

Chapter 4 CONFLEX5 Keyword Options

With CONFLEX5, detailed information about geometrically optimized molecular structures and conformational space search is available. Otherwise, physical analysis for normal vibrations, thermodynamic quantities, ultraviolet and visible light spectrum, circular dichroism spectrum and NMR coupling constants can be done while taking multiple conformations into consideration. The outputted calculation results of CONFLEX5 can be analyzed using the graphical user interface BARISTA.

The standard setting alone cannot implement all the features of CONFLEX5, and neither can all the features be utilized. In order to take advantage of the many features in CONFLEX5, a configuration file must be prepared containing the password to corresponding functions. In order to do so, it is necessary to understand the keywords setting the optional functions in CONFLEX5.

Initial setting file is created using text documents. As for the keyword type, it is necessary to define only the keyword, or the optional setting value. For example,

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MMFF CONFLEX SEL=1.0D0
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Under option, there is a keyword that can assign multiple options. For example,

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MMFF DEBUG=(HYBRID,CLASS0,EVAL)
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In doing so, no spaces can be included in the parenthesis. If multiple options are assigned for a keyword that usually displays only one option, it is undetermined which option will function.

The keywords and its contents to be used in CONFLEX5 are listed below. However, keywords marked with (*) are currently being developed, thus please keep in mind that they are not guaranteed to function correctly.

4.1 Keyword

4.1.1 Force field setup keyword

Keyword	Option	Description
EMM2		Extended MM2 force field is used for calculation.
MM2(*)		MM2 force field is used for calculation.
MM3(*)		MM3(92) force field is used for calculation.
MMFF MMFF94		MMFF94 force field is used for calculation.
MMFF94S		MMFF94s force field is used for calculation.(Default)

4.1.2 Geometry optimization keyword

Keyword	Option	Description
OPT=	<i>STEEPD</i> <i>CONGRD</i> <i>VARMET</i> <i>NEWTON</i> <i>NONE</i>	Geometry optimization method. - steepest decent method (STEEPD) - conjugate gradient method (CONGRD) - variable metric (VARMET) - full-matrix Newton-Raphson method (NEWTON) Default is the full-matrix Newton-Raphson method (NEWTON). In the case of "OPT=NONE", only energy calculation will be performed for the input structure. Example : OPT=VARMET
OPTBY=	<i>ENERGY</i> <i>GRADIENT</i>	Objective function to be minimized during geometry optimization. Default is ENERGY. Example : OPTBY=GRADIENT
TG=	<i>ff.ff</i>	Gradient threshold for pre-optimization (steepest decent Method). By default TG is set to 5.0 kcal·mol ⁻¹ ·Å ⁻¹ . Example : TG=2.5
GCVNRG=	<i>ff.ff</i>	Threshold of gradient convergence for geometry optimization. By default GCVNRG is set to 1.0E-6 kcal·mol ⁻¹ ·Å ⁻¹ . Example : GCVNRG=1.0E-5

XCNVRG=	<i>ff.ff</i>	Threshold of atom displacement convergence for geometry optimization. By default XCNVRG is set to $1.0E-6 \text{ kcal} \cdot \text{mol}^{-1} \cdot \text{Å}^{-1}$. Example : XCNVRG=1.0E-5
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4.1.3 CONFLEX conformation space search keyword

Keyword	Option	Description
CONFLEX		Conformation search will be performed.
SEL=	<i>ff.ff</i>	The value of "SEL" defines the search limit that controls the range from which the initial structures are selected. If the value of "SEARCH" is "ENERGY", the search limit is defined in kcal/mol, and if "BOLTZ", the search limit is defined in % population according to Boltzmann distribution. By default, this value is set to 1.0kcal/mol, namely, the corresponding keywords as follows: Example : SEL=1.0D0 SEARCH=ENERGY See also "SEARCH="
SEARCH=	<i>ENERGY</i> <i>BOLTZ</i>	Definition of the evaluation unit for the search limit. If the value of "SEARCH=" is "ENERGY", the search limit is defined in kcal/mol, and if "BOLTZ", the search limit is defined in % population according to Boltzmann distribution. By default, this value is set to ENERGY. See also "SEL=". Example : SEARCH=ENERGY
MAXINIT=	<i>n</i>	Number of the initial structures that are used at a generating process of trial structures. Example : MAXINIT=120
MAXCYCLE=	<i>n</i>	Number of search cycles is fixed. In general, the number of search cycles can not defined by user, because of SEL value control (see "SEL="). This keyword, that forcibly sets the limit of search cycles, should be used only for evaluating an time-consuming of the practical conformation search. Example : MAXCYCLE=1
FLIP		If the edge-flipping perturbation is possible, it will be performed.
NOFLIP		The edge-flipping perturbation is prohibited, even if it is possible.

