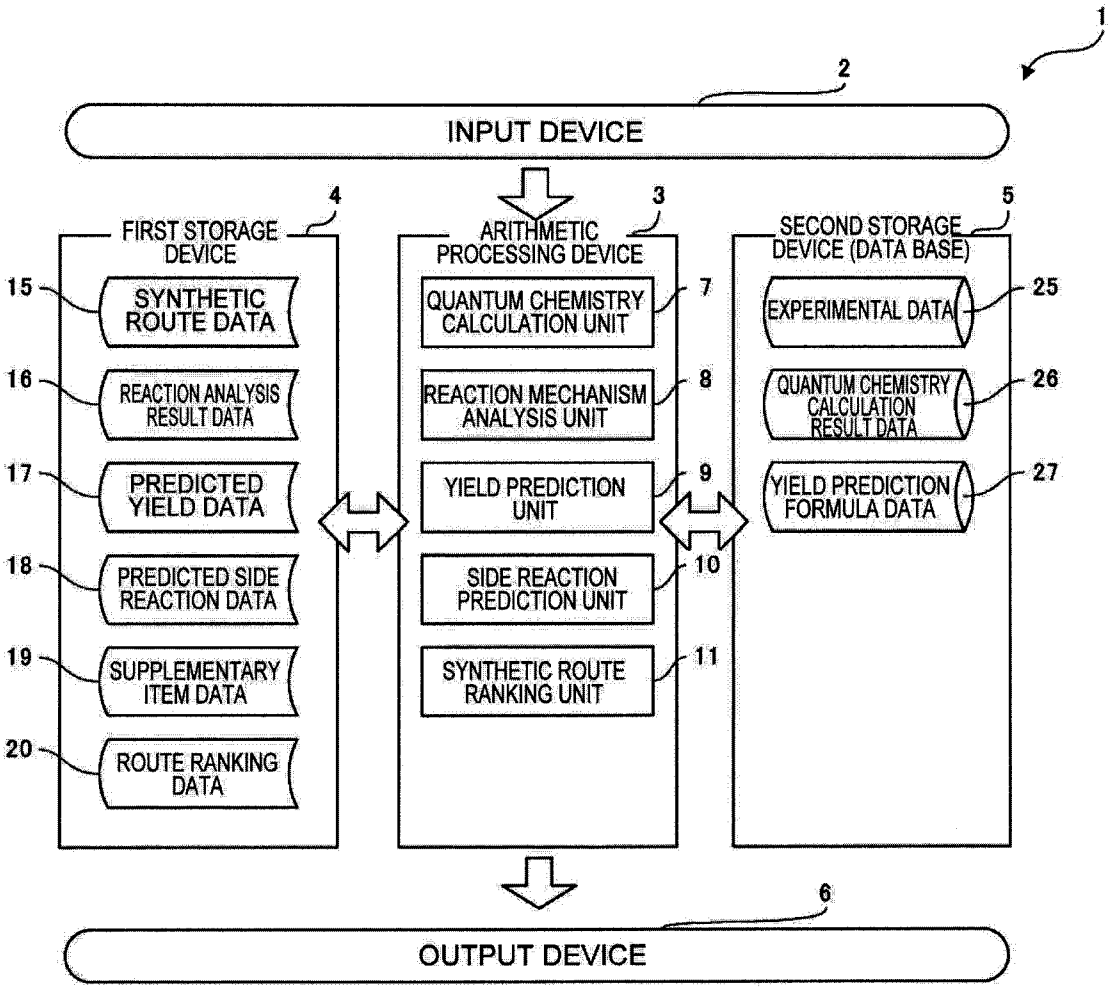

1
2
INPUT DEVICE
4
FIRST STORAGE DEVICE
3
ARITHMETIC PROCESSING DEVICE
5
SECOND STORAGE DEVICE (DATA BASE)
15
SYNTHETIC ROUTE DATA
16
REACTION ANALYSIS RESULT DATA
17
PREDICTED YIELD DATA
18
PREDICTED SIDE REACTION DATA
19
SUPPLEMENTARY ITEM DATA
20
ROUTE RANKING DATA
7
QUANTUM CHEMISTRY CALCULATION UNIT
8
REACTION MECHANISM ANALYSIS UNIT
9
YIELD PREDICTION UNIT
10
SIDE REACTION PREDICTION UNIT
11
SYNTHETIC ROUTE RANKING UNIT
25
EXPERIMENTAL DATA
26
QUANTUM CHEMISTRY CALCULATION RESULT DATA
27
YIELD PREDICTION FORMULA DATA
6
OUTPUT DEVICE

FIG. 1

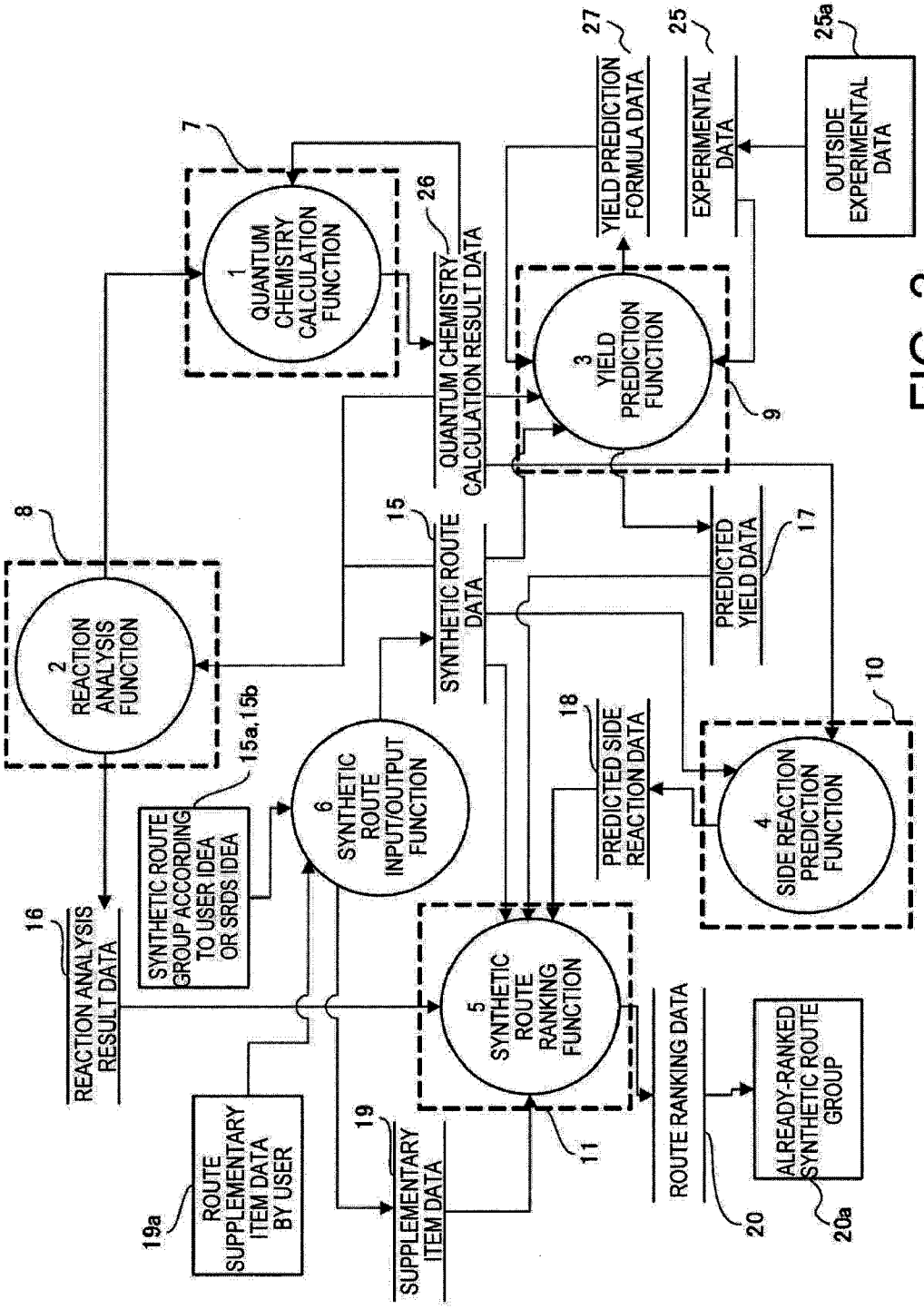

1 QUANTUM CHEMISTRY CALCULATION FUNCTION
2 REACTION ANALYSIS FUNCTION
3 YIELD PREDICTION FUNCTION
4 SIDE REACTION PREDICTION FUNCTION
5 SYNTHETIC ROUTE RANKING FUNCTION
6 SYNTHETIC ROUTE INPUT/OUTPUT FUNCTION
7
8
9
10
11
15
16
17
18
19
19a
20
20a
25
25a
26
27
QUANTUM CHEMISTRY CALCULATION RESULT DATA
YIELD PREDICTION FORMULA DATA
EXPERIMENTAL DATA
OUTSIDE EXPERIMENTAL DATA
SYNTHETIC ROUTE DATA
PREDICTED YIELD DATA
PREDICTED SIDE REACTION DATA
REACTION ANALYSIS RESULT DATA
SYNTHETIC ROUTE GROUP ACCORDING TO USER IDEA OR SRDS IDEA
15a, 15b
ROUTE SUPPLEMENTARY ITEM DATA BY USER
SUPPLEMENTARY ITEM DATA
ROUTE RANKING DATA
ALREADY-RANKED SYNTHETIC ROUTE GROUP

FIG. 2

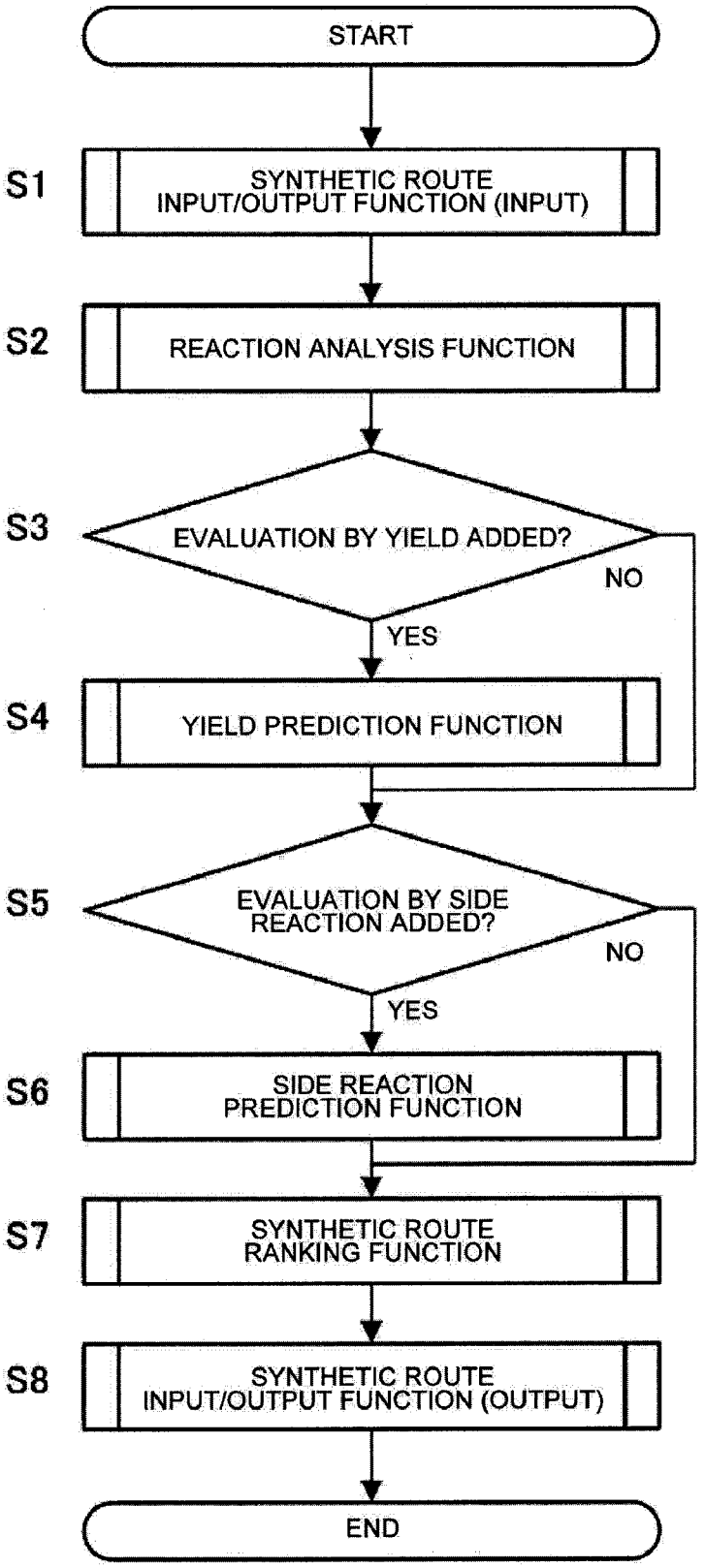

START
S1
SYNTHETIC ROUTE INPUT/OUTPUT FUNCTION (INPUT)
S2
REACTION ANALYSIS FUNCTION
S3
EVALUATION BY YIELD ADDED?
NO
YES
S4
YIELD PREDICTION FUNCTION
S5
EVALUATION BY SIDE REACTION ADDED?
NO
YES
S6
SIDE REACTION PREDICTION FUNCTION
S7
SYNTHETIC ROUTE RANKING FUNCTION
S8
SYNTHETIC ROUTE INPUT/OUTPUT FUNCTION (OUTPUT)
END

FIG. 3

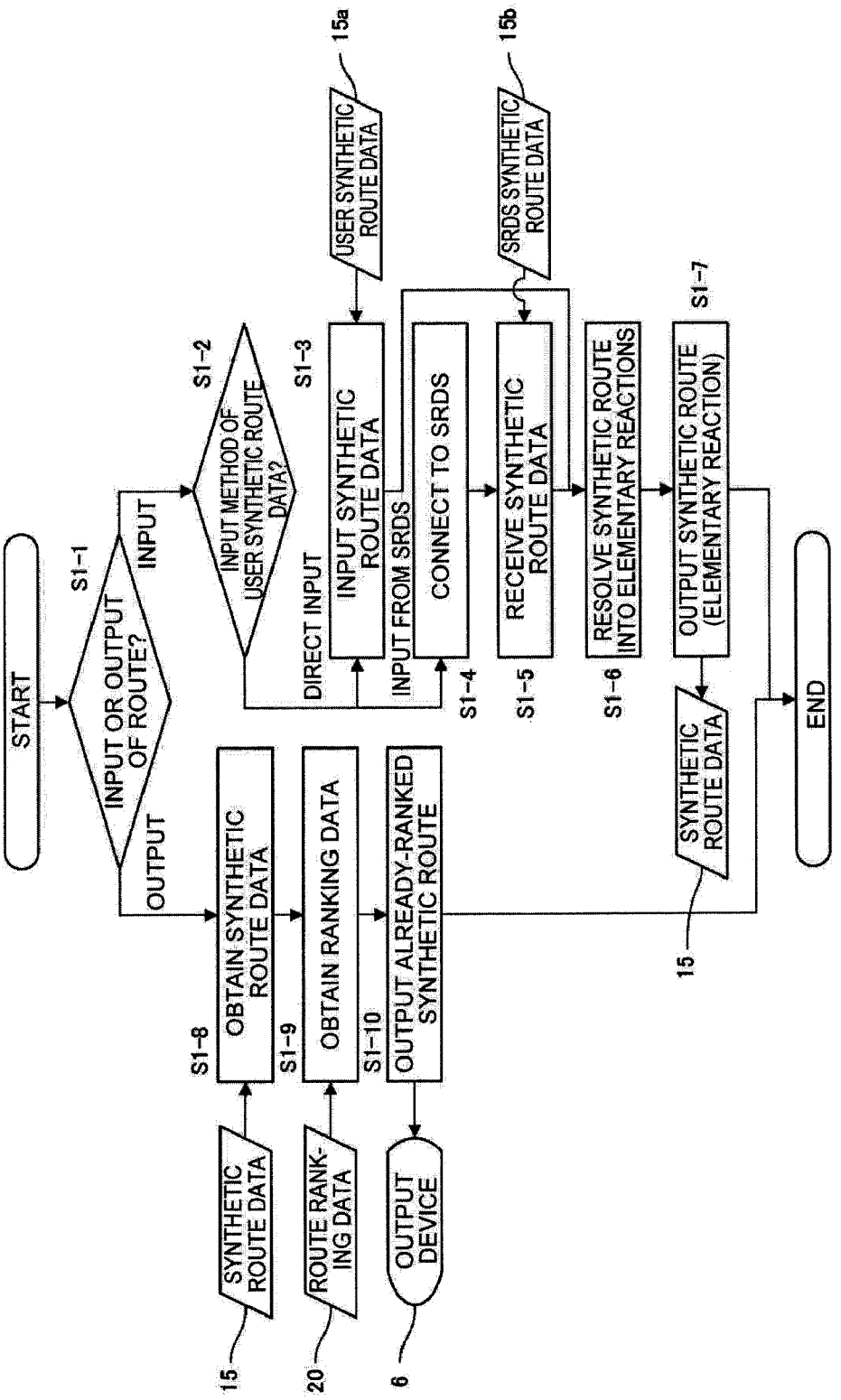

START
S1-1
INPUT OR OUTPUT OF ROUTE?
INPUT
OUTPUT
S1-2
INPUT METHOD OF USER SYNTHETIC ROUTE DATA?
DIRECT INPUT
INPUT FROM SRDS
15a
USER SYNTHETIC ROUTE DATA
S1-3
INPUT SYNTHETIC ROUTE DATA
S1-4
CONNECT TO SRDS
15b
SRDS SYNTHETIC ROUTE DATA
S1-5
RECEIVE SYNTHETIC ROUTE DATA
S1-6
RESOLVE SYNTHETIC ROUTE INTO ELEMENTARY REACTIONS
S1-7
OUTPUT SYNTHETIC ROUTE (ELEMENTARY REACTION)
SYNTHETIC ROUTE DATA
15
END
S1-8
OBTAIN SYNTHETIC ROUTE DATA
SYNTHETIC ROUTE DATA
15
S1-9
OBTAIN RANKING DATA
ROUTE RANK-ING DATA
20
S1-10
OUTPUT ALREADY-RANKED SYNTHETIC ROUTE
OUTPUT DEVICE
6