NOFLIP=	<i>n</i>	Number of prohibited flipping bonds is defined. This keyword is very useful if some parts of the target molecular structure will be fixed. This option must be combined with "XFLIP=" option. It may also be combined with "NOFLAP=" option
XFLIP=	<i>(n,m)</i>	Two atom numbers of bonded (connected) atoms to be prohibited during the edge flipping perturbation. Example : NOFLAP=2 NOFLIP=3 XFLAP=1 XFLIP=(7,1) XFLAP=2 XFLIP=(1,2) XFLIP=(2,3)
FLAP		If the corner-flapping perturbation is possible, it will be performed.
NOFLAP		The corner-flapping perturbation is prohibited, even if it is possible.
NOFLAP=	<i>n</i>	Number of prohibited flapping atoms is defined. This keyword is very useful if some parts of the target molecular structure will be fixed. This option must be combined with "XFLAP=" option. It may also be combined with "XFLIP=" option.
XFLAP=	<i>n</i>	The atom number to be fixed during the corner flapping perturbation. Example : NOFLAP=3 NOFLIP=2 XFLAP=25 XFLIP=(25,26) XFLAP=26 XFLIP=(26,29) XFLAP=29
SROT		If the stepwise rotation perturbation is possible, it will be performed.
NOSROT		The stepwise rotation perturbation is prohibited, even if it is possible.
NOSROT=	<i>n</i>	Number of prohibited rotational bonds is defined. This keyword is very useful if some parts of the target molecular structure will be fixed. This option must be combined with "XSROT=" option.
XSROT=	<i>(n,m)</i>	Specifies 2 atom numbers bonded (connected). The rotation around the bond connecting these 2 atoms to be fixed during stepwise rotation perturbation. Example : NOSROT=1 XSROT=(5,7)
TROT (*)		If the thermal rotation perturbation is possible, it will be performed.

NOTROT (*)		The thermal rotation perturbation is prohibited, even if it is possible.
NOTROT= (*)	<i>n</i>	Number of prohibited rotational bonds is defined. This keyword is very useful if some parts of the target molecular structure will be fixed. This option must be combined with "XTROT=" option.
XTROT= (*)	<i>(n,m)</i>	Specifies 2 atom numbers bonded. The rotation around the bond connecting these 2 atoms to be fixed during stepwise rotation perturbation. Example : NOTROT=1 XTROT=(3,7)
CHECK=	<i>XCORD</i> <i>TORSION</i> <i>MOMENT</i> <i>NOENERGY</i>	This keyword defines the conformational similarity indices. In conformational space search, the program must check the conformation redundancy of the newly optimized structures with the already-known structures stored in conformation database. In CONFLEX5, the potential energy values are always used in this purpose, because the severe full-matrix Newton optimization can reach to $1.0\text{D-}6 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{Å}^{-1}$. In scarce cases, however, the energy does not work enough for the correct distinction of conformation. That is why the following similarity indices are prepared for the additional comparison between two conformers: <i>XCORD</i> : the difference of the molecular coordinates that are reoriented to a standard orientation based on the moment of inertia, is directly compared. <i>TORSION</i> : the sum of Root-mean-square differences in the corresponding pair of torsion angles of skeleton bonds is compared. <i>MOMENT</i> : the difference of the axis components in the moment of inertia is compared. <i>NOENERGY</i> : those additional comparisons without the potential energy comparison are performed. Otherwise, the energy check is always performed. Example : CHECK=TORSION