FIG. 4

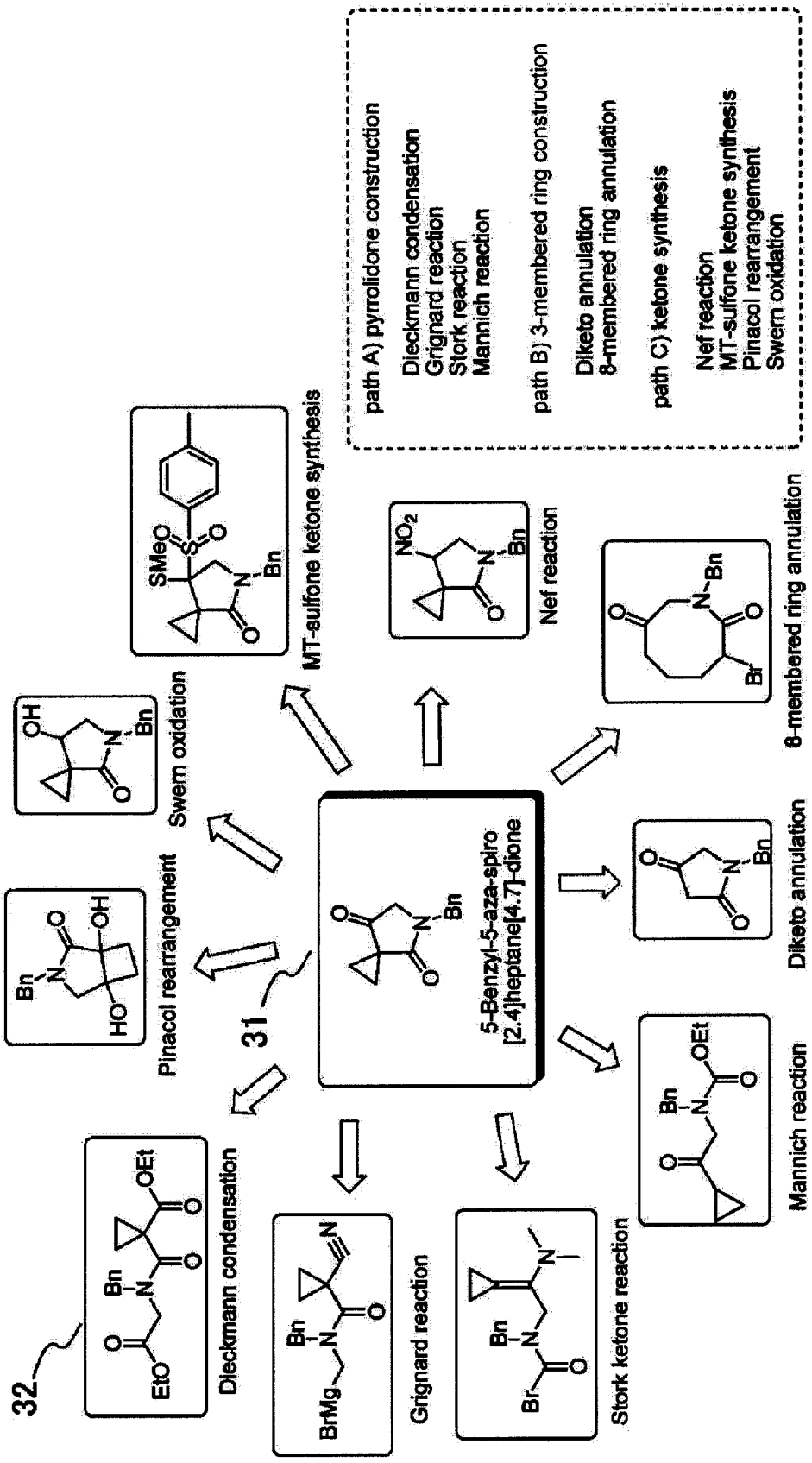

path A) pyrrolidone construction
Dieckmann condensation
Grignard reaction
Stork reaction
Mannich reaction
path B) 3-membered ring construction
Diketo annulation
8-membered ring annulation
path C) ketone synthesis
Nef reaction
MT-sulfone ketone synthesis
Pinacol rearrangement
Swern oxidation
5-Benzyl-5-aza-spiro [2.4]heptane[4.7]-dione
31
32
MT-sulfone ketone synthesis
Nef reaction
8-membered ring annulation
Swern oxidation
Pinacol rearrangement
Diketo annulation
Dieckmann condensation
Grignard reaction
Stork ketone reaction
Mannich reaction

FIG. 5

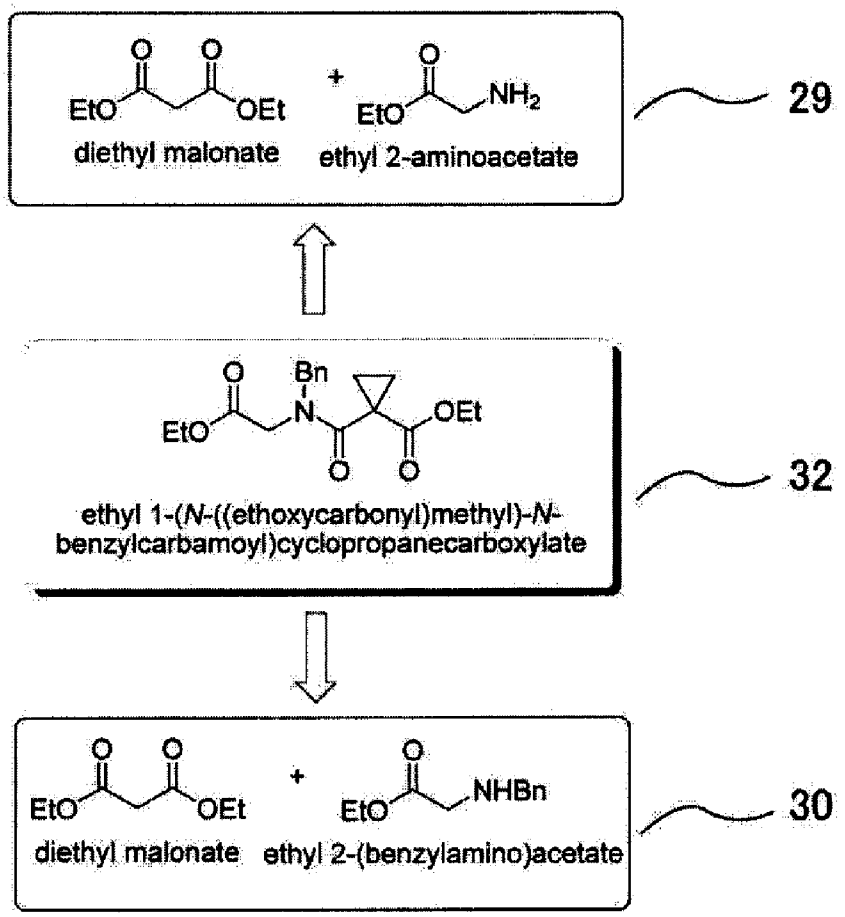

EtO
OEt
diethyl malonate
+
EtO
NH2
ethyl 2-aminoacetate
29
Bn
N
EtO
OEt
ethyl 1-(N-((ethoxycarbonyl)methyl)-N-benzylcarbamoyl)cyclopropanecarboxylate
32
EtO
OEt
diethyl malonate
+
EtO
NHBn
ethyl 2-(benzylamino)acetate
30

FIG. 6

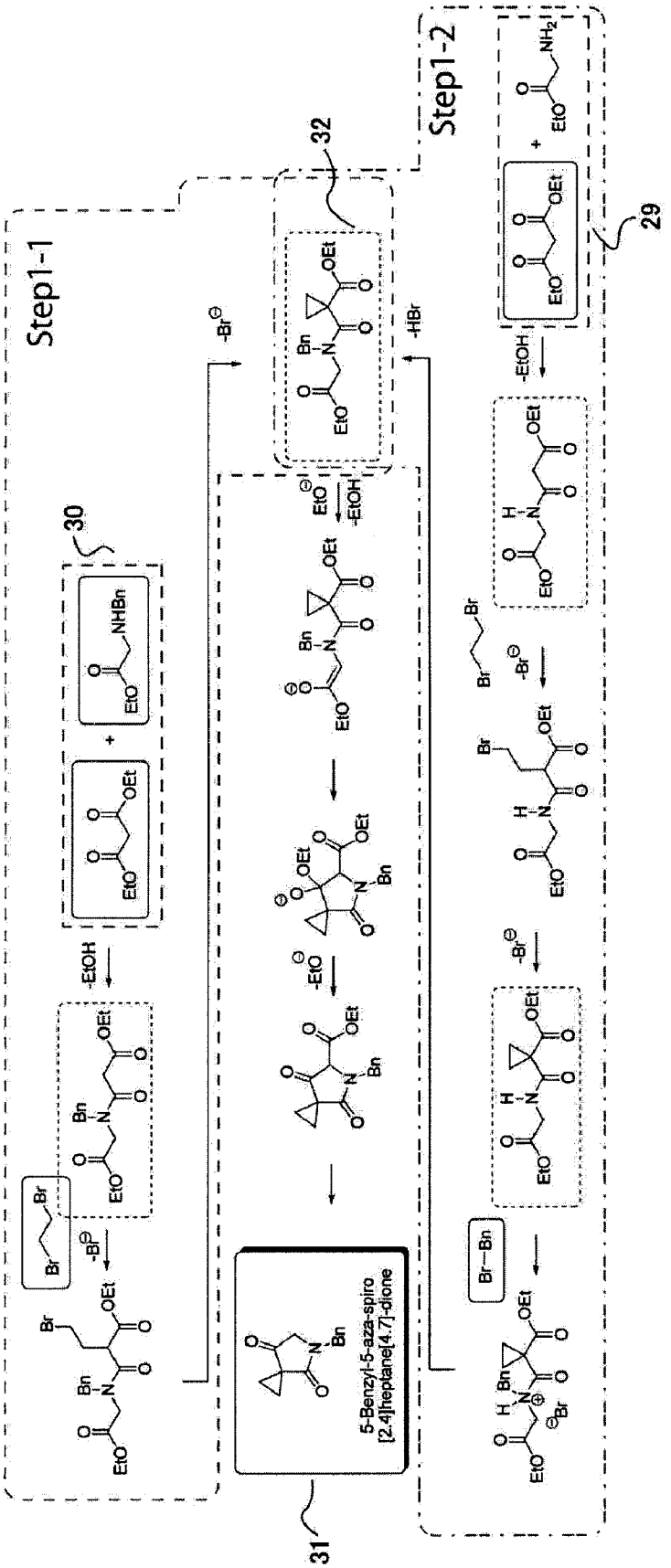

Step1-1
Step1-2
30
32
29
31
5-Benzyl-5-aza-spiro [2.4]heptane[4.7]-dione
-EtOH
-HBr
-Br⊖
-EtO⊖

FIG.7

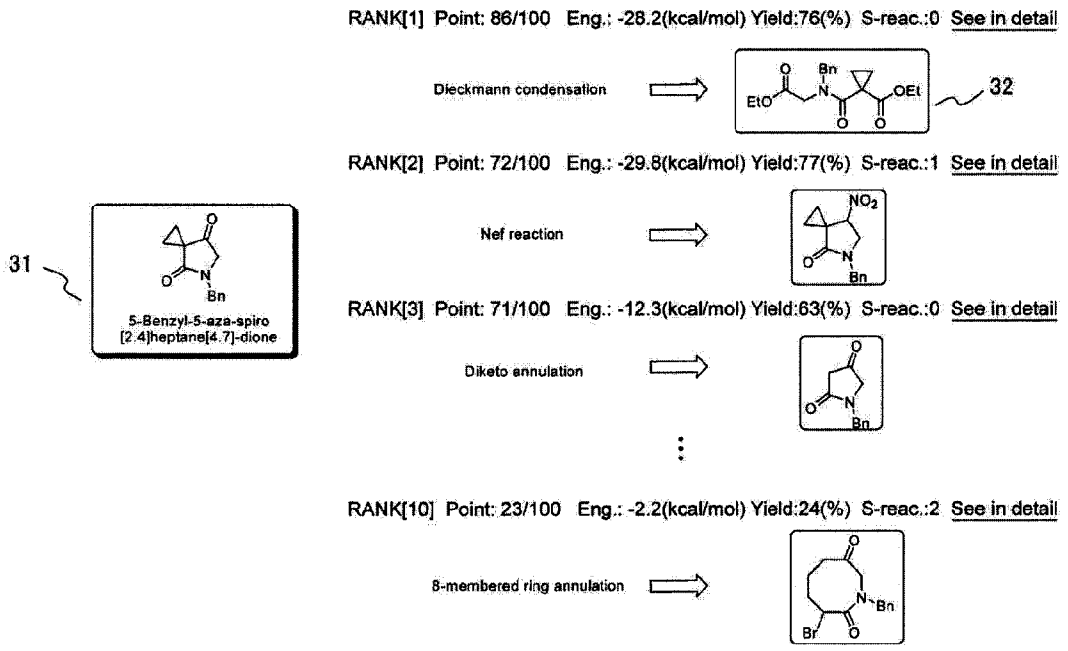

RANK[1] Point: 86/100 Eng.: -28.2(kcal/mol) Yield:76(%) S-reac.:0 See in detail
Dieckmann condensation
32
RANK[2] Point: 72/100 Eng.: -29.8(kcal/mol) Yield:77(%) S-reac.:1 See in detail
Nef reaction
RANK[3] Point: 71/100 Eng.: -12.3(kcal/mol) Yield:63(%) S-reac.:0 See in detail
Diketo annulation
RANK[10] Point: 23/100 Eng.: -2.2(kcal/mol) Yield:24(%) S-reac.:2 See in detail
8-membered ring annulation
31
5-Benzyl-5-aza-spiro [2.4]heptane[4.7]-dione

FIG. 8

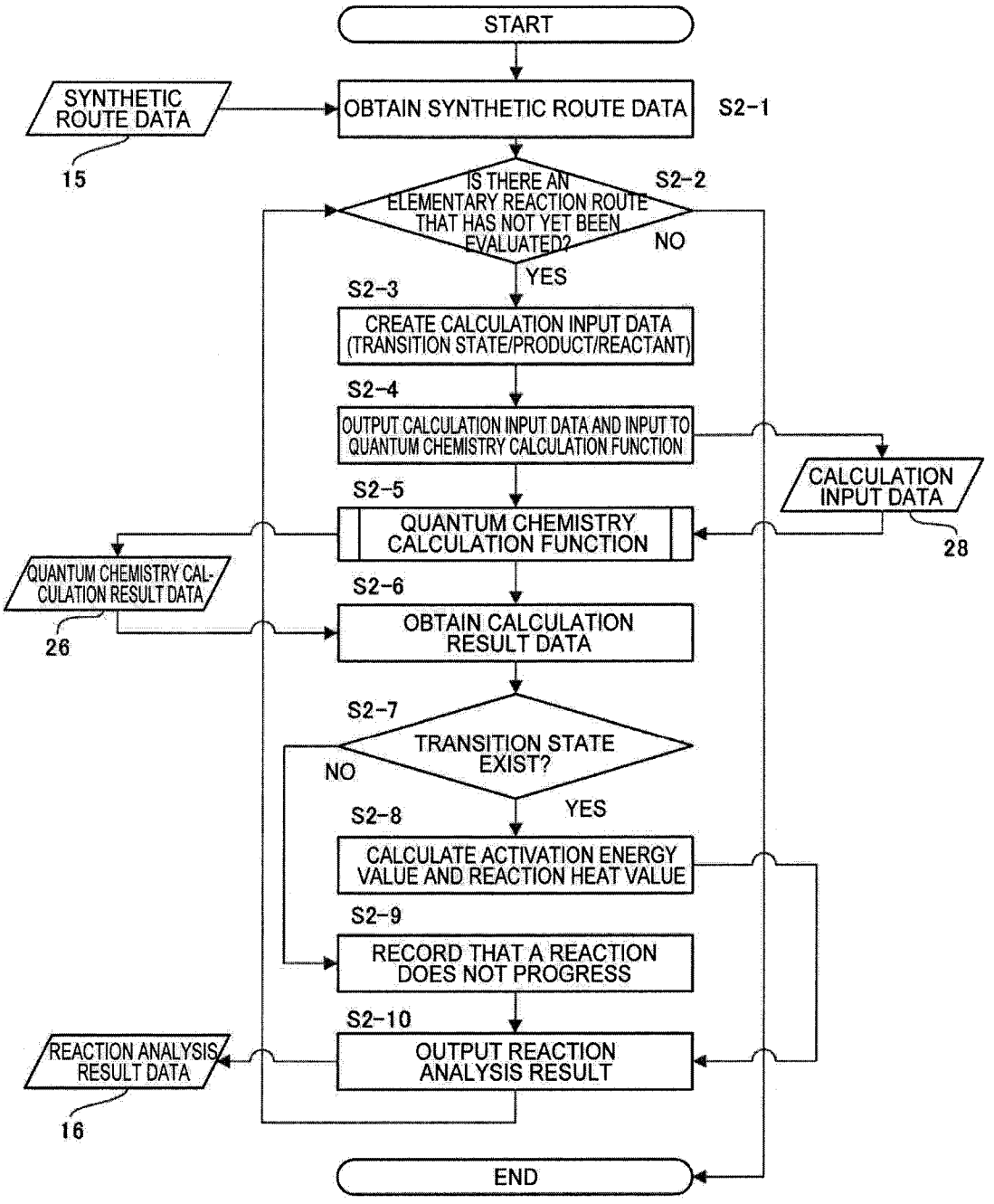

START
SYNTHETIC ROUTE DATA
15
OBTAIN SYNTHETIC ROUTE DATA
S2-1
IS THERE AN ELEMENTARY REACTION ROUTE THAT HAS NOT YET BEEN EVALUATED?
S2-2
NO
YES
S2-3
CREATE CALCULATION INPUT DATA (TRANSITION STATE/PRODUCT/REACTANT)
S2-4
OUTPUT CALCULATION INPUT DATA AND INPUT TO QUANTUM CHEMISTRY CALCULATION FUNCTION
CALCULATION INPUT DATA
28
S2-5
QUANTUM CHEMISTRY CALCULATION FUNCTION
QUANTUM CHEMISTRY CALCULATION RESULT DATA
26
S2-6
OBTAIN CALCULATION RESULT DATA
S2-7
TRANSITION STATE EXIST?
NO
YES
S2-8
CALCULATE ACTIVATION ENERGY VALUE AND REACTION HEAT VALUE
S2-9
RECORD THAT A REACTION DOES NOT PROGRESS
S2-10
OUTPUT REACTION ANALYSIS RESULT
REACTION ANALYSIS RESULT DATA
16
END

FIG. 9

```
#p b3lyp/6-31g(d) opt 6d optcyc=200

Product Optimization

0  1
O    -2.893480    1.617314   -2.283900
C    -3.793891    2.871509   -4.071981
C    -2.949973    1.664146   -3.713003
C    -2.365612    0.507220   -1.699642
C    -2.552326    0.476426   -0.187898
N    -1.249032    0.741810    0.484236
C    -1.416835    1.476049    1.762554
C    -1.218983    2.979908    1.687928
C    -2.532291    3.706303    1.580560
O    -2.772139    5.023330    1.313227
C    -1.688491    6.538833    2.887938
C    -1.819744    6.057667    1.455433
O    -1.836607   -0.340035   -2.393096
C     1.047877   -0.093800    0.828432
C     1.673062   -0.439323    2.027397
C     3.011278   -0.121623    2.233050
C     3.731037    0.544233    1.246973
C     3.110828    0.891547    0.051137
C     1.774437    0.571860   -0.161278
C    -0.380721   -0.474592    0.587384
O    -1.645313    0.883240    2.792794
O    -3.621685    3.168855    1.641422
C    -0.066467    3.518549    2.504485
C     0.042509    3.469436    1.016195
H    -3.876260    2.959576   -5.162765
H    -3.359152    3.806944   -3.695810
H    -4.811790    2.799829   -3.666486
H    -3.392166    0.731452   -4.112678
H    -1.921809    1.748777   -4.111204
H    -2.969634   -0.513765    0.096064
H    -3.298226    1.235712    0.130068
H    -1.114019    7.472764    2.924390
H    -1.164610    5.803771    3.520670
H    -2.665678    6.731517    3.349625
H    -2.269197    6.835300    0.811400
H    -0.839034    5.783236    1.017090
H     1.110472   -0.965587    2.807962
H     3.498524   -0.399931    3.173307
H     4.785311    0.790792    1.409256
H     3.677242    1.411889   -0.728171
H     1.290424    0.831572   -1.110474
H    -0.451269   -1.021840   -0.375681
H    -0.745320   -1.170006    1.374645
H     0.516826    2.826816    3.124927
H    -0.173143    4.480372    3.030300
H     0.021420    4.400817    0.431466
H     0.708772    2.740316    0.529823
```