ESAV=	<i>ff.ff</i>	<p>Defines the highest potential energy (EGYMAX) of the stored conformer: $EGYMAX = ESAV +$ the potential energy of the global energy-minimum conformer (GEM). By default, ESAV is set to $N/2$ kcal/mol ($N =$ total number of atoms in the molecule).</p> <p>Those conformers having the relative potential energies smaller than ESAV from the GEM, are stored into the conformation database, but those having potential energy higher than EGYMAX are discarded. The efficiency and the reliability of CONFLEX5 search is greatly influenced by the number of stored structures. A small ESAV leads to a smaller number of stored structures and less computer time, but the risk of missing significant conformers increases. This is because unstable conformers sometimes produce stable conformers upon local perturbation. On the other hand, a large ESAV ensures finding all significant conformers but leads to longer calculation time.</p> <p>Example : ESAV=6.5</p>
EDIF_HARD=	<i>ff.ff</i>	<p>Threshold of the basic comparison in potential energies if "CHECK=NOENERGY" is not specified. See also "CHECK=".</p> <p>Example : EDIF_HARD=1.0D-5</p>
EDIF_LOOSE=	<i>ff.ff</i>	<p>Threshold for the comparison of potential energies in the first stage of redundancy test when "CHECK=TORSION" is specified. If a new conformer has the same potential energy, within this range, with one of the stored structures, the program proceeds to the torsion angles test. The default is $3N/100$ kcal/mol.</p> <p>Example : EDIF_LOOSE=2.0</p>
GRMS_HARD=	<i>ff.ff</i>	<p>One of the thresholds in the RMS average of the final gradient for the termination of the geometry optimization.</p> <p>Example = GRMS_HARD=1.0D-5</p>
GRMS_LOOSE	<i>ff.ff</i>	<p>One of the thresholds for the RMS average of the final gradient for the termination of the geometry optimization.</p> <p>Example : GRMS_LOOSE=1.0D-7</p>
XCOD_MAX=	<i>ff.ff</i>	<p>One of the thresholds in the maximum displacement of each optimized step during the iterative geometry optimization.</p> <p>Example : XCOD_MAX=1.0</p>

XCOD_RMS=	<i>ff.ff</i>	One of the thresholds in the RMS averaged displacement of each optimization step during the geometry optimization. Example : XCOD_RMS=4.0
TORS_MAX	<i>ff.ff</i>	Threshold of the comparison in the maximum difference in torsion angles if "CHECK=TORSION" is specified. Example :) TORS_MAX=1.0D-2
TORS_RMS	<i>ff.ff</i>	Threshold of the comparison in the RMS average of difference in torsion angles if "CHECK=TORSION" is specified. Example: TORS_TMS=1.0D-1
MOMT_MAX	<i>ff.ff</i>	Threshold of the comparison in the maximum difference in the components of the moment of inertia for the optimized structure if "CHECK=MOMENT" is specified. Example : MOMT_MAX=0.5
MOMT_RMS	<i>ff.ff</i>	Threshold of the comparison in the RMS average of difference in the components of the moment of inertia for the optimized structure if "CHECK=MOMENT" is specified. Example : MOMT_RMS=0.1

4.1.4 Vibration analysis setup keyword

Keyword	Option	Description
THERMO=	<i>XYZ INTER HEVYLP</i>	Vibrational analysis, that is equivalent to the normal mode analysis using the mass weighted second derivative matrix, will be performed if the structure enough to be optimized is given. Thermodynamics functions, the vibrational frequencies and the corresponding mass weighted vibrational modes are also printed. "XYZ" and "INTER" control the printing form in Cartesian and internal coordinate system, respectively. The default is "XYZ". If "HEVYLP" is specified, lone pairs are packed into the elements of the second derivative matrix at the attached heavy atom. Example : THERMO=XYZ
NOTHERMO		Does not perform any thermodynamic calculation and also print out any vibrational mode or eigenvectors.