33

FIG. 10

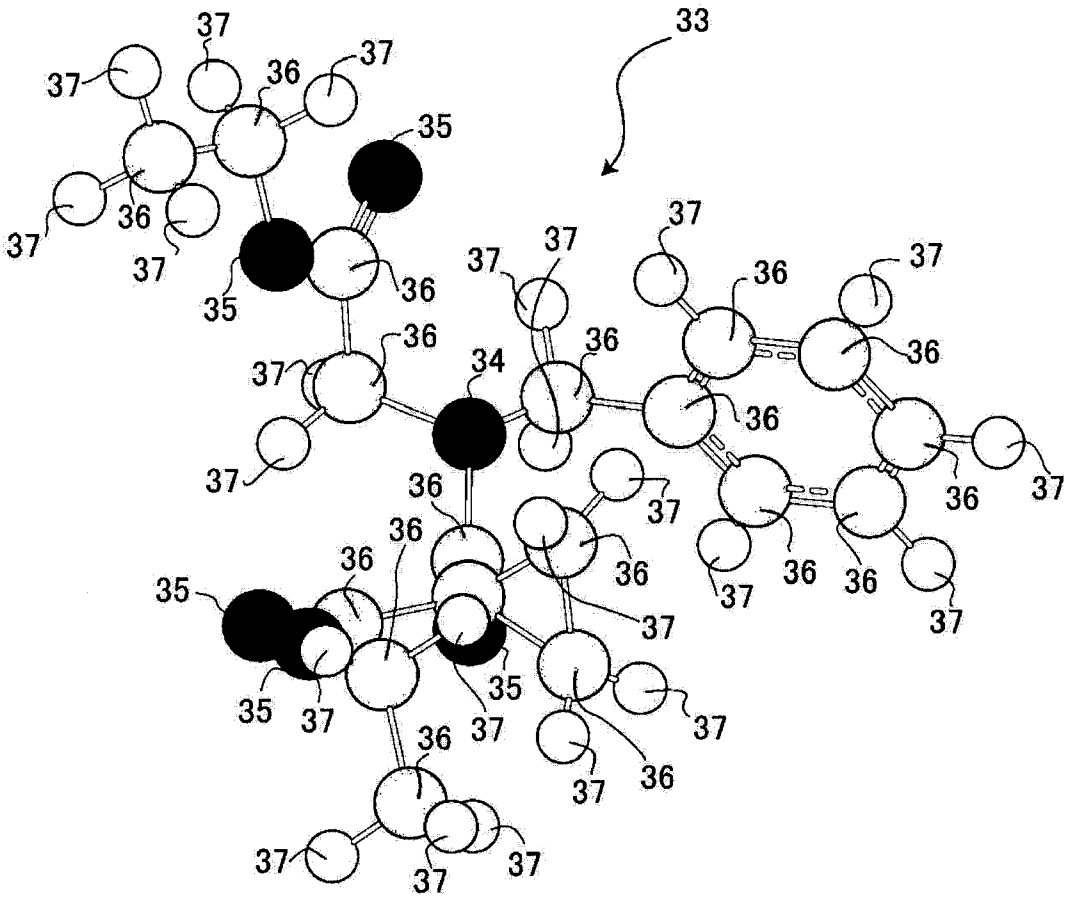


FIG. 11

41

1\1\GINC-TSTCL4\FOpt\RPM3\ZDO\C18H24Br1N1O5\PCUSER\23-May-2008\0\\# 6d
PM3 opt optcyc=200 nosym\\Title for Gaussian98\\0,1\C,0.3369983483,-2
.3555518762,-0.3785949265\C,1.8151458276,-2.4746123598,-0.662762157\C,
-0.1838173,0.7919813851,-0.315061679\H,0.8176599465,0.6414267293,-0.77
82432292\O,2.5077305509,-3.4600581584,-0.5284265675\O,2.3674150874,-1.
3012287884,-1.0989851988\C,3.7741063498,-1.2154467216,-1.3048238253\H,
4.1606831718,-2.1030137879,-1.8400205378\H,3.820798548,-0.3497191205,-
1.989206152\C,-0.0929565565,0.798414645,1.2037917302\O,-0.9932242161,0
.9805538036,1.9937926705\O,1.1862917693,0.6203848202,1.6328047346\C,1.
4351729925,0.5710320182,3.0417232791\H,1.1450163773,1.5336710637,3.502
2410466\H,0.8184400429,-0.2270840333,3.49769752\C,2.9176691985,0.29282
50945,3.1948012436\H,3.1809308048,0.2447709441,4.2588933149\H,3.209592
6452,-0.6626866454,2.7348732682\H,3.5361805952,1.0747796711,2.73311612
38\C,4.5292583829,-0.9620770434,-0.0146677261\H,4.4784942844,-1.821309
4702,0.6680051935\H,5.5883029632,-0.772902731,-0.2300067881\H,4.139467
4083,-0.0911432289,0.5323554112\N,-1.1656814817,-0.240647037,-0.839679
7183\H,-1.9017516212,-0.6543858107,-0.0691206816\C,-0.3834367975,-1.47
2411252,-1.3565958851\O,-0.3962605358,-1.665690253,-2.5457519813\C,-0.
069571882,-2.5301306285,1.0724032387\C,-0.3929208031,-3.6029634515,0.0
930932196\H,0.7203870271,-2.678254568,1.8198386408\H,-0.8841155767,-1.
9306100975,1.5081284042\H,0.140312349,-4.5610298778,0.1089608534\H,-1.
4437493757,-3.7456350049,-0.207365793\H,-0.506484353,1.8136991553,-0.6
277141115\C,-2.0678393862,0.3515447938,-1.9328859523\H,-2.834612604,-0
.4259425597,-2.1589397597\H,-1.4829752606,0.5255966226,-2.861194109\Br
,-3.1970274094,-1.7521658974,0.2553847111\C,-2.7443615001,1.613862278,
-1.5049343189\C,-2.3194521106,2.8383176459,-2.030016213\C,-3.836817230
9,1.5713664611,-0.6369233579\C,-2.974698863,4.0108902436,-1.6767620273
\H,-1.4801941344,2.8765458142,-2.7347730503\C,-4.485161065,2.751488994
5,-0.285298422\H,-4.1828694612,0.6066800795,-0.2292000326\C,-4.0560889
215,3.9689387803,-0.801187636\H,-2.6418989176,4.9681176962,-2.09145550
43\H,-5.3379907127,2.7147364172,0.4015413023\H,-4.5700965945,4.8950752
462,-0.5228485648\\Version=AM64L-G03RevD.02\HF=-0.2532052\RMSD=0.000e+
00\RMSF=3.268e-06\Thermal=0.\Dipole=2.7000364,2.3596994,-0.456675\PG=C
01 [X(C18H24Br1N1O5)]\\@

FIG. 12

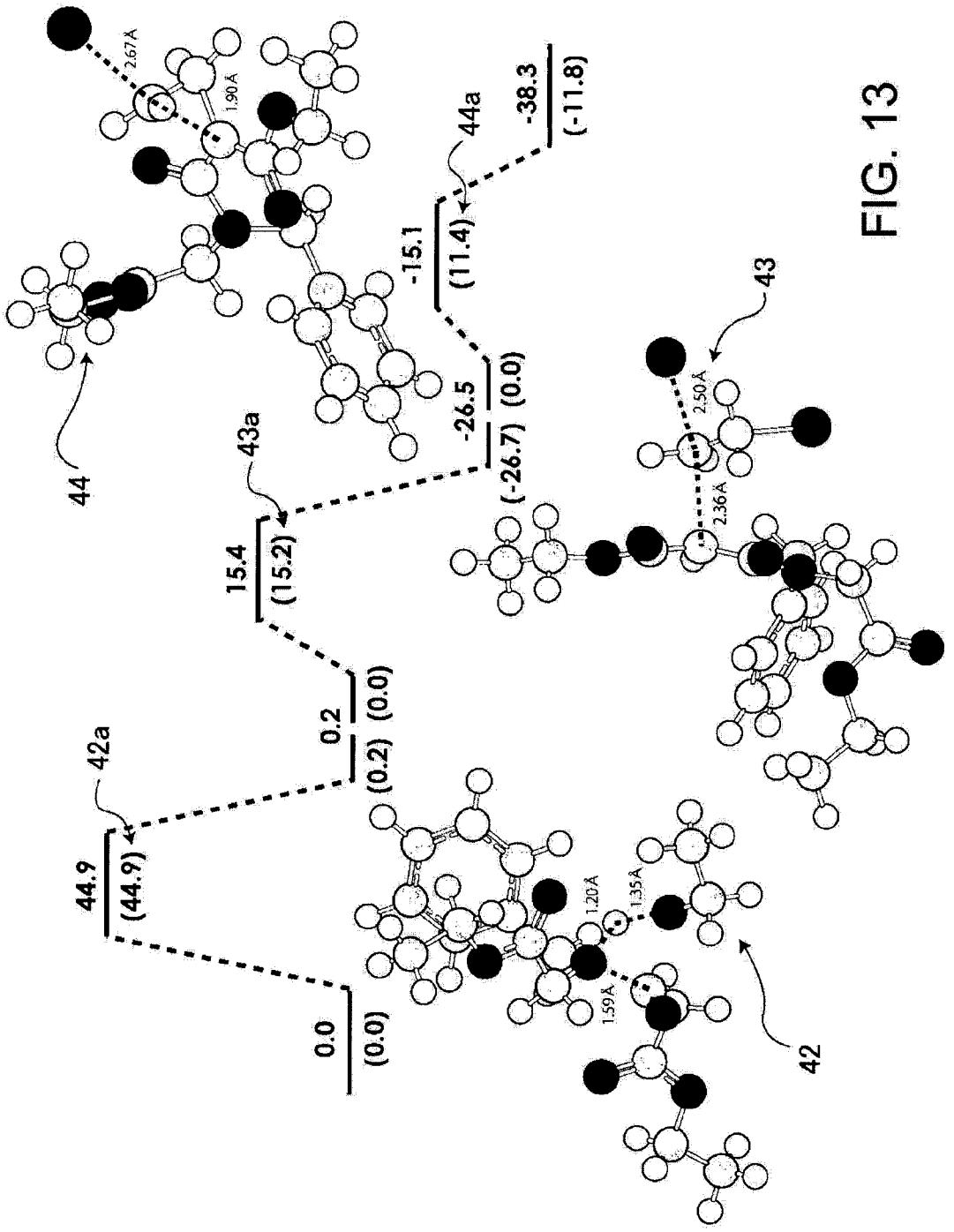

44.9
(44.9)
42a
0.2
(0.2)
0.0
(0.0)
0.0
(0.0)
15.4
(15.2)
43a
-26.5
(-26.7)
-15.1
(11.4)
44a
-38.3
(-11.8)
44
42
43
2.67Å
1.90Å
1.20Å
1.35Å
1.59Å
2.50Å
2.36Å

FIG. 13

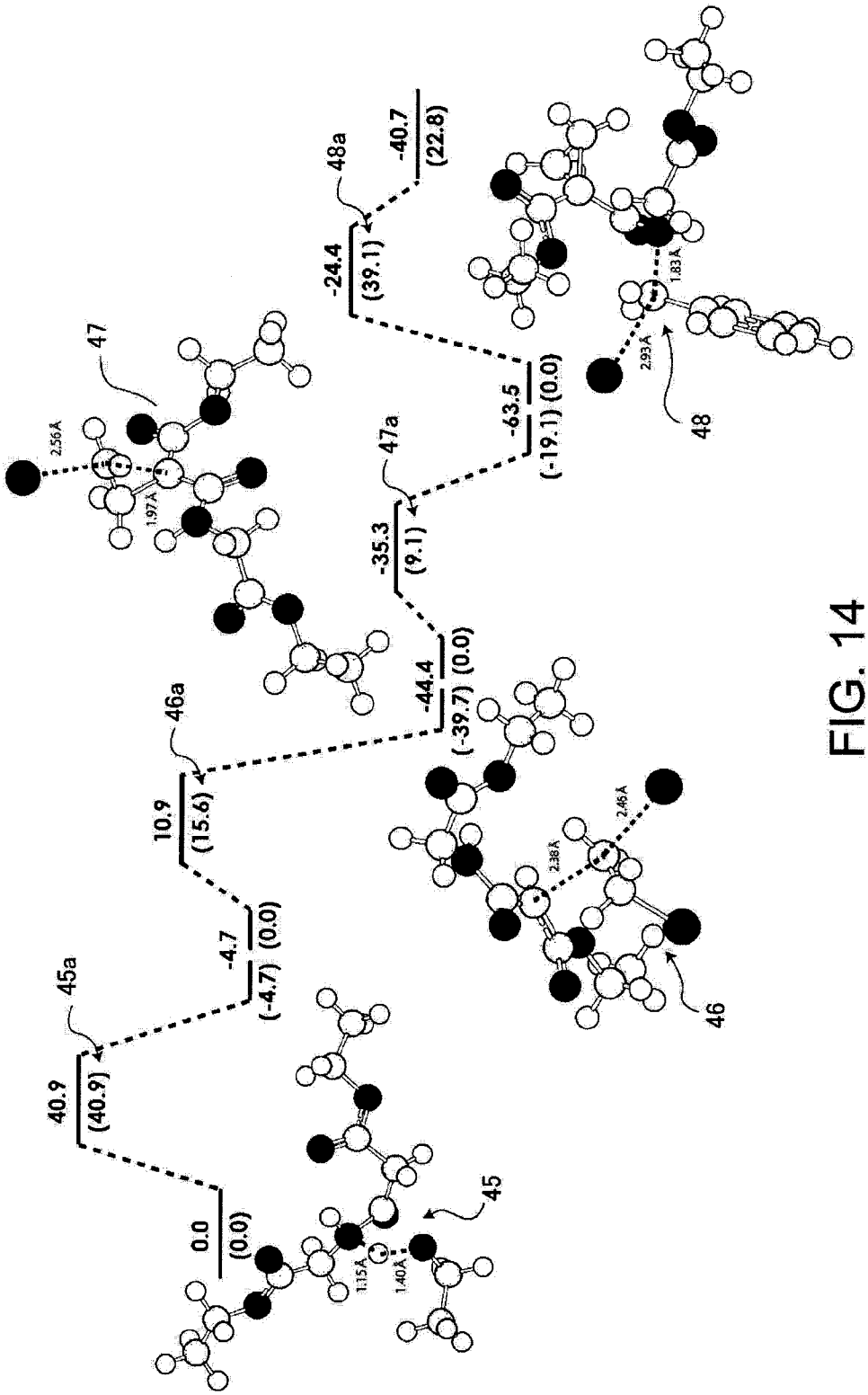

0.0
(0.0)
40.9
(40.9)
-4.7
(-4.7)
10.9
(15.6)
-44.4
(-39.7)
(0.0)
-35.3
(9.1)
-63.5
(-19.1)
(0.0)
-24.4
(39.1)
-40.7
(22.8)
45
45a
46
46a
47
47a
48
48a
1.15Å
1.40Å
2.38Å
2.46Å
2.56Å
1.97Å
2.93Å
1.83Å

FIG. 14

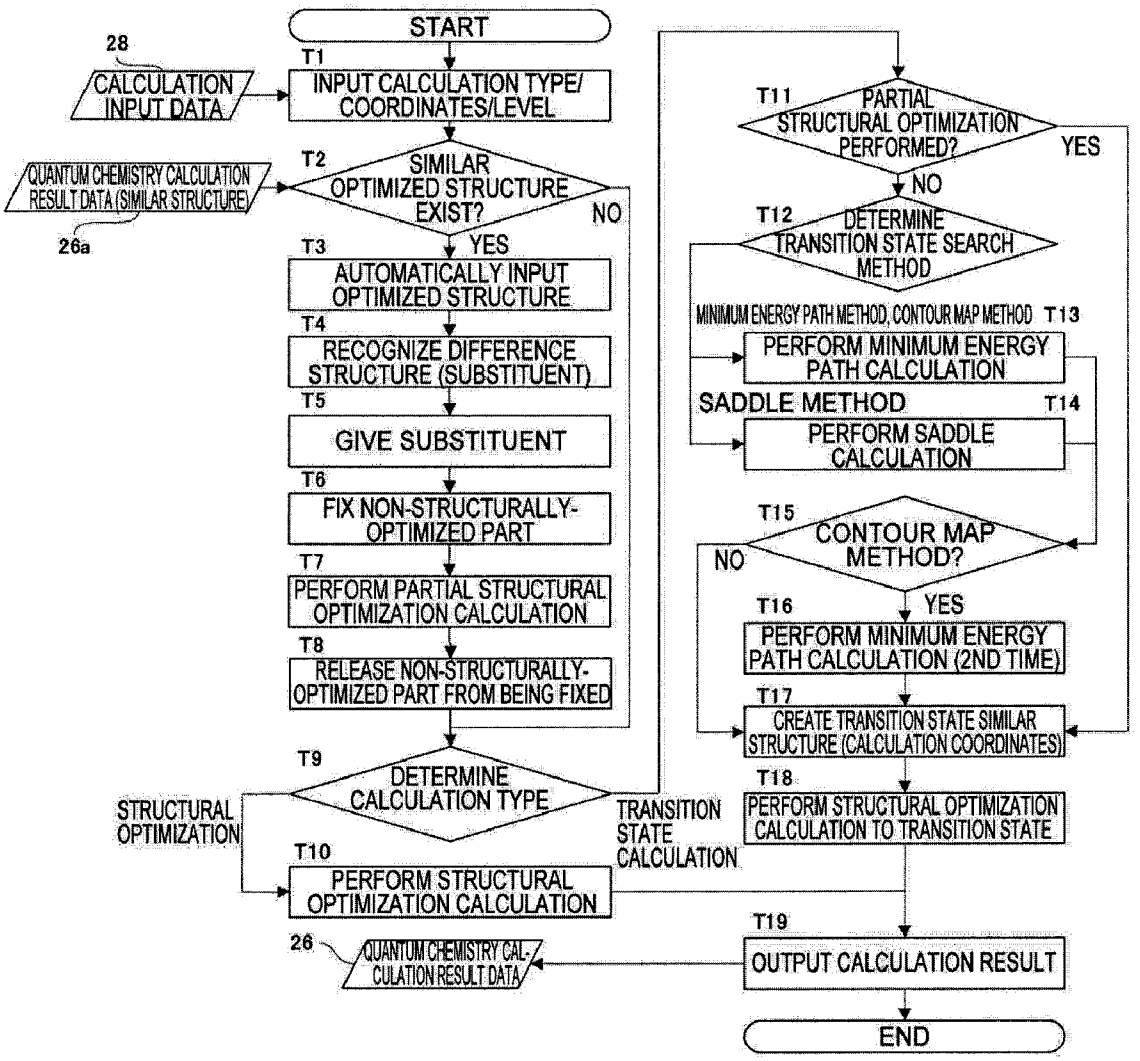

START
28
CALCULATION INPUT DATA
T1
INPUT CALCULATION TYPE/ COORDINATES/LEVEL
QUANTUM CHEMISTRY CALCULATION RESULT DATA (SIMILAR STRUCTURE)
26a
T2
SIMILAR OPTIMIZED STRUCTURE EXIST?
NO
YES
T3
AUTOMATICALLY INPUT OPTIMIZED STRUCTURE
T4
RECOGNIZE DIFFERENCE STRUCTURE (SUBSTITUENT)
T5
GIVE SUBSTITUENT
T6
FIX NON-STRUCTURALLY-OPTIMIZED PART
T7
PERFORM PARTIAL STRUCTURAL OPTIMIZATION CALCULATION
T8
RELEASE NON-STRUCTURALLY-OPTIMIZED PART FROM BEING FIXED
T9
DETERMINE CALCULATION TYPE
STRUCTURAL OPTIMIZATION
TRANSITION STATE CALCULATION
T10
PERFORM STRUCTURAL OPTIMIZATION CALCULATION
26
QUANTUM CHEMISTRY CALCULATION RESULT DATA
T11
PARTIAL STRUCTURAL OPTIMIZATION PERFORMED?
YES
NO
T12
DETERMINE TRANSITION STATE SEARCH METHOD
MINIMUM ENERGY PATH METHOD, CONTOUR MAP METHOD
T13
PERFORM MINIMUM ENERGY PATH CALCULATION
SADDLE METHOD
T14
PERFORM SADDLE CALCULATION
T15
CONTOUR MAP METHOD?
NO
YES
T16
PERFORM MINIMUM ENERGY PATH CALCULATION (2ND TIME)
T17
CREATE TRANSITION STATE SIMILAR STRUCTURE (CALCULATION COORDINATES)
T18
PERFORM STRUCTURAL OPTIMIZATION CALCULATION TO TRANSITION STATE
T19
OUTPUT CALCULATION RESULT
END

FIG. 15

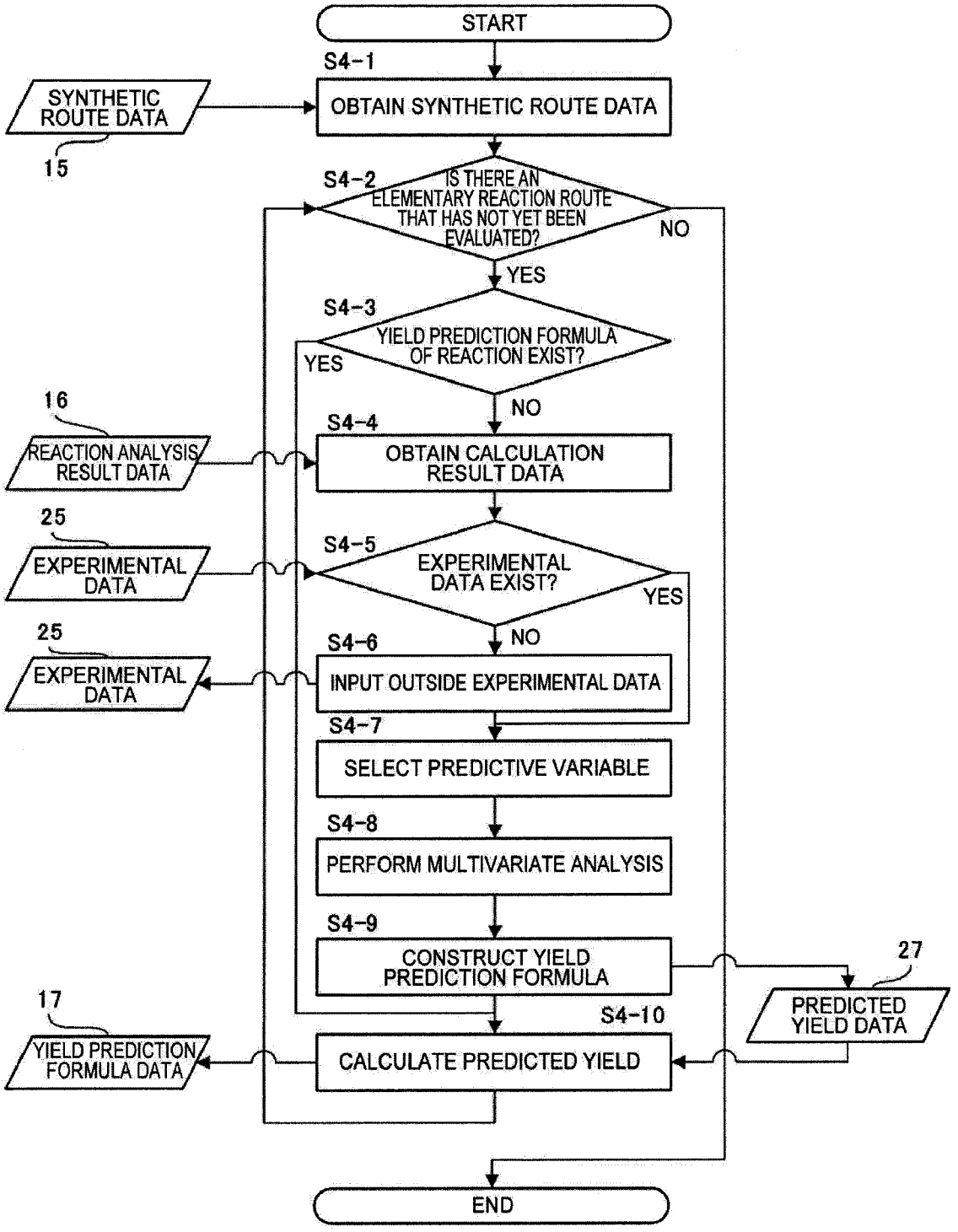

START
S4-1
OBTAIN SYNTHETIC ROUTE DATA
SYNTHETIC ROUTE DATA
15
S4-2
IS THERE AN ELEMENTARY REACTION ROUTE THAT HAS NOT YET BEEN EVALUATED?
NO
YES
S4-3
YIELD PREDICTION FORMULA OF REACTION EXIST?
YES
NO
16
REACTION ANALYSIS RESULT DATA
S4-4
OBTAIN CALCULATION RESULT DATA
25
EXPERIMENTAL DATA
S4-5
EXPERIMENTAL DATA EXIST?
YES
NO
25
EXPERIMENTAL DATA
S4-6
INPUT OUTSIDE EXPERIMENTAL DATA
S4-7
SELECT PREDICTIVE VARIABLE
S4-8
PERFORM MULTIVARIATE ANALYSIS
S4-9
CONSTRUCT YIELD PREDICTION FORMULA
27
PREDICTED YIELD DATA
17
YIELD PREDICTION FORMULA DATA
S4-10
CALCULATE PREDICTED YIELD
END

FIG. 16

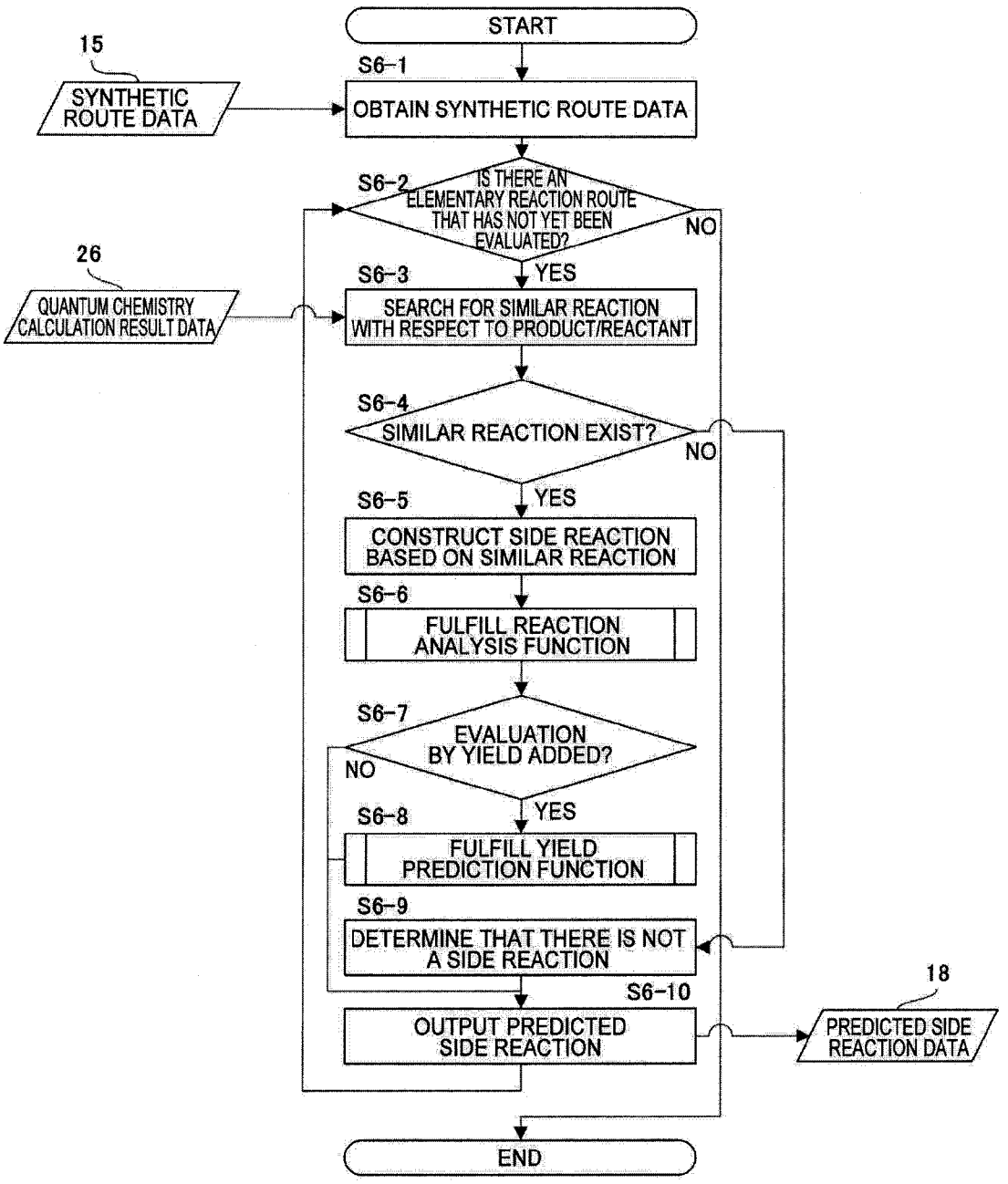

START
15
SYNTHETIC ROUTE DATA
S6-1
OBTAIN SYNTHETIC ROUTE DATA
S6-2
IS THERE AN ELEMENTARY REACTION ROUTE THAT HAS NOT YET BEEN EVALUATED?
NO
YES
26
QUANTUM CHEMISTRY CALCULATION RESULT DATA
S6-3
SEARCH FOR SIMILAR REACTION WITH RESPECT TO PRODUCT/REACTANT
S6-4
SIMILAR REACTION EXIST?
NO
YES
S6-5
CONSTRUCT SIDE REACTION BASED ON SIMILAR REACTION
S6-6
FULFILL REACTION ANALYSIS FUNCTION
S6-7
EVALUATION BY YIELD ADDED?
NO
YES
S6-8
FULFILL YIELD PREDICTION FUNCTION
S6-9
DETERMINE THAT THERE IS NOT A SIDE REACTION
S6-10
OUTPUT PREDICTED SIDE REACTION
18
PREDICTED SIDE REACTION DATA
END

FIG. 17

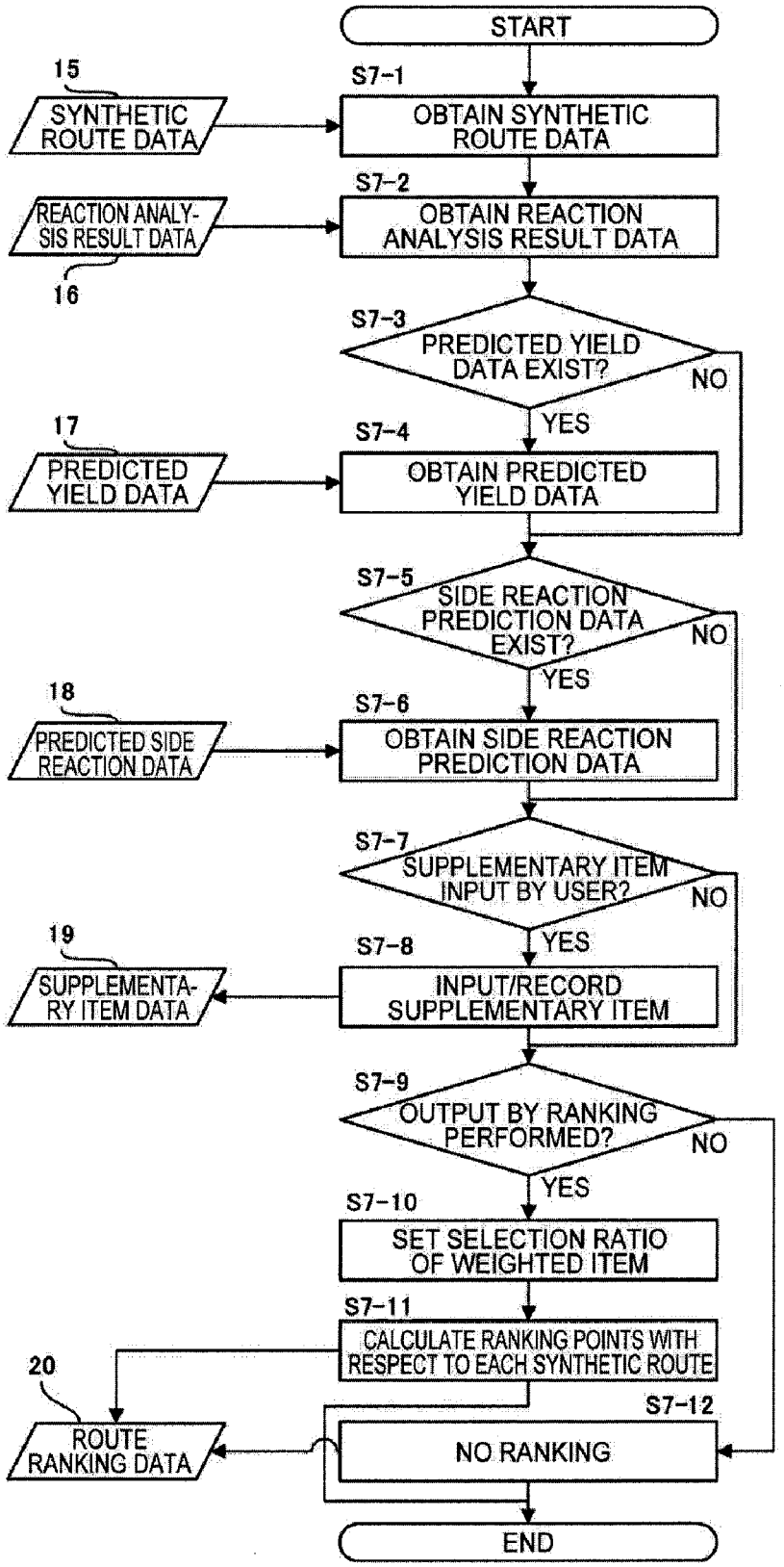
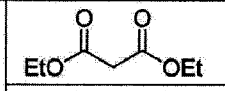
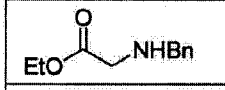
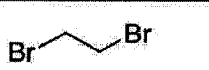
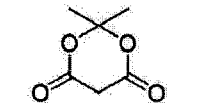
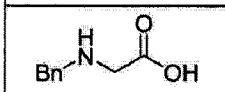
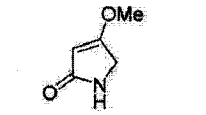
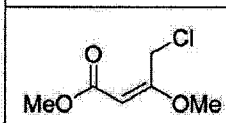
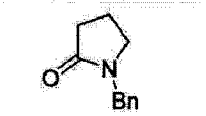
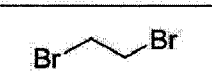
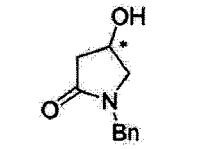
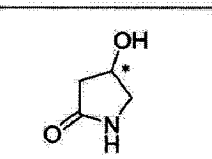
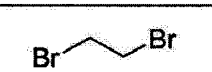

START
15
SYNTHETIC ROUTE DATA
S7-1
OBTAIN SYNTHETIC ROUTE DATA
S7-2
REACTION ANALYSIS RESULT DATA
OBTAIN REACTION ANALYSIS RESULT DATA
16
S7-3
PREDICTED YIELD DATA EXIST?
NO
YES
17
PREDICTED YIELD DATA
S7-4
OBTAIN PREDICTED YIELD DATA
S7-5
SIDE REACTION PREDICTION DATA EXIST?
NO
YES
18
PREDICTED SIDE REACTION DATA
S7-6
OBTAIN SIDE REACTION PREDICTION DATA
S7-7
SUPPLEMENTARY ITEM INPUT BY USER?
NO
YES
19
SUPPLEMENTARY ITEM DATA
S7-8
INPUT/RECORD SUPPLEMENTARY ITEM
S7-9
OUTPUT BY RANKING PERFORMED?
NO
YES
S7-10
SET SELECTION RATIO OF WEIGHTED ITEM
S7-11
CALCULATE RANKING POINTS WITH RESPECT TO EACH SYNTHETIC ROUTE
20
ROUTE RANKING DATA
S7-12
NO RANKING
END

FIG. 18

ROUTE	SYNTHESIS STARTING SUBSTANCE		
	STRUCTURAL FORMULA	CAS No.	PRICE (¥)
Dieckmann condensation		105-53-3	500 ml ¥ 4400 (TCI)
		6436-90-4	25 g ¥ 14700 (TCI)
		106-93-4	500 g ¥ 4500 (TCI)
Diketo annulation		2033-24-1	500 g ¥ 42300 (TCI)
		17136-36-6 (HCl salt)	25 g ¥ 20000(Wako)
		69778-83-2	1g ¥ 11600 (Ald)
	BnBr	100-39-0	500 g ¥ 19700 (TCI)
		110104-60-4	25 g ¥ 17400 (TCI)
	BnBr	100-39-0	500 g ¥ 19700 (TCI)
Nef reaction		5291-77-0	25 g ¥ 9500 (Ald)
		106-93-4	500 g ¥ 4500 (TCI)
Swern oxidation		(S):191403-66-4	1 g ¥ 9000 (Wako)
		106-93-4	500 g ¥ 4500 (TCI)
		(S):68108-18-9	5 g ¥ 47600 (Ald)
		(R):22677-21-0	5 g ¥ 48100 (Ald)
		106-93-4	500 g ¥ 4500 (TCI)

19

FIG. 19

SYNTHESIS PATH EVALUATION SYSTEM AND METHOD AND PROGRAM THEREOF

TECHNICAL FIELD

[0001] This invention relates to a synthetic route evaluation system for extracting an optimal synthetic route from a plurality of synthetic routes to synthetically produce a target compound, a synthetic route evaluation method thereof, and a synthetic route evaluation program thereof.

BACKGROUND ART

[0002] To create a novel compound that is a constituent of a new medicine or the like, it is necessary to find synthetic routes used to synthetically produce the compound in a chemical plant or a laboratory. So far, a proposal for synthetic routes by use of computers has been regarded as an extremely difficult problem, and, even if the proposal can be carried out by the computers, determination of whether syntheses can be achieved by the routes proposed thereby has not been able to be made without actually performing experiments.

[0003] Roughly, the following three steps exist before synthetically producing a target compound:

(1) Step of proposing synthetic routes for the target compound,

(2) Step of selecting routes that enable synthesis from the proposed synthetic routes, and

(3) Step of performing synthesis by use of the selected synthetic routes.

[0004] These steps are repeatedly performed through a trial and error process, and an optimal synthetic route is finally selected. If such an optimal synthetic route cannot be selected, a long time will be spent to synthetically produce the target compound, or costs will be raised, or, in the worst case, the target compound will not be synthetically produced. Therefore, it is very important to select optimal routes shown at step (2) mentioned above. Herein, step (1) has been known as being able to be proposed by a cheminformatics-aided means. When new synthetic routes for a target compound are created, it is known that computers are used to analyze reaction mechanisms (see Patent Documents 1 and 2).

[0005] However, a synthetic route is formed of a process having the flow: Select an appropriate synthesis starting substance→Allow the starting substance to react appropriately→Reach a target substance. When consideration is paid to its reaction stage, several stages to tens of stages occur in most cases. For example, if ten-stage reactions are required to synthetically produce a target compound and if the number of reaction patterns at each stage is two, the number of synthetic routes is the 10th power of 2, i.e., 1024. It is step (2) where an optimal one is selected from among these synthetic routes. However, a method of performing this process with computers has not yet been invented. The reason is that whether a compound can be synthetically produced along synthetic routes has been regarded as being unable to be determined without actually performing experiments.