EIGVEC=	XYZ INTER HEVYLP	Normal mode analysis without the mass weighted second derivative matrix will be performed, and then eigen values and eigenmodes are written to the output file. "XYZ" and "INTER" control whether the information is written to the output file as Cartesian or Internal coordinate formats, respectively. If "HEVYLP" is specified, lone pairs are packed into the elements of the second derivative matrix at the attached heavy atom. Default is "XYZ". Example : EIGVEC=XYZ
TEMP=	ff.ff	Temperature is specified to ff.ff degrees centigrade (°C); by default it is set to 25.0 °C (298.15K). Example : TEMP=30.0
ALLMODE		Print out all vibrational modes computed.
LOWMODE=	<i>n</i>	Print out vibrational modes or eigenvectors less than <i>n</i> th of them.
NOMODE		Thermodynamic calculation will be performed, but never been printed any vibrational mode or eigenvectors.

4.1.5 PDB-file reading keyword

Keyword	Option	Description
PDB_HETATM		All atoms in "HETATM" records are considered for calculation. (default)
PDB_NOHETATM		All atoms in "HETATM" records are ignored.
PDB_WATER		"HOH" atoms in "HETATM" records are used for calculation. (default)
PDB_NOWATER		"HOH" atoms in "HETATM" records are ignored.
PDB_MODEL_NO=	<i>n</i>	Selection of the model serial number that specifies an ensemble to. Default is the first model that is corresponding to "PDB_MODEL_NO=1". If no entry of "MODEL" record in the PDB file, all atoms are used for calculation.
PDB_SSBOND		Connect the S-S bonds that are specified in "SSBOND" record.
PDB_NOSSBOND		All "SSBOND" records are ignored.
PDB_SSB_DIST=	ff.f	Distance threshold of S-S bond connection

PDB_CONECT=	(<i>I,J,K</i>)	Bonding between <i>I</i> and <i>J</i> atoms with <i>K</i> -bond type <i>K</i> =1: SINGLE <i>K</i> =2: DOUBL <i>K</i> =3: TRIPLE <i>K</i> =4: IONIC(<i>I+,J-</i>)
PDB_DISCONNECT=	(<i>I,J</i>)	A bond between <i>I</i> and <i>J</i> atoms is forcibly disconnected.
PDB_CHARGE=	(<i>I,K</i>)	Put a formal charge <i>K</i> on <i>I</i> atom. For example, when you explicitly specify that a calcium ion with atom No.1354 has +2 formal charge, keyword description is "PDB_CHARGE=(1354,+2)".

4.1.6 Conformation cluster analysis keyword

Keyword	Option	Description
CLUSTER		Conformation clustering will be performed by using a single linkage algorithm. This keyword should be used with "CONFLEX" keyword.
CCLUS_DISTANCE=	<i>TORSION</i> <i>ATOM</i>	Definition of conformation distance (similarity) to be used for conformation clustering. <ul style="list-style-type: none"> - rms difference of torsion angles (<i>TORSION</i>) - rms difference of atomic position after super-imposing (<i>SUPER-IMPOSE</i>)
CCLUS_REFALL=	<i>TORSION</i> <i>COMPAR</i> <i>PHIPSI</i> <i>ALPHA</i> <i>HEAVY</i> <i>NOHYD</i>	Automatically defines the reference atoms or torsion angles to determine the conformation distance. When "TORSION" is selected to the conformation distance ("CCLUS_DISTANCE="), the following options can be specified: <ul style="list-style-type: none"> - all torsion angles to be used for energy calculation (<i>TORSION</i>) - all torsion angles to be used for comparison with conformers (<i>COMPAR</i>) - all phi/psi torsion angles of peptide (<i>PHIPSI</i>) (only for peptide) When "ATOM" is selected to the conformation distance ("CCLUS_DISTANCE="), the following options can be specified: <ul style="list-style-type: none"> - all alpha carbons of peptide (<i>ALPHA</i>) (only for peptide) - all heavy atoms (<i>HEAVY</i>) - all atoms except for hydrogens (<i>NOHYD</i>)
CCLUS_IREF=	<i>I</i> (<i>I,J</i>)	The atom number of the referenced atom, or atom numbers of the central bond of the reference torsion angle. This keyword uses one line to specify one reference.

CCLUS_XREF=	<i>I</i> <i>(I,J)</i>	The atom number of the atom to be excluded from reference atoms, the atom numbers of the central bond to be excluded from reference torsion angles. This keyword uses one line to specify one reference.
CCLUS_LIMIT=	<i>f.ff</i> <i>AUTO</i>	Threshold of conformation clustering - automatically prepares the threshold of conformation distance (AUTO)
CCLUS_LIMIT_MAX=	<i>f.ff</i>	Threshold of for constraint clustering
CCLUS_EGFUNC=	<i>STERIC</i> <i>FREE</i>	Sort index is specified. - sorted by the "STERIC" energy order - sorted by the Gibbs' "FREE" energy order
CCLUS_MAXCONF=	<i>n</i>	Maximum number of conformers referenced in conformation clustering.

4.1.7 UV/Vis/CD spectral and PPP/SCF-MO link keyword

Keyword	Option	Description
UVCD		UV/Vis/CD Spectrum calculation will be performed.
CDUV		Same with "UVCD"
PIA_OPT=	<i>NOPEP</i> <i>NOATE</i>	In PPP/SCF-MO calculation, all PI-atoms are automatically selected. However, SCF Instability is often caused by including some types of PI-atoms, carbonyl and peptide bonds in widely distributed aromatic system. NOPEP: excluding all peptide bonds (CONH) NOATE: excluding all carboxyl groups (COO)
PIA_DEL=	<i>I</i>	Excluding I atom from PI-atoms
SCF=	<i>PPP</i> <i>VE SCF</i>	Selection of SCF methods PPP: General PPP/SCF-MO calculation VE SCF: Variable electronegativity calculation (Allinger's approach)
PPP=	<i>VB</i> <i>VG</i> <i>NEWG</i>	Extensions of SCF-PPP calculation. VB: Variable beta method VG: Variable gamma method NEWG: New gamma method Example: PPP=(VB,VG)
SCF_ITER=	<i>N</i>	Maximum number of SCF iterations.
SCF_CONV=	<i>f.ff</i>	Threshold of SCF convergence.
CIS=	<i>(Nomo,Numo)</i>	Specifies the number of the occupied and unoccupied electrons for Single-CI calculation. Example: CIS=(10,10)

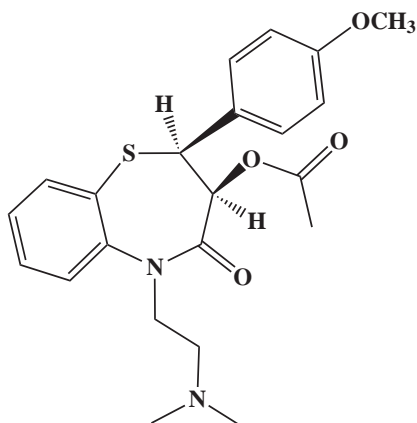
CURVE_PLOT=	<i>(f1,f2,f3)</i>	Range of spectrum, and incremental width for curve-fitting based on the gauss approximation. f1: Starting point in wave number (cm ⁻¹) f2: Terminal point in wave number (cm ⁻¹) f3: Incremental step width in wave number (cm ⁻¹) Default: CURVE_PLOT=(10000.0,70000.0,200.0) In this case, the spectrum values at total 301 points are reported.
CURVE_DSIGMA=	<i>f.ff</i>	Standard deviation of the Gaussian distribution. Default value is 2000.0 cm ⁻¹ .

4.1.8 Other keywords

Keyword	Option	Description
TIME=	<i>ff.ff</i>	The total CPU time allowed for the current job is limited to ff.ff seconds (default). Alternative specifications of the time are T=ff.ffD, T=ff.ffH, T=ff.ffM, which define the time in ff.ff days, hours, minutes, respectively. If this TIME keyword is not used, by default the time is 3 days (=259,200 seconds). Example : TIME=10.00D
DEBUG		Specification of "DEBUG" keyword provides debugging information for all subroutines. "DEBUG" keyword is corresponding to "DEBUG=ALL", see below.
DEBUG=	<i>CONCHK HYBRID DEFINE CASSALL CASS[0-8] CLASSPPP SYMM EVAL OPT SCFMO ALL</i>	Debugging information can be provided for the following subroutines: CONCHK, HYBRID, DEFINE, CLASSALL, CLASS[0-8], CLASSPPP, SYMM, EVAL, OPT, ALL, NEWTON. Example : DEBUG=(CONCHK,SYMM)
PRINT= NOPRINT=	<i>INPUT MODE LATEST PARAM SYMM NEGEIG SCFMO</i>	Options are used to specify what information should (or should not) be output.