[0006] Therefore, under existing circumstances at the present time, step (2) is performed while relying on the knowledge and experience of a person who is called a synthetic chemist. However, it is extremely difficult to select an optimal one from the 1024 synthetic routes mentioned above even if the person is an experienced chemist.

PRIOR ART DOCUMENTS

Patent Documents

[0007] Patent Document 1: Japanese Published Unexamined Patent Application No. 2002-262869

[0008] Patent Document 2: Japanese Published Unexamined Patent Application No. 2004-119742

BRIEF SUMMARY OF THE INVENTION

Problems to be Solved by the Invention

[0009] Therefore, the present invention provides a synthetic route evaluation system that is capable of proposing synthetic routes obtained by automatically ranking and narrowing down a plurality of synthetic routes given for a target compound to be synthetically produced, provides a synthetic route evaluation method thereof, and provides a synthetic route evaluation program thereof.

Means for Solving the Problems

[0010] To achieve the above-mentioned object, a synthetic route evaluation system which is an invention of claim **1** is characterized in that, in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced, the synthetic route evaluation system comprises an arithmetic processing means, which is composed of a quantum chemistry calculation unit, a reaction mechanism analysis unit, and a synthetic route ranking unit, and a storage means for storing data (hereinafter, referred to as synthetic route data) relative to the synthetic routes, wherein the synthetic route data is composed of structure data pairs the number of which is equal to the number of precursors from which the target compound can be synthetically produced, the structure data pairs being formed by correlating structure data relative to the target compound and structure data relative to the plurality of starting compounds with each other; wherein the quantum chemistry calculation unit executes a step of reading the synthetic route data from the storage means, performing a calculation in such a manner as to substitute the structure data relative to the starting compounds and the target compound into a structural optimization function, and obtaining structure data relative to the starting compounds structurally optimized and structure data relative to the target compound structurally optimized; and a step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function, and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data relative to the transition state under the condition of the presence of the transition state; wherein the reaction mechanism analysis unit executes a step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key from the storage means, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and wherein the synthetic route ranking unit executes a step of setting the activation energy and/or the

reaction heat calculated while being correlated with the plurality of starting compounds as a key, and creating a data set in which the activation energy and/or the reaction heat are arranged in desired order along with the starting compounds and/or the target compound.

[0011] The invention of claim **2** is the synthetic route evaluation system according to claim **1**, and is characterized in that the quantum chemistry calculation unit executes a step of performing a calculation in such a manner as to substitute the structure data relative to the transition state into the structural optimization function and obtaining structure data relative to a transition state structurally optimized, and the reaction mechanism analysis unit performs a calculation in such a manner as to substitute the structure data relative to a transition state structurally optimized into the activation energy calculation function.

[0012] The invention of claim **3** is the synthetic route evaluation system according to claim **1** or claim **2**, and is characterized in that the arithmetic processing means includes a yield prediction unit, wherein the yield prediction unit executes a step of, if there is a yield prediction formula pre-stored in the storage means, reading the yield prediction formula, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data into the yield prediction formula, and obtaining a predicted yield of each starting compound, or executes a step of, if there is not a yield prediction formula pre-stored in the storage means, reading experimental data relative to a reaction similar to a reaction caused to synthetically produce a target compound from the starting compounds stored in the storage means, then analyzing the yield prediction formula by use of a result of the experimental data, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data into the analyzed yield prediction formula, and obtaining a predicted yield of the starting compound, and wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds is arranged in desired order along with the starting compounds and/or the target compound while setting the activation energy and/or the reaction heat as a key or setting the predicted yield as a key.

[0013] The invention of claim **4** is the synthetic route evaluation system according to claim **3**, and is characterized in that the arithmetic processing means includes a side reaction prediction unit, wherein the side reaction prediction unit executes a step of searching for data relative to a similar reaction pre-stored in the storage means while setting the target compound and the starting compounds as a key, and defining and constructing a reaction similar to a synthetic route relative to a combination of the target compound and the starting compounds as a side reaction, and wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds or the predicted yield or the number of the side reactions is set as a key and is arranged in desired order along with the starting compounds and/or the target compound.

[0014] The invention of claim **5** is the synthetic route evaluation system according to claim **4**, and is characterized in that the arithmetic processing means includes a side reaction prediction unit, wherein the side reaction prediction unit executes a step of searching for data relative to a similar reaction pre-stored in the storage means while setting the target compound and the starting compounds as a key, and defining and constructing a reaction similar to a synthetic route relative to a combination of the target compound and the starting compounds as a side reaction, wherein the yield prediction unit executes a step of obtaining a predicted yield with respect to the target compound and the starting compounds in the constructed side reaction, and wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds, or the predicted yield or the number of the side reactions, or the predicted yield of the side reaction is set as a key and is arranged in desired order along with the starting compounds and/or the target compound.

[0015] The invention of claim **6** is the synthetic route evaluation system according to any one of claim **1** to claim **5**, and is characterized by further comprising an output means for outputting the data set created by the synthetic route ranking unit.

[0016] The invention of claim **7** is a synthetic route evaluation method for, in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced while a computer performs each step, analyzing data (hereinafter, referred to as synthetic route data) relative to the synthetic routes, transition states halfway along the synthetic routes, and activation energy relative to the transition states and evaluating the optimal synthetic route, and the synthetic route evaluation method comprises a first quantum chemical calculation step of performing a calculation in such a manner as to substitute structure data relative to the target compound included in the synthetic route data and structure data relative to a plurality of starting compounds from which the target compound can be synthetically produced into a structure optimizing function and obtaining structure data relative to the starting compounds structurally optimized and structure data relative to the target compound structurally optimized; a second quantum chemical calculation step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data relative to the transition state under the condition of the presence of the transition state; a reaction analysis step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and a synthetic route ranking step of setting the activation energy and/or the reaction heat calculated in correlation with the plurality of starting compounds as a key and creating a data set in which the activation energy and/or the reaction heat is arranged in desired order along with the starting compounds and/or the target compound.

[0017] The invention of claim **8** is a synthetic route evaluation program for, in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced by use of a computer, analyzing data (hereinafter, referred to as synthetic route data) relative to the synthetic routes, transition states halfway along the synthetic routes, and activation energy relative to

the transition states and evaluating the optimal synthetic route, and the synthetic route evaluation program allows the computer to perform a first quantum chemical calculation step of performing a calculation in such a manner as to substitute structure data relative to the target compound included in the synthetic route data and structure data relative to a plurality of starting compounds from which the target compound can be synthetically produced into a structure optimizing function and obtaining structure data relative to the precursors structurally optimized and structure data relative to the target compound structurally optimized; a second quantum chemical calculation step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data relative to the transition state under the condition of the presence of the transition state; a reaction analysis step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and a synthetic route ranking step of setting the activation energy and/or the reaction heat calculated in correlation with the plurality of starting compounds as a key and creating a data set in which the activation energy and/or the reaction heat is arranged in desired order along with the starting compounds and/or the target compound.

Effects of the Invention

[0018] In the synthetic route evaluation system of the present invention, synthetic routes from a plurality of existing starting compounds to a target compound can be evaluated by use of a quantum chemistry calculation result or a reaction analysis result when new or already-known compounds are synthesized. Additionally, the synthetic routes can be ranked in desired order based on an evaluation thereof. Therefore, an optimal synthetic route can be extracted, and can be obtained without newly performing experiments, and a development time for synthetic routes can be remarkably shortened, and, at the same time, development cost can be reduced. Additionally, a synthetic chemist who has expert knowledge is not necessarily needed, and the number of experiments can be reduced, and an environment-friendly new compound, such as a new medicine, can be synthetically produced swiftly and safely.

[0019] Additionally, especially in the invention of claim **2**, structure data relative to a transition state optimized can be used, and therefore activation energy and/or reaction heat can be calculated for the same calculation time with higher accuracy or for a shorter calculation time with the same accuracy.

[0020] Additionally, especially in the invention of claim **3**, it is possible to calculate not only activation energy and/or reaction heat but also a predicted yield of each starting compound for a target compound, and therefore an optimal synthetic route can be extracted while considering many more factors.

[0021] Especially in the inventions of claim **4** and claim **5**, an optimal synthetic route can be calculated while considering many more factors including a side reaction prediction.

[0022] In the inventions of claims **7** and **8**, the invention of claim **1** is defined as a method invention and as a program invention performed by use of a computer, respectively, and, synthetic routes from a plurality of existing starting compounds to a target compound can be evaluated in the same way as in the synthetic route evaluation system, and, at the same time, the synthetic routes can be ranked in desired order based on an evaluation thereof. Therefore, an optimal synthetic route can be extracted, and can be obtained without newly performing experiments, and a development time for synthetic routes can be remarkably shortened, and, development cost can be reduced. Additionally, a synthetic chemist who has expert knowledge is not necessarily needed, and the number of experiments can be reduced, and an environment-friendly new compound, such as a new medicine, can be synthetically produced swiftly and safely.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. **1** is a schematic view of a synthetic route evaluation system according to an embodiment of the present invention.

[0024] FIG. **2** is a functional schematic view of the synthetic route evaluation system according to the embodiment.

[0025] FIG. **3** is a process flowchart of the synthetic route evaluation system according to the embodiment.

[0026] FIG. **4** is a process flowchart of a synthetic route input/output function of an arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0027] FIG. **5** is a conceptual diagram of synthetic route data showing the relationship between a target compound (product) and starting compounds (reactants).

[0028] FIG. **6** is a conceptual diagram of synthetic route data in a Dieckmann condensation reaction.

[0029] FIG. **7** is a conceptual diagram of synthetic route data in a Dieckmann condensation reaction.

[0030] FIG. **8** is a conceptual diagram of the output of synthetic routes, which have been ranked, for a target compound.

[0031] FIG. **9** is a process flowchart of a reaction analysis function of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0032] FIG. **10** is a conceptual diagram of a calculation input file of a product obtained at a first stage of a synthetic route in the Dieckmann condensation reaction.

[0033] FIG. **11** is a three-dimensional conceptual diagram of the calculation input file of the product obtained at the first stage of the synthetic route in the Dieckmann condensation reaction.

[0034] FIG. **12** is a conceptual diagram showing an archive part of a file of quantum chemistry calculation result data of the product obtained at the first stage of the synthetic route in the Dieckmann condensation reaction.

[0035] FIG. **13** is a conceptual diagram that visualizes one of two pieces of reaction analysis data at a second stage of the synthetic route in the Dieckmann condensation reaction.

[0036] FIG. **14** is a conceptual diagram that visualizes the other one of the two pieces of reaction analysis data at the second stage of the synthetic route in the Dieckmann condensation reaction.

[0037] FIG. **15** is a process flowchart of a quantum chemistry calculation function of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0038] FIG. **16** is a process flowchart of a reaction yield prediction function in a yield prediction unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0039] FIG. **17** is a process flowchart of a side reaction prediction function in a side reaction prediction unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0040] FIG. **18** is a process flowchart of a synthetic route ranking function in a synthetic route ranking unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0041] FIG. **19** is a conceptual diagram showing data relative to supplementary items that are added during processing of the synthetic route ranking function in the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0042] **1** . . . Synthetic route evaluation system
[0043] **2** . . . Input device
[0044] **3** . . . Arithmetic processing device
[0045] **4** . . . First storage device
[0046] **5** . . . Second storage device
[0047] **6** . . . Output device
[0048] **7** . . . Quantum chemistry calculation unit
[0049] **8** . . . Reaction mechanism analysis unit
[0050] **9** . . . Yield prediction unit
[0051] **10** . . . Side reaction prediction unit
[0052] **11** . . . Synthetic route ranking unit
[0053] **15** . . . Synthetic route data
[0054] **15***a* . . . User synthetic route data
[0055] **15***b* . . . SRDS synthetic route data
[0056] **16** . . . Reaction analysis result data
[0057] **17** . . . Predicted yield data
[0058] **18** . . . Predicted side reaction data
[0059] **19** . . . Supplementary item data
[0060] **20** . . . Route ranking data
[0061] **20***a* . . . Already-ranked synthetic route group
[0062] **25** . . . Experimental data
[0063] **25***a* . . . Outside experimental data
[0064] **26** . . . Quantum chemistry calculation result data
[0065] **26***a* . . . Quantum chemistry calculation result data
[0066] **27** . . . Yield prediction formula data
[0067] **28** . . . Calculation input data
[0068] **29** . . . Reactant
[0069] **30** . . . Reactant
[0070] **31** . . . Product
[0071] **32** . . . Reactant
[0072] **33** . . . Calculation input data structure
[0073] **34** . . . Nitrogen atom
[0074] **35** . . . Oxygen atom
[0075] **36** . . . Carbon atom
[0076] **37** . . . Hydrogen atom
[0077] **41** . . . Data calculation result file structure
[0078] **42** . . . First transition state
[0079] **42***a* . . . Activation energy
[0080] **43** . . . Second transition state
[0081] **43***a* . . . Activation energy
[0082] **44** . . . Third transition state
[0083] **44***a* . . . Activation energy
[0084] **45** . . . First transition state
[0085] **45***a* . . . Activation energy
[0086] **46** . . . Second transition state
[0087] **46***a* . . . Activation energy
[0088] **47** . . . Third transition state
[0089] **47***a* . . . Activation energy
[0090] **48** . . . Fourth transition state
[0091] **48***a* . . . Activation energy

BEST MODE FOR CARRYING OUT THE INVENTION

[0092] With reference to FIG. **1** to FIG. **19**, a description will be hereinafter given of a synthetic route evaluation system, a synthetic route evaluation method, and a synthetic route evaluation program according to a most preferred embodiment of the present invention.

[0093] FIG. **1** is a schematic view of the synthetic route evaluation system according to the embodiment. In FIG. **1**, the synthetic route evaluation system **1** according to the embodiment is composed of five constituents, i.e., an input device **2**, an arithmetic processing device **3**, a first storage device **4**, a second storage device (data base) **5**, and an output device **6**.

[0094] First, various pieces of data are input from the input device **2**, are then processed in the arithmetic processing device **3**, and are stored in the first storage device **4** serving as a main storage device that is capable of temporarily storing data and in the second storage device (data base) **5** that is capable of persistently storing data. Data stored therein are also read and processed by each constituent of the arithmetic processing device **3**. Data obtained by being processed by the arithmetic processing device **3** are displayed by the output device **6** or is output to an external device.

[0095] Specifically, the input device **2** is any one of or any combination of a plurality of kinds of devices, i.e., a keyboard, a mouse, a pen tablet, an optical or magnetic reader, and a receiver that receives data via a communication line from, for example, an analyzer or a measuring device such as a computer.

[0096] The arithmetic processing device **3** is composed of a quantum chemistry calculation unit **7**, a reaction mechanism analysis unit **8**, a yield prediction unit **9**, a side reaction prediction unit **10**, and a synthetic route ranking unit **11**.

[0097] The first storage device **4** is a storage device that stores synthetic route data **15**, reaction analysis result data **16**, predicted yield data **17**, predicted side reaction data **18**, supplementary item data **19**, and route ranking data **20**, whereas the second storage device **5** is a storage device that stores experimental data **25**, quantum chemistry calculation result data **26**, and yield prediction formula data **27**.

[0098] Specifically, a CRT, liquid crystal, plasma, or organic EL, etc., display device, a display device of, for example, a printer, or a signal sending device, such as a transmitter, for sending signals toward an external device can be used as the output device **6**.

[0099] Next, with reference to FIG. **2** and FIG. **3** in addition, a description will be given of the function of the arithmetic processing device **3** and the flow of data processed by the arithmetic processing device **3**.

[0100] FIG. **2** is a functional schematic view of the synthetic route evaluation system according to the embodiment. In FIG. **2**, each part enclosed by a dotted line is each constituent of the arithmetic processing device **3** of the synthetic route evaluation system **1** shown in FIG. **1**, and a function that can be fulfilled by each constituent is shown in each part enclosed thereby. FIG. **3** is a process flowchart of the synthetic route evaluation system according to the embodiment.

[0101] A synthetic route input/output function in FIG. **2** is a function that can be fulfilled by the whole of the synthetic route evaluation system **1**, and, more specifically, it is a function that can be first fulfilled when the system is operated as shown in FIG. **3**.

[0102] In the synthetic route evaluation system **1** according to the embodiment, the synthetic route input/output function of the arithmetic processing device **3** is first used, and data relative to synthetic routes is input from the input device **2** so as to be stored in the first storage device **4** as shown in step S**1** of FIG. **3**. More specifically, as shown in FIG. **2**, user synthetic route data **15***a* and SRDS synthetic route data **15***b* are input via the input device **2**, and are stored in the first storage device **4** in the form of synthetic route data **15**. Herein, the term "SRDS" is an abbreviation of Synthesis Routes Designing System, and denotes a system that has already been put to practical use. In the SRDS, generally, a plurality of synthetic routes can be proposed, and are, however, increased in number in geometric progression if a reaction is considered in a multistage manner, and therefore there is a case in which a synthetic chemist will hesitate to make a selection from the synthetic routes even if the synthetic chemist is an experienced one. In other words, in a case in which a target synthetic substance is synthetically produced not by one reaction formula (single stage) but by a plurality of reaction formulas (multiple stages), a synthetic route can exist for each reaction, and therefore combinations thereof will be brought into a geometric-progression increase.

[0103] In the embodiment according to the present invention, user synthetic route data **15***a* set by a user of the synthetic route evaluation system **1** according to the embodiment of the claimed invention and SRDS synthetic route data **15***b* that can be created by the SRDS are both input via the input device **2** in the form of synthetic route data **15**, and an analysis is performed using this data.

[0104] A detailed process flow in step S**1** will be described with reference to FIG. **4**. FIG. **4** is a process flowchart of the synthetic route input/output function in the arithmetic processing device of the synthetic route evaluation system according to the embodiment. In FIG. **4**, at step S**1**-**1** of determining whether synthetic routes are input or output, an automatic determination can be made by judging the timing of processing or the presence or absence of synthetic route data **15** to be output. In other words, for example, after starting the synthetic route evaluation system **1**, synthetic route data **15** does not exist from that timing, and therefore it can be determined that synthetic routes are input, whereas there is a need to output synthetic route data **15** together with analysis results of a quantum chemical calculation, a reaction mechanism analysis, or an analysis of a yield prediction or of a side reaction prediction at the timing after completing these analyses, and therefore it can be determined that synthetic routes are output.

[0105] At step S**1**-**2**, a question about an input method of user synthetic route data is posed. It is possible to use two input methods, i.e., a method in which data is directly input by a user and a method in which data is input from the above-mentioned SRDS. This question is shown on a display of the output device **6**, and can be input by the input device **2**. If data is directly input by the user, the process proceeds to step S**1**-**3**, at which user synthetic route data **15***a* is input via the input device **2**, such as a keyboard or a tablet, and, if it is selected that data is input from the SRDS, the input device **2** of the synthetic route evaluation system **1** is connected to the SRDS at step S**1**-**4**, and then SRDS synthetic route data **15***b* is received at step S**1**-**5**. The "connection of the input device **2** to the SRDS" denotes that an electrical connection for calling up information is made, and a wait for the information is performed in a state in which pieces of hardware, such as cables, have already been connected.

[0106] In either input method, the synthetic route data is provided in the form of a binary data type showing a route group indicated by the following two-dimensional structure. Herein, as shown in FIG. **5**, an example of the synthetic route data by the SRDS of 5-Benzyl-5-aza-spiro[2.4] heptane[4.7]-dione is mentioned as the example.

[0107] FIG. **5** is a conceptual diagram of synthetic route data showing the relationship between a target compound (product) and starting compounds (reactants). A structure is shown in which first reactants **32** that are starting compounds are disposed around a product **31** expressed as 5-Benzyl-5-aza-spiro[2.4] heptane[4.7]-dione. If routes along which the product **31** is synthetically produced from these reactants **32** are classified according to the reaction type, there are three routes (paths) of A) a reaction of Pyrrolidone construction type, B) a reaction of 3-membered ring construction type, and C) a reaction of Ketone synthesis type as shown in FIG. **5**. Synthetic route data **15** is formed as combinations of the target compound (product **31**) and the plurality of starting compounds (reactants **32**) used to synthetically produce the target compound. In the synthetic route data **15** shown in FIG. **5**, ten reactants **32** exist with respect to the one product **31**, and the data is composed of ten structure data pairs resulting from combinations of the product **31** and the reactants **32**. The "structure data pair" will be hereinafter referred to simply as "structure data" if necessary.

[0108] FIG. **6** shows an example of user synthetic route data relative to routes to generate reactants of a Dieckmann condensation reaction among the ten routes of FIG. **5**.

[0109] User synthetic route data **15***a* and SRDS synthetic route data **15***b* that have been input or received are resolved into elementary reaction routes as shown in step S**1**-**6** of FIG. **4**. Based on the user synthetic route data **15***a* and the SRDS synthetic route data **15***b* that have been input, the elementary reaction routes are automatically resolved, are then output to the first storage device **4** as synthetic route data **15** (step S**1**-**7**), and are stored therein. As shown in FIG. **7**, the synthetic route data **15** is stored in the form of a binary data type showing an elementary reaction group for each route shown by a two-dimensional structure. FIG. **7** is a conceptual diagram of synthetic route data in a Dieckmann condensation reaction shown as the example. Information (synthetic route data **15**) relative to the elementary reaction routes of the resolved synthetic routes may be displayed on the output device **6** for user convenience or may be output to an external device.

[0110] In FIG. **7**, when a product **31** is synthetically produced, it is understood that there are two routes, i.e., a route in which a third reactant **32** is first synthetically produced from a first reactant **30**, and then the product **31** is synthetically produced from the third reactant **32** as shown at Step**1**-**1**, and a route in which a third reactant **32** is synthetically produced from a second reactant **29**, and then the product **31** is synthetically produced from the third reactant **32** as shown at Step**1**-**2**. Therefore, even if the data is synthetic route data **15** expressed by combining the product **31** and the reactants **32** together as shown in FIG. **5**, it is important to recognize the possibility that a plurality of routes will be generated while resolving the data into elementary reactions, and the reason

for the existence of step S1-6 mentioned above will be understood. Herein, the term "elementary reaction" denotes a reaction shown by an arrow (→) of, for example, in FIG. 7. Step1-1 is composed of three elementary reactions, and Step1-2 is composed of five elementary reactions.

[0111] An example of a method of resolving the synthetic route data **15** into elementary reactions is carried out in such a manner that data (elementary reaction data) relative to elementary reactions are pre-registered in a data base, are then read from the data base, are then compared and collated, and are resolved into elementary reactions included in the synthetic route data **15**. If user synthetic route data **15***a*, SRDS synthetic route data **15***b*, etc., are pre-resolved into data for each elementary reaction, data resolved into elementary reactions are included in the synthetic route data **15** without changes, and therefore step S1-6 may be removed.

[0112] The accuracy of an analysis relative to synthetic routes can be heightened by resolving data into elementary reactions.

[0113] On the other hand, the output of synthetic routes is shown in detail in step S1-8 to step S1-10 of FIG. **4** although that is also shown in step S8 of FIG. **3**. In this case, the process proceeds from step S1-1 to step S1-8, and the arithmetic processing device **3** reads and obtains the synthetic route data **15** stored in the first storage device **4**. Likewise, route ranking data **20** stored in the first storage device **4** is read and obtained at step S1-9. Thereafter, at step S1-10, the arithmetic processing device **3** displays the synthetic route data **15** and the route ranking data **20** obtained therefrom on the output device **6**, or outputs these data to an external device. The synthetic route data **15** mentioned here denotes data relative to routes already ranked by some factors.

[0114] FIG. **8** is a conceptual diagram of the output of synthetic routes, which have been ranked, for a target compound. In FIG. **8**, a target compound (product **31**) is shown on the left, and starting compounds (reactants **32**) used to synthetically produce this target compound are shown as RANK [1] to RANK [4], respectively. In FIG. **8**, ranking is represented as, for example, points, and a route having the highest number of points is regarded as the best route. A user of the synthetic route evaluation system **1** according to the embodiment of the present invention can browse data relative to each calculation result based on which ranking points are determined, i.e., can browse reaction analysis data (Eng.: reaction heat of entire routes), predicted yield data (Yield: predicted yields), predicted side reaction data (S-reac.: number of predicted side reactions), etc., in addition to confirmation of the output of the ranking points as shown in FIG. **8**.

[0115] Therefore, the user can select a presumably optimal route while comprehensively considering these pieces of data without being influenced by ranking points. Data is output in the form of a binary data type that shows synthetic route groups shown by a two-dimensional structure to which ranking points have been added as shown in FIG. **8**. In FIG. **8**, the output of an already-ranked route of 5-Benzyl-5-aza-spiro[2.4] heptane[4.7]-dione is shown as an example.

[0116] The arithmetic processing device **3** stores supplementary item data **19** input from the input device **2** in the first storage device **4** while using the synthetic route input/output function. This supplementary item data **19** is data relative to supplementary items for the evaluation of a ranking order that is used when the synthetic route ranking unit **11** fulfills a synthetic route ranking function (see FIG. **2**).

[0117] Referring back to FIG. **1** to FIG. **3** and referring to a new process flowchart, a description will be hereinafter given of each analysis performed in the arithmetic processing device **3** of the synthetic route evaluation system **1** although, as above, a description has been given of the input of the user synthetic route data **15***a* and the SRDS synthetic route data **15***b* to the synthetic route evaluation system **1** and the data output after completing an analysis while placing a central focus on the input function and the output function of the synthetic route input/output function of the arithmetic processing device **3**.

[0118] Synthetic route data **15** is stored in the first storage device **4** at step S1 of FIG. **3**, and then the reaction mechanism analysis unit **8** can fulfill the reaction analysis function at step S2. A quantum chemistry calculation function described later is included in the reaction analysis function shown at step S2 of FIG. **3**.

[0119] The reaction mechanism analysis unit **8** of the arithmetic processing device **3** of FIG. **2** executes a process flow shown in FIG. **9**. FIG. **9** is a process flowchart of the reaction analysis function in the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0120] First, the reaction mechanism analysis unit **8** reads synthetic route data **15** stored in the first storage device **4** (step S2-1), and searches for the presence or absence of elementary reaction routes, which have not been evaluated, among elementary reactions included in the synthetic route data **15** (step S2-2). The "evaluation" mentioned here denotes that data corresponding to the quantum chemistry calculation result data **26** and the reaction analysis result data **16**, which can be obtained through step S2-3 and steps subsequent to step S2-3, have already been obtained. Therefore, if elementary reaction routes that have not been evaluated do not exist at step S2-2, the process proceeds directly to End, and the process flow relative to the reaction analysis function at step S2 is completed.

[0121] On the other hand, if elementary reaction routes that have not been evaluated exist, the process proceeds to step S2-2, at which a quantum chemical calculation and a reaction analysis are performed, and quantum chemistry calculation result data **26** and reaction analysis result data **16** are obtained.

[0122] Referring to FIG. **2** and FIG. **9** to FIG. **17**, a description will be hereinafter given of the reaction analysis function (step S2 of FIG. **3**) that can be fulfilled by the reaction mechanism analysis unit **8** and the quantum chemistry calculation unit **7**.

[0123] In FIG. **9**, if elementary reaction routes that have not been evaluated exist at step S2-2, the reaction mechanism analysis unit **8** of the arithmetic processing device **3** creates a structure data pair of the product **31** and the reactant **32** in the elementary reaction route that have not been evaluated and structure data (transition state structure data) relative to a transition state in this elementary reaction route from the synthetic route data **15** previously read from the first storage device **4**. This transition state structure data is created by using the structure data pair consisting of the product **31** and the reactant **32** regardless of the presence or absence of a transition state in the elementary reaction route. For example, a mean value is taken from structure data about the product **31** and the reactant **32**, and is employed as transition state structure data. There is another conceivable method in which averaging is achieved by weighting a component of each structure

data without employing a mean value. In other words, based merely on a structural calculation, temporary structure data is calculated without determining whether a transition state exists in an elementary reaction route. A calculation for a transition-state-similar structure or for optimizing a structure to a transition state is performed by using such transition state structure data as described later.

[0124] The creation of calculation input data at step S**2**-**3** denotes that two-dimensional synthetic route data **15** is converted into three-dimensional data in order to perform a quantum chemical calculation or that a computer fixes an appointment in conformity with a calculation environment when a quantum chemical calculation is performed.

[0125] In the reaction analysis function fulfilled in the reaction mechanism analysis unit **8**, data relative to synthetic routes for performing a reaction analysis is obtained, and all elementary reaction routes that have not been evaluated are subjected to reaction analysis processing. Calculation input data **28** relative to structure data about the product **31**, about the reactants **32**, and about the transition state is created in an ASCII form in which keyword groups (data) necessary for three-dimensional structure coordinates and quantum chemical calculations are recorded. For example, wave function kind data (RHF, B3LYP, MP2, etc.) used for a quantum chemical calculation, base function kind data (6-31G*, LANL2DZ, etc.), and calculation type data (structural optimization, structural optimization to a transition state, an oscillation calculation, a mere energy calculation, etc.) are included in the keyword groups (data) necessary for a quantum chemical calculation.

[0126] FIG. **10** shows a calculation input data structure **33** of a calculation input file of ethyl 1-(N-((ethoxycarbonyl) methyl)-N-benzylcarbamoyl) cyclopropa necarboxylate, which is a product in the first stage of a Dieckmann condensation route, as an example of the calculation input data **28**.

[0127] In FIG. **10**, atomic symbols are shown on the extreme left, and three pieces of data on the right thereof respectively show coordinate points on the orthogonal coordinates based on a three-dimensional structure. The order from above is based on the order (number) of atoms arbitrarily specified by a user. Therefore, this order is not fixed, and may be appropriately determined by the user. The above-mentioned keyword group (data) necessary for a quantum chemical calculation is shown at the uppermost row. More specifically, "b3lyp" designates wave function data, and "6-31g" designates base function kind data. Additionally, "opt" designates data for a structural optimization calculation.

[0128] FIG. **11** is a conceptual diagram that three-dimensionally shows the calculation input data structure **33** of the calculation input file of the product in the first stage of the synthetic route in the Dieckmann condensation reaction shown in FIG. **10**. In FIG. **11**, reference numerals **34**, **35**, **36**, and **37** designate a nitrogen atom **34**, an oxygen atom **35**, a carbon atom **36**, and a hydrogen atom **37**, respectively.

[0129] Created calculation input data **28** is transmitted from the reaction mechanism analysis unit **8** to the quantum chemistry calculation unit **7** at step S**2**-**4**, and a calculation is performed by the quantum chemistry calculation unit **7** that has received the calculation input data **28** at step S**2**-**5**.

[0130] When the calculation performed by the quantum chemistry calculation unit **7** is completed, the quantum chemistry calculation unit **7** forms a calculation result file including the quantum chemistry calculation result data **26**. The quantum chemistry calculation result data **26** is created in an ASCII form including the output of a halfway calculation process and the like. An example of this quantum chemistry calculation result data **26** is shown in FIG. **12**. FIG. **12** is a conceptual diagram showing an archive part of the file of the quantum chemistry calculation result data of the product in the first stage of the synthetic route in the Dieckmann condensation reaction.

[0131] The quantum chemistry calculation result data **26** is stored in the second storage device **5** by the quantum chemistry calculation unit **7** as shown in FIG. **1**.

[0132] Thereafter, the quantum chemistry calculation unit **7** reads the quantum chemistry calculation result data **26** obtained as a result of a calculation from the second storage device **5**, and checks whether the transition state of a reaction exists in the elementary reaction route by use of calculation result data relative to transition states included in the quantum chemistry calculation result data **26** (step S**2**-**7**). If a transition state exists, an activation energy value and reaction heat in this transition state are calculated by use of calculation result data relative to transition states included in the quantum chemistry calculation result data **26**, calculation result data relative to reactants, and calculation result data relative to products (step S**2**-**8**), and are output as reaction analysis result data **16** (step S**2**-**10**).

[0133] If a transition state does not exist, the quantum chemistry calculation unit **7** regards this reaction as not progressing, and allows the output device **6** to output a signal showing that the reaction does not progress in the reaction analysis result data, and transmits information to a user by displaying its contents (step S**2**-**9**).

[0134] The reaction analysis result data **16** output therefrom is stored in the first storage device **4** in a table form. Data relative to two reaction analysis results corresponding to the first stage of Dieckmann condensation is shown in Table 1 as an example of this reaction analysis result data **16**. Step-**1** and Step-**2** included in Table 1 are common to the steps shown in FIG. **7**, respectively. Reaction analysis result data **16** relative to each step is shown in Table 1. Num designates a number to specify a transition state, Level designates a combination of the base function and the kind of the wave function used when a quantum chemical calculation is performed, Reac [a.u.] designates a value shown in each atom of all energy of the reactants **32**, Prod [a.u.] designates a value shown in each atom of all energy of the product **31**, Ea [kcal/mol] designates the activation energy of each transition state, and ΔE [kcal/mol] designates reaction heat before and after a transition state.

[0135] [Table 1]

[0136] FIG. **13** is a conceptual diagram obtained by visualizing Step-**1** of Table 1 of two pieces of reaction analysis data in the second stage of the synthetic route in a Dieckmann condensation reaction, and likewise, FIG. **14** is a conceptual diagram obtained by visualizing Step-**2** of two pieces of reaction analysis data in the second stage of the synthetic route in a Dieckmann condensation reaction.

[0137] The figure shows the fact that there are three transition states, i.e., a first transition state **42**, a second transition state **43**, and a third transition state **44** in the elementary reaction route shown at Step-**1** as also shown in Table 1, and the activation energy in each transition state is represented as activation energy **42***a*, activation energy **43***a*, and activation energy **44***a* in FIG. **13**.

[0138] Likewise, the figure shows the fact that there are four transition states, i.e., a first transition state **45**, a second transition state **46**, a third transition state **47**, and a fourth transition state **48** in the elementary reaction route shown at Step-**2** as shown in Table 1, and the activation energy in each transition state is represented as activation energy **45***a*, activation energy **46***a*, activation energy **47***a*, and activation energy **48***a* in FIG. **14**.

[0139] The above-mentioned reaction analysis is performed about all elementary reaction routes, and the reaction analysis function is ended.

[0140] As above, a description has been given of the reaction analysis function in the reaction mechanism analysis unit **8** of the synthetic route evaluation system **1** according to the embodiment with reference to the process flowchart of FIG. **9**. Next, a description will be provided of the quantum chemistry calculation function shown in step S**2**-**5** of FIG. **9** with reference to FIG. **15**.

[0141] FIG. **15** is a process flowchart of the quantum chemistry calculation function in the arithmetic processing device of the synthetic route evaluation system according to the embodiment. Processing with the quantum chemistry calculation function is performed in the quantum chemistry calculation unit **7** of the arithmetic processing device **3**. At step S**2**-**4** of FIG. **9**, the quantum chemistry calculation unit **7** that has received a transmission of the calculation input data **28** from the reaction mechanism analysis unit **8** reads calculation type data, coordinate data relative to the structure of the reactants **32** and that of the product **31** at step T**1**, and level data from the calculation input data **28**. As described above, the calculation type data is data relative to whether to perform calculations, such as an oscillation calculation or an energy calculation, in addition to a calculation relative to structural optimization or a calculation relative to the transition state search function. The level data is data in which the wave function data and the base function data mentioned above are combined with each other.

[0142] At step T**2**, while referring to the level data and the coordinate data relative to the structure of the reactants **32** and that of the product **31** read at step T**1** as a key, the quantum chemistry calculation unit **7** searches whether data has already been stored in the second storage device **5** as quantum chemistry calculation result data **26***a* having a similar optimized structure. If a similar optimized structure is found by this search, the quantum chemistry calculation unit **7** reads the quantum chemistry calculation result data **26***a* relative to the similar optimized structure from the second storage device **5**, and inputs the data to itself (step T**3**).

[0143] This quantum chemistry calculation result data **26***a* takes a data structure having a table form, and is stored in the second storage device **5**. An example of the quantum chemistry calculation result data **26***a* relative to a Dieckmann condensation reaction is shown in Table 2. Likewise, the same data as the calculation input data **28** is included in the quantum chemistry calculation result data **26***a*.

[0144] [Table 2]

[0145] Furthermore, the quantum chemistry calculation unit **7** calculates a difference between the structure of a reactant to execute the structural optimization included in the calculation input data **28** and the optimized structure of a similar reactant included in the quantum chemistry calculation result data **26***a*, and searches and recognizes its difference structure, i.e., the structure of a substituent (step T**4**). This difference is recognized by a difference in the number/type of atoms that are constituents of reactants included in the calculation input data **28** and in the quantum chemistry calculation result data **26***a* and by a difference in a connective relationship.

[0146] If the quantum chemistry calculation unit **7** recognizes a substituent lacking in a similar optimized structure at step T**4**, this substituent is given to the similar optimized structure (step T**5**). The number of substituents lacking therein is not limited to one, and is two or more in some cases. If the substituent is given, a part to which this substituent has been given will not have an optimized structure, and therefore only this part will be optimized. Accordingly, a difference with the optimized structure of the similar reactant is calculated, and, as a result, an analysis can be performed by giving a substituent, and therefore a very efficient analysis becomes possible.

[0147] Therefore, at step T**6**, the quantum chemistry calculation unit **7** fixes parts other than the part to which the substituent has been given as non-structurally-optimized parts, and specifies the part to which the substituent has been given as a structurally optimized part, and executes partial structural optimization by use of the structural optimization function built into the quantum chemistry calculation unit **7** (step T**7**).

[0148] The structure of atoms in the part to which the substituent has been given is optimized by performing a partial structural optimization calculation. The structural optimization is achieved by repeatedly performing an SCF (Self Consistent Field) calculation for obtaining all energy of the structure and an operation for changing the structure. The SCF calculation is a general method for a quantum chemical calculation performed to obtain all energy of the structure by use of a wave function and a base function. While calculating all energy with respect to a plurality of structures, a local minimum point of energy is calculated according to an energy gradient method based on a Newton algorithm, a Monte Carlo algorithm, etc. Optimization is achieved when this local minimum point is reached. In other words, the structural optimization calculation denotes the performance of the SCF calculation mentioned above, and the function for performing this series of calculations is called a structural optimization function in this claimed invention.

[0149] Thereafter, at step T**9**, the quantum chemistry calculation unit **7** reads calculation type data included in the calculation input data **28**, and draws a distinction between the calculation types. If the calculation type data is data relative to structural optimization, the process proceeds to step T**10**, at which a calculation for structural optimization is performed. A calculation result of the structural optimization is output at step T**19**, and is stored in the second storage device **5** by the quantum chemistry calculation unit **7** as quantum chemistry calculation result data **26**.

[0150] On the other hand, if the calculation type data is data relative to a transition state calculation, the process proceeds to step T**11**, at which a transition state calculation is performed.

[0151] At step T**11**, if a calculation for partial structural optimization has already been performed at step T**7** previous thereto, the process proceeds to step T**17**, at which transition-state-similar structure data is created without performing a search included in the transition state calculation. The reason is that, in this case, it is understood that a similar optimized structure has already existed, and a structural optimization calculation to a transition state has also been completed in this

similar optimized structure, and hence data (transition-state-similar structure data) relative to a structure similar to a transition state can be obtained when a partial structural optimization calculation is ended by giving a substituent. The transition-state-similar structure is not an optimized transition state structure, and denotes a structure at a stage previous to performing a calculation for optimization.