4.2 Analysis Sample by CONFLEX5

4.2.1 Diltiazem/Caldizem, Tiazac: Herbesser®



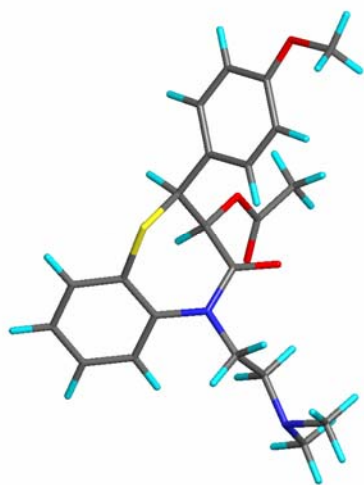
Diltiazem is one form of calcium antagonist prescribed in tablets and capsules for angina, irregular angina, or essential hypertension; and in injectable solutions for tachyarrhythmia, abnormally high blood pressure during surgeries, hypertensive emergencies, and unstable angina. One effect of this substance includes vascular dilation by suppressing the inflow of calcium ions to the vascular smooth muscle cells of the coronary and peripheral blood vessels, exhibiting curative properties against myocardial ischemia and antihypertensive effects. Although the antihypertensive effects are less in comparison to another calcium antagonist nifedipine, it is still relatively easy to use for angina patients with low blood pressure.

The characteristic trait of Diltiazem is the 7-ring member constituting the basic skeleton. The structural flexibility of this 7-ring member is thought to be interacting with the protein substance regulating the calcium ions. (For beginners of conformational search using CONFLEX, the sample of this structure was chosen to teach the structural flexibility of the 7-ring member part.)

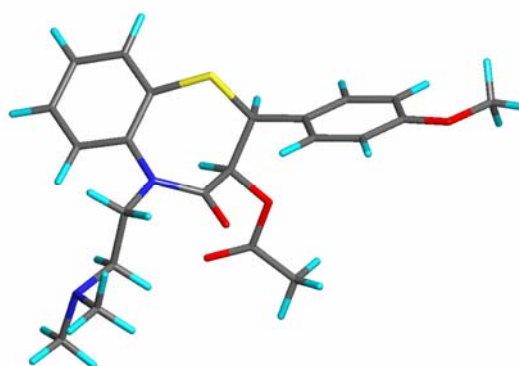
According to conformational search results, the conformation derived from the structural flexibility of the 7-ring member part differs largely in the most stable conformation and the 2nd most stable conformation. When the 2 conformations are superimposed and compared, the positional relationship between the acetyl group, p-methoxyphenyl group and the benzene ring of the basic skeleton differs significantly due to the conformation of the 7-ring member part. In

the most stable conformation, the methyl group of the acetyl group flops over the benzene ring of the basic skeleton. In the 2nd most stable conformation on the other hand, the 7 ring member of the basic skeleton is used to flip over to the back side of the paper, and the 3 substitute groups will position themselves to mutually minimize repulsion to one another.

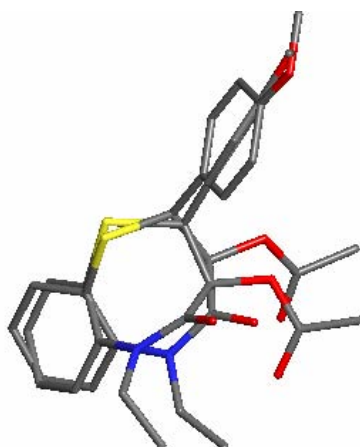
Diltiazem consists of 874 conformations total. However, the energy window of chemically significant conformations is up to 2kcal/mol. This energy region accounts for 94.6% of the total conformation, of which 19 conformations are chemically significant and all are within this window. Also, there are 10 conformations within 0~1 kcal/mol alone that accounts for 83.6% of the total conformation.