[0152] On the other hand, if the partial structural optimization calculation is not performed at step T**11**, the process proceeds to step T**12**, at which the quantum chemistry calculation unit **7** draws a distinction between transition state search methods. If the partial structural optimization calculation is not performed, the presence or absence of a transition state is not recognized, and hence transition-state-similar structure data has not yet been formed, and therefore transition-state-similar structure data is formed while searching for a transition state.

[0153] Examples of methods for searching for a transition state include a minimum energy path method, a contour map method, and a saddle method as mentioned at steps T**13** and T**14** of FIG. **15**. Among these methods, a minimum energy path calculation is performed at step T**13** according to the minimum energy path method and the contour map method, whereas a saddle calculation is performed at step T**14** according to the saddle method. These calculation methods are performed by use of functions, respectively, and each of the function is referred to as a transition state search function in this claimed invention. The quantum chemistry calculation unit **7** includes these transition state search functions built thereinto, and performs a calculation in such a manner as to substitute structure data relative to reactants and products in synthetic routes into these transition state search functions, and, as a result, obtains transition state structure data (transition-state-similar structure data) and data relative to the presence or absence of a transition state. This calculation method itself is already known well, and therefore the contents of the calculation are not especially described in this claimed invention.

[0154] The process proceeds from steps T**13** and T**14** to step T**15**, at which a minimum energy path calculation is performed once for two directions, i.e., is performed two times in total according to the contour map method, and, of course, it is possible to employ a flowchart having three situations divided into the above-mentioned minimum energy path method, the contour map method, and the saddle method, respectively.

[0155] If the contour map method is employed at step T**15**, a second minimum energy path calculation is performed at step T**16**, and, if the methods other than the contour map method are employed, the process proceeds to step T**17**. If the second minimum energy path calculation is performed at step T**16**, the process likewise proceeds to step T**17**.

[0156] A search for a transition state can be conducted by performing steps T**12** to T**16** and obtaining the result as described above. In other words, the presence or absence of a transition state can be determined.

[0157] If it is determined that a transition state exists, the quantum chemistry calculation unit **7** forms transition-state-similar structure data from the calculation result, then outputs this data as quantum chemistry calculation result data **26**, and stores the data in the second storage device **5**. The quantum chemistry calculation unit **7** may transmit the contents of the quantum chemistry calculation result data **26** to the output device **6** so as to be displayed, or may output the data to an external device.

[0158] Each transition state search method (transition state search function) is carried out, and, as a result, a plurality of structures each of which is expected to have a transition state are generated from a series of reactions from reactants to products, and all energy in each of the structures is calculated, and one of the structures having the highest energy is regarded as a transition-state-similar structure. Accordingly, coordinates of this transition-state-similar structure are obtained, and are used as calculation coordinates (step T**17**).

[0159] After obtaining the calculation coordinates as a transition-state-similar structure at step T**17**, the quantum chemistry calculation unit **7** performs a structural optimization calculation to a transition state at step T**18**. The contents of the structural optimization calculation are the same as described above. The calculation result is output at step T**19**, and may be displayed though the output device **6** as quantum chemistry calculation result data **26**, or may be output to an external device via the output device **6**. The quantum chemistry calculation unit **7** stores the quantum chemistry calculation result data **26** in the second storage device **5**.

[0160] In the embodiment, a structural optimization calculation is performed from transition state structure data (transition-state-similar structure data) at step T**18**, and, as a result of this calculation, it is possible to obtain transition state structure data with higher accuracy for the same calculation time or with the same accuracy for a shorter calculation time, and, in addition, it is possible to heighten the accuracy of a synthetic route evaluation. If simplification is allowed and if accuracy is ignored, quantum chemistry calculation result data **26** may be formed without performing a structural optimization calculation by use of transition state structure data (transition-state-similar structure data). However, if so, accuracy will become lower than at step T**18** as described above.

[0161] If a similar optimized structure does not exist in quantum chemistry calculation result data **26***a* at step T**2** of FIG. **15**, steps T**3** to T**8** are not executed, and the process proceeds to step T**9**, at which calculation type data is read from the calculation input data **28**, and a calculation type is determined.

[0162] Steps ranging from step T**3** to step T**9** are executed, and, as a result, a calculation time required for structural optimization or for a transition state search at the following steps can be shortened. In other words, the use of a similar optimized structure makes it possible to optimize only a part to which a substituent has been given and shorten a calculation time for the entire optimization.

[0163] As above, a description has been given of the quantum chemistry calculation function fulfilled by the quantum chemistry calculation unit **7** of the arithmetic processing device **3** at step S**2**-**5** of FIG. **9**. Referring back to FIG. **9**, the quantum chemistry calculation result data **26** obtained at step S**2**-**5** (step T**19** of FIG. **15**) is read by the reaction mechanism analysis unit **8** (step S**2**-**6**).

[0164] Whether a transition state exists is determined by searching for the transition state structure data in this quantum chemistry calculation result data **26** (step S**2**-**7**). If a transition state exists, the reaction mechanism analysis unit substitutes optimized reactant structure data, product structure data, and transition state structure data into the activation

energy calculation function built in itself, and calculates an activation energy value and/or a reaction heat value at step S2-8.

[0165] On the other hand, if a transition state does not exist, the reaction mechanism analysis unit 8 determines that a reaction does not progress, and records this fact onto the quantum chemistry calculation result data 26 (step S2-9).

[0166] Both of or either of the activation energy value and the reaction heat value calculated at step S2-8 is output by the reaction mechanism analysis unit 8 as a reaction analysis result at step S2-10, and the reaction analysis result data 16 is stored in the first storage device 4. If it is determined that a reaction does not progress at step S2-9, the process likewise proceeds to step S2-10, at which the fact that a reaction does not progress is output as a result, because there is no transition state. Although the reaction analysis result data 16 is stored in the first storage device 4, a signal may be output by the reaction mechanism analysis unit 8 to the output device 6 so as to display the contents of the reaction analysis result data 16, or may be transmitted to an external device.

[0167] The reason why a processing line for going up again to step S2-2 exists at step S2-10 is that processing in the reaction mechanism analysis unit 8 and the quantum chemistry calculation unit 7 gives consideration to a case in which there are a plurality of elementary reaction routes and that steps ranging from step S2-2 to step S2-10 are executed for all of the elementary reaction routes.

[0168] A description of the process up to step S2 of FIG. 2 is finished here.

[0169] Next, as shown in FIG. 2, it is determined at step S3 whether an evaluation by yields is required, thereafter the process flow of a yield prediction function is shown at step S4, thereafter it is determined at step S5 subsequent thereto whether an evaluation by side reactions is required, and the process flow of a side reaction prediction function is shown at step S6. In the synthetic route evaluation system 1, these functions are chosen and fulfilled, and the synthetic route ranking function is fulfilled at step S7, so that an evaluation of which synthetic route is most desirable is performed and output (step S8).

[0170] Next, step S4 of FIG. 2 mentioned above will be described with reference to FIG. 16.

[0171] FIG. 16 is a process flowchart of the reaction yield prediction function in the yield prediction unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0172] The yield prediction unit 9 of the arithmetic processing device 3 reads and obtains synthetic route data 15 from the first storage device 4 at step S4-1. Thereafter, whether an elementary reaction route whose yield has not yet been evaluated exists is searched (step S4-2). If it does not exist, a calculation for a predicted yield can be regarded as having already been ended, and therefore processing by the yield prediction unit 9 is ended in that state. A subsequent analysis can be efficiently carried out by pre-checking the presence or absence of an elementary reaction route that has not yet been evaluated at step S4-2.

[0173] On the other hand, if an elementary reaction route that has not yet been evaluated does not exist, a predicted yield is evaluated. The yield prediction unit 9 searches for yield prediction formula data 27 pre-stored in the second storage device 5, and inspects the existence of a yield prediction formula in a reaction relative to the synthetic route data 15 in the yield prediction formula data 27 (step S4-3).

[0174] If an elementary reaction route that has not yet been evaluated exists, the process proceeds to step S4-10, at which the yield prediction unit 9 reads the yield prediction formula, and substitutes a reactant and a structure data pair of the reactant into the formula, and, as a result, predicted yield data 17 is obtained by calculating the predicted yield. This predicted yield data 17 is stored in the first storage device 4 by the yield prediction unit 9. This data may be displayed via the output device 6, or may be output to an external device.

[0175] If a yield prediction formula is not present in the yield prediction formula data 27 in which the yield prediction formula is pre-stored at step S4-3, the yield prediction unit 9 reads and obtains reaction analysis result data 16 from the first storage device 4 at step S4-4. Thereafter, to determine the presence or absence of experimental data 25 relative to the same reaction as the elementary reaction route at step S4-5, the second storage device 5 is accessed, and the experimental data 25 pre-stored therein is searched. If the experimental data 25 is present therein, this experimental data 25 relative to the reaction of the elementary reaction route is read. Likewise, the existence of the yield prediction formula of a reaction is pre-checked at step S4-3, and therefore a subsequent analysis can be performed according to the presence or absence thereof, thus making it possible to perform an efficient analysis.

[0176] The experimental data 25 is stored in the form of a table. Herein, as one example, a part of the experimental data of a similar reaction relative to Dieckmann condensation is shown in Table 3. With respect to items arranged in a row herein, "Exp. Num." designates an experimental number, "Yield" designates an experimental yield, "Temp." designates an experimental temperature, "Time" designates an experimental time, "a" designates the initial concentration of a solute when an experiment starts, and "ϵ" designates the dielectric constant of a solvent.

[0177] [Table 3]

[0178] To perform a multivariate analysis when reaction analysis data and experimental data become ready to be used, the yield prediction unit 9 selects a predictive variable (step S4-7), and performs a multivariate analysis (step S4-8). It is recommended to pre-store this predictive variable in the second storage device 5 as apart of the yield prediction formula data 27.

[0179] On the other hand, if experimental data is not included in the experimental data 25 pre-stored at step S4-5 and if the same or similar experimental data exists in outside experimental data, the yield prediction unit 9 inputs the experimental data 25 from the outside experimental data at step S4-6, then likewise selects a predictive variable at step S4-7, and performs a multivariate analysis (step S4-8). It is recommended to allow a function relative to the multivariate analysis to be pre-included in the yield prediction formula data 27, or to be solely stored in the first storage device 4 or the second storage device 5 so that the yield prediction unit 9 reads and analyzes this function, or to be built in the yield prediction unit 9 itself. If experimental data 25 pre-stored therein does not exist, the same or similar experimental data is input to outside experimental data, and therefore a higher general-purpose analysis can be performed.

[0180] The yield prediction unit 9 constructs a yield prediction formula based on the result of the above-mentioned multivariate analysis (step S4-9). The yield prediction formula constructed based thereon depends on how the predictive variable is selected and depends on the multivariate

analysis result, and, for example, is expressed as follows. Herein, "Zcalc" designates a predicted yield, "E" designates the dielectric constant of a solvent obtained from experimental data, "t" designates a reaction time obtained from experimental data, "R" designates a gas constant, "T" designates a reaction temperature obtained from the experimental data **25**, "Ea" designates activation energy obtained from the reaction analysis result data **16**, and "A", "B", "C", and "D" designate constant values obtained from a multivariate analysis, respectively. The constructed yield prediction formula data **27** is stored in the second storage device **5** by the yield prediction unit **9**. The yield prediction unit **9** may display the data via the output device **6** or may output the data to an external device.

[0181] [Formula 1]

[0182] The yield prediction formula data **27** is stored in the form of a table. Herein, as one example, the yield prediction formula data **27** relative to four reactions including that of Dieckmann condensation is shown in Table 4.

TABLE 4

Number of terms
Constant A
Constant B
Constant C
Constant D
Product of A term
Product of B term
Product of C term
Product of D term

[0183] Thereafter, the yield prediction unit **9** predicts the yield of this reaction by use of the yield prediction formula data **27** (step S**4**-**10**). The predicted yield is stored in the first storage device **4** as predicted yield data **17**. The predicted yield data **17** is stored in the form of a table that shows a yield with respect to each elementary reaction route. Herein, as one example, the predicted yield data **17** relative to two routes that correspond to the first stage of Dieckmann condensation is shown in Table 5.

[0184] [Table 5]

[0185] When the yield prediction is completed with respect to all routes, the reaction yield prediction function is ended. In other words, when completed, step S**4** of FIG. **3** is ended.

[0186] Next, step S**6** of FIG. **2** mentioned above will be described with reference to FIG. **17**.

[0187] FIG. **17** is a process flowchart of the side reaction prediction function in the side reaction prediction unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0188] The side reaction prediction unit **10** obtains synthetic route data from the first storage device **4** at step S**6**-**1**. Thereafter, the presence or absence of an elementary reaction route in which a side reaction has not yet been evaluated is searched (step S**6**-**2**). If this elementary reaction route is absent, a calculation of the side reaction can be regarded as having already been ended, and therefore processing by the side reaction prediction unit **10** is ended in that state.

[0189] On the other hand, if an elementary reaction route that has not yet been evaluated does not exist, the side reaction is evaluated. The side reaction prediction unit **10** searches for the quantum chemistry calculation result data **26** pre-stored in the second storage device **5**, and the presence or absence of a similar reaction with respect to products and reactants in this quantum chemistry calculation result data **26** is searched (step S**6**-**3**). If a similar reaction is detected, it is determined that a side reaction exists (step S**6**-**4**), and a side reaction relative to a reaction of that elementary reaction route is constructed based on the similar reaction (step S**6**-**5**). A reaction analysis of the thus constructed side reaction is performed at step S**6**-**6**. This reaction analysis is the processing of step S**2** of FIG. **3**. The "construction" mentioned here denotes that the side reaction relative to the similar reaction is directly extracted as a side reaction of an elementary reaction route that is being analyzed.

[0190] It is determined at step S**6**-**7** whether an evaluation by yields is required. If required, processing by the yield prediction unit **9** is performed at step S**6**-**8** as already described with reference to FIG. **16**.

[0191] If the evaluation of a yield at step S**6**-**8** is ended and if an evaluation by yields at step S**6**-**7** is not performed, the side reaction prediction unit **10** outputs the constructed side reaction (step S**6**-**10**), and stores this in the first storage device **4** as predicted side reaction data **18**. The side reaction prediction unit **10** may display the predicted side reaction data **18** via the output device **6** or may transmit this data to an external device.

[0192] If there is no similar reaction at step S**6**-**4**, the process proceeds to step S**6**-**9**, at which the side reaction prediction unit **10** determines that there is no side reaction, and the process proceeds to step S**6**-**10**. Herein, a result to the effect that there is no side reaction is output as a piece of information, and is likewise stored in the first storage device **4** as predicted side reaction data **18**. In the same way as above, the predicted side reaction data **18** may be displayed via the output device **6** or may be transmitted to an external device.

[0193] If the number of side reactions and a yield prediction about the side reactions are analyzed, data relative to the predicted yield about the side reactions is also included in the predicted side reaction data **18**.

[0194] FIG. **18** is a process flowchart of the synthetic route ranking function in the synthetic route ranking unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0195] The synthetic route ranking unit **11** of the arithmetic processing device **3** reads and obtains synthetic route data **15** from the first storage device **4** at step S**7**-**1**. Thereafter, reaction analysis result data **16** is read and obtained from the first storage device **4** at step S**7**-**2**.

[0196] At step S**7**-**3**, the synthetic route ranking unit **11** accesses the first storage device **4** and searches for the presence or absence of predicted yield data **17**. If predicted yield data **17** exists, the predicted yield data **17** is read and obtained from the first storage device **4** at step S**7**-**4**.

[0197] Furthermore, if it is understood that the predicted yield data **17** does not exist at step S**7**-**3** or if the predicted yield data **17** has been obtained at step S**7**-**4**, the process proceeds to step S**7**-**5**, at which the first storage device **4** is accessed, and the presence or absence of predicted side reaction data **18** is searched.

[0198] If the predicted side reaction data **18** exists, the predicted side reaction data **18** is read and obtained from the first storage device **4** at step S**7**-**6**.

[0199] Furthermore, if it is understood that the predicted side reaction data **18** does not exist at step S**7**-**5** or if the predicted side reaction data **18** has been obtained at step S**7**-**6**, the process proceeds to step S**7**-**7**, at which the first storage device **4** is accessed, and the presence or absence of supplementary item data **19** is searched.

[0200] If the supplementary item data **19** exists, the supplementary item data **19** is read and obtained from the first storage device **4** at step S**7**-**8**.

[0201] If it is understood that the supplementary item data **19** does not exist at step S**7**-**7** or if the supplementary item data **19** has been obtained at step S**7**-**8**, the process proceeds to step S**7**-**9**, at which a question of whether the output by ranking is required is displayed via the output device **6** in order to ask a user about determination whether the output by ranking is performed, and the input, which is performed by the user via the input device **2**, of a signal about whether the output by ranking is required is awaited. Of course, at the steps previous to step S**7**-**1**, a question about whether the output by ranking is required may be pre-input via the input device **2** of the synthetic route evaluation system **1** in the form of some data, and data relative to whether the output by ranking is required may be automatically read, and it may be determined whether the output by ranking is required at step S**7**-**9**.

[0202] If the synthetic route ranking unit **11** receives a signal (information) to perform the output in some form at step S**7**-**9**, the selection ratio of a priority item about which one of the reaction analysis result data **16**, the predicted yield data **17**, the predicted side reaction data **18**, and the supplementary item data **19** is weighted (i.e., is highly valued) is displayed via the output device **6** so as to be arbitrarily input via the input device **2** (step S**7**-**10**). Thereafter, points for ranking are calculated including the selection ratio of weight input by the user via the input device **2** at step S**7**-**11**. The selection ratio of the weight can, of course, be freely selected in the predicted yield data **17**, the predicted side reaction data **18**, and the supplementary item data **19** other than the reaction analysis result data **16**, and hence there is a case in which that is not selected. In that case, the synthetic route ranking unit **11** is not required to display the item at step S**7**-**10**.

[0203] The supplementary item data **19** is appropriately added by the user, and is pre-stored in the first storage device **4**. This makes it possible for the user to add a user's own evaluation item for an elementary reaction route and to reflect it in the ranking. The supplementary item data is input in the form of a table in which items are arranged in a row whereas each route is arranged in the column. Herein, as one example of the supplementary item data **19**, FIG. **19** shows a data example in which the price of a synthesis starting substance is given to each route of 5-Benzyl-5-aza-spiro[2.4] heptane[4. 7]-dione that is a product **31** as a supplementary item. There is a case in which the number of the supplementary item is two or more, and, in this case, each item can be individually weighted.

[0204] FIG. **19** is a conceptual diagram that shows data relative to supplementary items added at the processing of the synthetic route ranking function in the synthetic route ranking unit of the arithmetic processing device of the synthetic route evaluation system according to the embodiment.

[0205] Finally, at step S**7**-**11**, obtained values are changed into points for each reaction route by use of Ranking Formula (2) shown below. Herein, "Ps" designates ranking points, "B" designates a highest point (bias value), "n" designates the number of evaluation items including the supplementary item, "W" designates the entire weight expressed by Formula (3), "Wi" designates the weight (selection ratio) of an evaluation item, "S" designates the number of synthetic routes, and "Ri" designates the ranking in the evaluation items, which is expressed by natural number 1 or greater and in which 1 is the highest in the ranking. Of course, Formulas (2) and (3) are examples, and, without being limited to Formulas (2) and (3), other formulas may be employed as long as these formulas can perform ranking including the reaction analysis result data **16**, the predicted yield data **17**, the predicted side reaction data **18**, and the supplementary item data **19**. The ranking formula may be pre-installed in the synthetic route ranking unit **11** including the weight function, or may be pre-stored in the first storage device **4** or the second storage device **5**, so that the synthetic route ranking unit **11** reads the ranking formula, and a calculation is performed in such a manner as to substitute the pieces of data **16** to **19** thereinto.