The most stable conformation



The second stable conformation



The two conformations superimposed (omit H)

Result 1 of Diltiazem conformational search

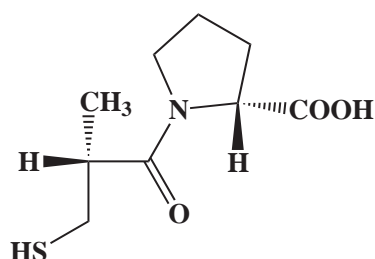
Energy Range of Conformers (kcal/mol)	No. of Conformers	Energy Range of Conformers (kcal/mol)	No. of Conformers
0 - 1	10	14 - 15	56(454)
1 - 2	9(19)	15 - 16	71(525)
2 - 3	22(41)	16 - 17	50(575)
3 - 4	16(57)	17 - 18	39(614)
4 - 5	7(64)	18 - 19	44(658)
5 - 6	10(74)	19 - 20	40(698)
6 - 7	25(99)	20 - 21	49(747)
7 - 8	27(126)	21 - 22	30(777)
8 - 9	30(156)	22 - 23	26(803)
9 - 10	54(210)	23 - 24	26(829)
10 - 11	50(260)	24 - 25	19(848)
11 - 12	29(289)	25 - 26	20(868)
12 - 13	65(354)	26 - 27	5(873)
13 - 14	44(398)	27 - 28	1(874)

Result 2 of Diltiazem conformational search

Energy Range of	Pop. of	Energy Range of	Pop. of
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Conformers (kcal/mol)	Conformers (%)	Conformers (kcal/mol)	Conformers (%)
0 - 1	83.55	14 - 15	0.00
1 - 2	11.00	15 - 16	0.00
2 - 3	4.44	16 - 17	0.00
3 - 4	0.92	17 - 18	0.00
4 - 5	0.07	18 - 19	0.00
5 - 6	0.01	19 - 20	0.00
6 - 7	0.00	20 - 21	0.00
7 - 8	0.00	21 - 22	0.00
8 - 9	0.00	22 - 23	0.00
9 - 10	0.00	23 - 24	0.00
10 - 11	0.00	24 - 25	0.00
11 - 12	0.00	25 - 26	0.00
12 - 13	0.00	26 - 27	0.00
13 - 14	0.00	27 - 28	0.00

4.2.2 Captopril/ Capozide: Captopril®



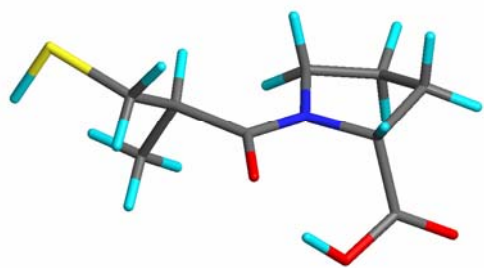
The production of Angiotensin II is suppressed by inhibiting the Angiotensin converter enzyme, which decreases total peripheral resistance and exposes anti-hypersensitive activity through the enlargement of the peripheral blood vessel. This suppresses the secretion of aldosterone, exposing a mild degree of Na excretion. Normal blood pressure was not affected and consecutive oral administration for extended periods of time proved ineffective. No rebound phenomenon was observed after cessation of the medication. Blood pressure declined in response to the dosage, generating increase in the cardiac output and decrease in peripheral vascular resistance, but showed no significant variation in heart rate. Moreover, even when the

blood pressure is dropping, blood flow to the stomach and brain significantly increased to the contrary. Prolonged administration improved cardiac enlargement due to high blood pressure, generating life prolongation as a result. Adaptation is due to essential hypertension, renal hypertension, renal defective hypertension, and malignant hypertension.

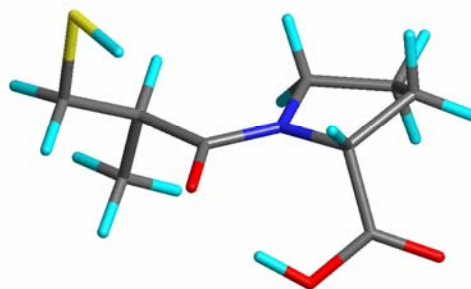
The distinguishing characteristic of captopril is its chemical compound comprised of simple amino acids. It can be assumed that a hydrogen bond exists between the carbonyl group and the hydrogen in the carboxylic acid, and also between the hydrogen in another SH group and the carbonyl group. (For beginners of conformational search using CONFLEX, a sample is taken to learn the conformational behavior when 2 chemical compounds similar to amino acids are condensed together.)