[0206] [Formula 2]

[0207] [Formula 3]

[0208] Ranking among the evaluation items is performed such that low reaction heat (ΔE) in total is ranked as being high in the reaction analysis data, and a high predicted yield is ranked as being high in the predicted yield data, and a side reaction small in number is ranked as being high in the side reaction prediction. However, these can be changed into desired order according to the setting by the user. The supplementary item of the user is ranked by the setting arranged by the user. Data in which ranking points have been calculated is stored in the form of a table as route ranking data. Herein, as one example thereof, route ranking data is shown in Table in which a product **31** is 5-Benzyl-5-aza-spiro[2.4]heptane[4. 7]-dione. In Table 6, the product **31** is shown, and factors based on which ranking is performed and ranking points are orderly shown according to the kind of each reaction route, such as a Dieckmann condensation reaction. However, reactants **32** may be shown instead of the kind of each reaction route.

[0209] [Table 6]

[0210] If processing in which the output by ranking is not performed is selected at step S**7**-**9**, the process proceeds to step S**7**-**12**, at which the synthetic route ranking unit **11** does not perform a ranking display. However, the synthetic route data **15**, the reaction analysis result data **16**, the predicted yield data **17**, and the predicted side reaction data **18**, each of which has been selected until then, and the supplementary item data **19**, which will be not-ranked data if selected, are included in the route ranking data **20** to be shown as user's evaluation and judging material. Thereafter, the ranking operation is ended.

[0211] As a data set, the route ranking data **20** is set with data relative to activation energy and/or reaction heat included in the selected reaction analysis result data **16** along with reactants and/or products included in the synthetic route data **15**, or is set with the predicted yield data **17**, or is set with the predicted side reaction data **18**.

[0212] If ranking points are calculated at step S**7**-**11**, the synthetic route ranking unit **11** creates route ranking data **20**. This data is arranged as a data set in which ranking points are included in addition to data relative to activation energy and/or reaction heat included in the selected reaction analysis result data **16** along with reactants and/or products included in the above-mentioned synthetic route data **15**, or in addition to the predicted yield data **17**, or in addition to the predicted side reaction data **18**.

[0213] In this embodiment, in the synthetic route ranking unit **11**, the predicted yield data **17**, the predicted side reaction data **18**, the supplementary item data **19**, etc., are selectively added to activation energy and/or reaction heat, and, based on the result, ranks can be shown according to a desired idea while performing weighting, and therefore synthetic routes

can be evaluated from various viewpoints, and an optimal synthetic route can be extracted.

[0214] Additionally, structural optimization is performed by use of structure data relative to transition states, and, as a result, it is possible to optimize not only structure data relative to reactants and products but also structure data relative to transition states, and therefore a quantum chemical calculation can be performed with higher accuracy for the same calculation time, or can be performed for a shorter calculation time with the same accuracy.

[0215] The synthetic route evaluation system according to this embodiment has been described as above, and, on the assumption that the system of FIG. **1** is a general-purpose computer and that a program for operating this computer is run in the manner of flowcharts shown in FIG. **3**, FIG. **4**, FIG. **9**, and FIG. **15** to FIG. **18**, the above description can be regarded as a description of an embodiment of a synthetic route evaluation method for evaluating an optimal synthetic route while the computer executes each step, and, at the same time, as a description of an embodiment of a program for operating the computer.

INDUSTRIAL APPLICABILITY

[0216] As described above, the invention according to claim **1** to claim **8** of the present invention can be used in the pharmaceutical field or the chemical field in which a new compound is synthetically produced widely and generally for new drug development or for agricultural chemical development.

[FIG. 1]

[0217] **2** Input device
[0218] **4** First storage device
[0219] **15** Synthetic route data
[0220] **16** Reaction analysis result data
[0221] **17** Predicted yield data
[0222] **18** Predicted side reaction data
[0223] **19** Supplementary item data
[0224] **20** Route ranking data
[0225] **3** Arithmetic processing device
[0226] **7** Quantum chemistry calculation unit
[0227] **8** Reaction mechanism analysis unit
[0228] **9** Yield prediction unit
[0229] **10** Side reaction prediction unit
[0230] **11** Synthetic route ranking unit
[0231] **5** Second storage device (data base)
[0232] **25** Experimental data
[0233] **26** Quantum chemistry calculation result data
[0234] **27** Yield prediction formula data
[0235] **6** Output device

[FIG. 2]

[0236] **16** Reaction analysis result data
[0237] **2** Reaction analysis function
[0238] **19***a* Route supplementary item data by user
[0239] **15***a*, **15***b* Synthetic route group according to user idea or SRDS idea
[0240] **1** Quantum chemistry calculation function
[0241] **19** Supplementary item data
[0242] **6** Synthetic route input/output function
[0243] **15** Synthetic route data
[0244] **26** Quantum chemistry calculation result data
[0245] **5** Synthetic route ranking function
[0246] **18** Predicted side reaction data
[0247] **3** Yield prediction function
[0248] **27** Yield prediction formula data
[0249] **25** Experimental data
[0250] **20** Route ranking data
[0251] **20***a* Already-ranked synthetic route group
[0252] **4** Side reaction prediction function
[0253] **17** Predicted yield data
[0254] **25***a* Outside experimental data

[FIG. 3]

[0255] Start
[0256] S**1** Synthetic route input/output function (input)
[0257] S**2** Reaction analysis function
[0258] S**3** Evaluation by yield added?
[0259] Yes
[0260] No
[0261] S**4** Yield prediction function
[0262] S**5** Evaluation by side reaction added?
[0263] Yes
[0264] No
[0265] S**6** Side reaction prediction function
[0266] S**7** Synthetic route ranking function
[0267] S**8** Synthetic route input/output function (output)
[0268] End

[FIG. 4]

[0269] Start
[0270] S**1-1** Input or output of route?
[0271] Output
[0272] Input
[0273] **15** Synthetic route data
[0274] S**1-8** Obtain synthetic route data
[0275] **20** Route ranking data
[0276] S**1-9** Obtain ranking data
[0277] **6** Output device
[0278] S**1-10** Output already-ranked synthetic route
[0279] S**1-2** Input method of user synthetic route data?
[0280] Direct input
[0281] S**1-3** Input synthetic route data
[0282] **15***a* User synthetic route data
[0283] Input from SRDS
[0284] S**1-4** Connect to SRDS
[0285] S**1-5** Receive synthetic route data
[0286] **15***b* SRDS synthetic route data
[0287] S**1-6** Resolve synthetic route into elementary reactions
[0288] **15** Synthetic route data
[0289] S**1-7** Output synthetic route (elementary reaction)
[0290] End

[FIG. 9]

[0291] Start
[0292] **15** Synthetic route data
[0293] S**2-1** Obtain synthetic route data
[0294] S**2-2** Is there an elementary reaction route that has not yet been evaluated?
[0295] Yes
[0296] No
[0297] S**2-3** Create calculation input data (transition state/product/reactant)
[0298] S**2-4** Output calculation input data and input to quantum chemistry calculation function

[0299] **28** Calculation input data
[0300] S**2-5** Quantum chemistry calculation function
[0301] **26** Quantum chemistry calculation result data
[0302] S**2-6** Obtain calculation result data
[0303] S**2-7** Transition state exist?
[0304] Yes
[0305] No
[0306] S**2-8** Calculate activation energy value and reaction heat value
[0307] S**2-9** Record that a reaction does not progress
[0308] S**2-10** Output reaction analysis result
[0309] **16** Reaction analysis result data
[0310] End

[FIG. 15]

[0311] Start
[0312] **28** Calculation input data
[0313] T**1** Input calculation type/coordinates/level
[0314] **26***a* Quantum chemistry calculation result data (similar structure)
[0315] T**2** Similar optimized structure exist?
[0316] Yes
[0317] No
[0318] T**3** Automatically input optimized structure
[0319] T**4** Recognize difference structure (substituent)
[0320] T**5** Give substituent
[0321] T**6** Fix non-structurally-optimized part
[0322] T**7** Perform partial structural optimization calculation
[0323] T**8** Release non-structurally-optimized part from being fixed
[0324] T**9** Determine calculation type
[0325] Structural optimization
[0326] Transition state calculation
[0327] T**10** Perform structural optimization calculation
[0328] **26** Quantum chemistry calculation result data
[0329] T**11** Partial structural optimization performed?
[0330] Yes
[0331] No
[0332] T**12** Determine transition state search method
[0333] Minimum energy path method, Contour map method
[0334] T**13** Perform minimum energy path calculation
[0335] Saddle method
[0336] T**14** Perform saddle calculation
[0337] T**15** Contour map method?
[0338] Yes
[0339] No
[0340] T**16** Perform minimum energy path calculation (second time)
[0341] T**17** Create transition state similar structure (calculation coordinates)
[0342] T**18** Perform structural optimization calculation to transition state
[0343] T**19** Output calculation result
[0344] End

[FIG. 16]

[0345] Start
[0346] **15** Synthetic route data
[0347] S**4-1** Obtain synthetic route data
[0348] S**4-2** Is there an elementary reaction route that has not yet been evaluated?
[0349] Yes
[0350] No
[0351] S**4-3** Yield prediction formula of reaction exist?
[0352] Yes
[0353] No
[0354] **16** Reaction analysis result data
[0355] S**4-4** Obtain calculation result data
[0356] **25** Experimental data
[0357] S**4-5** Experimental data exist?
[0358] Yes
[0359] No
[0360] **25** Experimental data
[0361] S**4-6** Input outside experimental data
[0362] S**4-7** Select predictive variable
[0363] S**4-8** Perform multivariate analysis
[0364] S**4-9** Construct yield prediction formula
[0365] **27** Yield prediction formula data
[0366] **17** Predicted yield data
[0367] S**4-10** Calculate predicted yield
[0368] End

[FIG. 17]

[0369] Start
[0370] **15** Synthetic route data
[0371] S**6-1** Obtain synthetic route data
[0372] S**6-2** Is there an elementary reaction route that has not yet been evaluated?
[0373] Yes
[0374] No
[0375] **26** Quantum chemistry calculation result data
[0376] S**6-3** Search for similar reaction with respect to product/reactant
[0377] S**6-4** Similar reaction exist?
[0378] Yes
[0379] No
[0380] S**6-5** Construct side reaction based on similar reaction
[0381] S**6-6** Fulfill reaction analysis function
[0382] S**6-7** Evaluation by yield added?
[0383] Yes
[0384] No
[0385] S**6-8** Fulfill yield prediction function
[0386] S**6-9** Determine that there is not a side reaction
[0387] S**6-10** Output predicted side reaction
[0388] **18** Predicted side reaction data
[0389] End

[FIG. 18]

[0390] Start
[0391] **15** Synthetic route data
[0392] S**7-1** Obtain synthetic route data
[0393] **16** Reaction analysis result data
[0394] S**7-2** Obtain reaction analysis result data
[0395] S**7-3** Predicted yield data exist?
[0396] Yes
[0397] No
[0398] **17** Predicted yield data
[0399] S**7-4** Obtain predicted yield data
[0400] S**7-5** Side reaction prediction data exist?
[0401] Yes
[0402] No
[0403] **18** Predicted side reaction data
[0404] S**7-6** Obtain side reaction prediction data

[0405] S7-7 Supplementary item input by user?
[0406] Yes
[0407] No
[0408] **19** Supplementary item data
[0409] S7-8 Input/record supplementary item
[0410] S7-9 Output by ranking performed?
[0411] Yes
[0412] No
[0413] S7-10 Set selection ratio of weighted item
[0414] S7-11 Calculate ranking points with respect to each synthetic route
[0415] **20** Route ranking data
[0416] S7-12 No ranking
[0417] End

[FIG. 19]

[0418] Route
[0419] Synthesis starting substance
[0420] Structural formula
[0421] Price (¥)

1. A synthetic route evaluation system comprising:
in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced,
an arithmetic processing means including a quantum chemistry calculation unit, a reaction mechanism analysis unit, and a synthetic route ranking unit; and
a storage means for storing data (hereinafter, referred to as synthetic route data relative to the synthetic routes;
wherein the synthetic route data is composed of structure data pairs the number of which is equal to the number of precursors from which the target compound can be synthetically produced,
wherein the structure data pairs are formed by correlating structure data relative to the target compound and structure data relative to the plurality of starting compounds with each other;
wherein the quantum chemistry calculation unit executes:
a step of reading the synthetic route data from the storage means, then performing a calculation in such a manner as to substitute the structure data relative to the starting compounds and the target compound into a structural optimization function, and obtaining structure data relative to the starting compounds structurally optimized and structure data relative to the target compound structurally optimized; and
a step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function, and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data (**26**) relative to the transition state under the condition of the presence of the transition state;
wherein the reaction mechanism analysis unit executes a step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key from the storage means, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and
wherein the synthetic route ranking unit executes a step of setting the activation energy and/or the reaction heat calculated while being correlated with the plurality of starting compounds as a key, and creating a data set in which the activation energy and/or the reaction heat are arranged in desired order along with the starting compounds and/or the target compound.

2. The synthetic route evaluation system according to claim **1**,
wherein the quantum chemistry calculation unit executes a step of performing a calculation in such a manner as to substitute the structure data relative to the transition state into the structural optimization function and obtaining structure data relative to a transition state structurally optimized, and
wherein the reaction mechanism analysis unit performs a calculation in such a manner as to substitute the structure data relative to a transition state structurally optimized into the activation energy calculation function.

3. The synthetic route evaluation system according to claim **1**,
wherein the arithmetic processing means includes a yield prediction unit,
wherein the yield prediction unit executes a step of, if there is a yield prediction formula pre-stored in the storage means, reading the yield prediction formula, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data into the yield prediction formula, and obtaining a predicted yield of each starting compound, or executes a step of, if there is not a yield prediction formula pre-stored in the storage means, reading experimental data relative to a reaction similar to a reaction caused to synthetically produce a target compound from the starting compounds stored in the storage means, then analyzing the yield prediction formula by use of a result of the experimental data, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data into the analyzed yield prediction formula, and obtaining a predicted yield of the starting compound, and
wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds is arranged in desired order along with the starting compounds and/or the target compound while setting the activation energy and/or the reaction heat as a key or setting the predicted yield as a key.

4. The synthetic route evaluation system according to claim **3**, wherein the arithmetic processing means includes a side reaction prediction unit,
wherein the side reaction prediction unit executes a step of searching for data relative to a similar reaction prestored in the storage means while setting the target compound and the starting compounds as a key, and defining and constructing a reaction similar to a synthetic route relative to a combination of the target compound and the starting compounds as a side reaction, and
wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds or the predicted yield or the number of the side reactions is set as a key and is arranged in desired order along with the starting compounds and/or the target compound.

5. The synthetic route evaluation system according to claim 4,

wherein the arithmetic processing means includes a side reaction prediction unit,

wherein the side reaction prediction unit executes a step of searching for data relative to a similar reaction pre-stored in the storage means while setting the target compound and the starting compounds as a key, and defining and constructing a reaction similar to a synthetic route relative to a combination of the target compound and the starting compounds as a side reaction,

wherein the yield prediction unit executes a step of obtaining a predicted yield with respect to the target compound and the starting compounds in the constructed side reaction, and

wherein the synthetic route ranking unit a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds, or the predicted yield, or the number of the side reactions, or the predicted yield of the side reaction is set as a key and is arranged in desired order along with the starting compounds and/or the target compound.

6. The synthetic route evaluation system according to claim 1 characterized by further comprising an output means for outputting the data set created by the synthetic route ranking unit.

7. A synthetic route evaluation method for, in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced while a computer performs each step, analyzing data (hereinafter, referred to as synthetic route data) relative to the synthetic routes, transition states halfway along the synthetic routes, and activation energy relative to the transition states, and evaluating the optimal synthetic route, the synthetic route evaluation method comprising:

a first quantum chemical calculation step of performing a calculation in such a manner as to substitute structure data relative to the target compound included in the synthetic route data and structure data relative to a plurality of starting compounds from which the target compound can be synthetically produced into a structure optimizing function, and obtaining structure data relative to the starting compounds structurally optimized and structure data relative to the target compound structurally optimized;

a second quantum chemical calculation step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function, and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data relative to the transition state under the condition of the presence of the transition state;

a reaction analysis step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and

a synthetic route ranking step of setting the activation energy and/or the reaction heat calculated in correlation with the plurality of starting compounds as a key and creating a data set in which the activation energy and/or the reaction heat is arranged in desired order along with the starting compounds and/or the target compound.

8. A synthetic route evaluation program for, in order to extract an optimal synthetic route from a plurality of synthetic routes for a target compound to be synthetically produced by use of a computer, analyzing data (hereinafter, referred to as synthetic route data) relative to the synthetic routes, transition states halfway along the synthetic routes, and activation energy relative to the transition states, and evaluating the optimal synthetic route, the synthetic route evaluation program allowing the computer to perform:

a first quantum chemical calculation step of performing a calculation in such a manner as to substitute structure data relative to the target compound included in the synthetic route data and structure data relative to a plurality of starting compounds from which the target compound can be synthetically produced into a structure optimizing function, and obtaining structure data relative to the starting compounds structurally optimized and structure data relative to the target compound structurally optimized;

a second quantum chemical calculation step of performing a calculation in such a manner as to substitute the structure data relative to the starting compounds structurally optimized and the structure data relative to the target compound structurally optimized into a synthetic-route transition state search function, and obtaining data relative to the presence or absence of a transition state in the synthetic routes and structure data relative to the transition state under the condition of the presence of the transition state;

a reaction analysis step of setting data relative to whether a transition state is present or absent in the synthetic routes as a key, and, if a transition state is present, performing a calculation in such a manner as to substitute structure data relative to the transition state into an activation energy calculation function, and obtaining activation energy and/or reaction heat in the transition state; and

a synthetic route ranking step of setting the activation energy and/or the reaction heat calculated in correlation with the plurality of starting compounds as a key, and creating a data set in which the activation energy and/or the reaction heat is arranged in desired order along with the starting compounds and/or the target compound.

9. The synthetic route evaluation system according to claim 2, wherein the arithmetic processing means includes a yield prediction unit,

wherein the yield prediction unit executes a step of, if there is a yield prediction formula pre-stored in the storage means, reading the yield prediction formula, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data into the yield prediction formula, and obtaining a predicted yield of each starting compound, or executes a step of, if there is not a yield prediction formula pre-stored in the storage means, reading experimental data relative to a reaction similar to a reaction caused to synthetically produce a target compound from the starting compounds stored in the storage means, then analyzing the yield prediction formula by use of a result of the experimental data, then performing a calculation in such a manner as to substitute the structure data pairs of the synthetic route data

into the analyzed yield prediction formula, and obtaining a predicted yield of the starting compound, and

wherein the synthetic route ranking unit executes a step of creating a data set in which activation energy and/or reaction heat calculated in correlation with the plurality of starting compounds is arranged in desired order along with the starting compounds and/or the target compound while setting the activation energy and/or the reaction heat as a key or setting the predicted yield as a key.

10. The synthetic route evaluation system according to claim **2** further comprising an output means for outputting the data set created by the synthetic route ranking unit.

11. The synthetic route evaluation system according to claim **3** further comprising an output means for outputting the data set created by the synthetic route ranking unit.

12. The synthetic route evaluation system according to claim **4** further comprising an output means for outputting the data set created by the synthetic route ranking unit.

13. The synthetic route evaluation system according to claim **5** further comprising an output means for outputting the data set created by the synthetic route ranking unit.

* * * * *