Conformational search results showed no significant difference between the most stable conformation and the second most stable conformation. When the two conformations are superimposed and compared to one another, the proline section of the 5-ring member were exactly identical. However, the difference is whether the SH group faces the direction of the carbonyl group, or the opposite direction. Also, in the most stable conformation, a hydrogen bond exists between hydrogen from the carboxylic acid and the carbonyl group, with the distance of 1.666 Å and the non-bonded interactive energy of 0.887 kcal/mol. On the other hand, because the charge-charge interactive energy is -55.161 kcal/mol, it is assumed that a strong hydrogen bond exists. In the second most stable conformation, a hydrogen bond exists between the hydrogen of carboxylic acid and the carbonyl group, with a distance of 1.668 Å and non-bonded interactive energy of 0.875 kcal/mol. On the other hand, the charge-charge interactive energy is -55.090 kcal/mol. The distance between the hydrogen of the SH group and carbonyl group is 2.592 Å, and the non-bonded interactive energy is 0.263 kcal/mol. The charge-charge interactive energy is -12.312 kcal/mol. When comparing the hydrogen bond between the hydrogen of the carboxylic acid and the carbonyl group, the hydrogen bond between the SH group and the carbonyl group is weak but still exists.

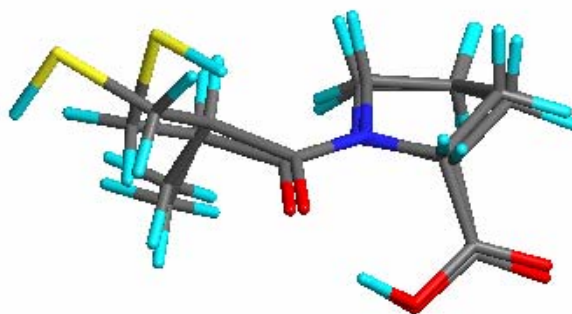
Captopril has a total of 267 conformations. However, the chemically significant energy window is up to 2 kcal/mol. There are 20 chemically significant conformations within this energy window that accounts for 94.8% of the total conformation. There are 6 conformations in 0~1 kcal/mol, but these 6 conformations account for 75.5% of the total conformation.



The most stable conformation



The second stable conformation



The two conformations superimposed

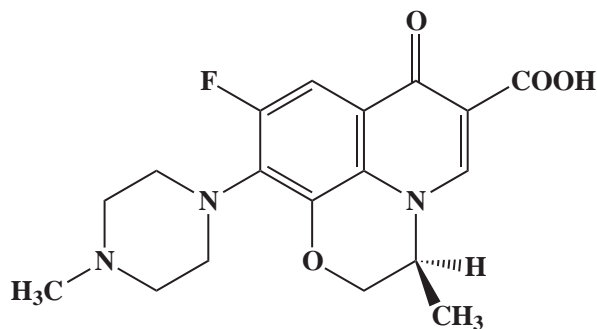
Energy
Conformation

1 - 2	14(20)	9 - 10	18(198)
2 - 3	13(33)	10 - 11	16(214)
3 - 4	19(52)	11 - 12	21(235)
4 - 5	28(80)	12 - 13	12(247)
5 - 6	21(101)	13 - 14	18(265)
6 - 7	27(128)	14 - 15	2(267)
7 - 8	31(159)		

Conformational search results 2 for Captopril

Energy Range of Conformers (kcal/mol)	Pop. of Conformers (%)	Energy Range of Conformers (kcal/mol)	Pop. of Conformers (%)
0 - 1	75.51	8 - 9	0.00
1 - 2	19.28	9 - 10	0.00
2 - 3	3.69	10 - 11	0.00
3 - 4	1.16	11 - 12	0.00
4 - 5	0.32	12 - 13	0.00
5 - 6	0.04	13 - 14	0.00
6 - 7	0.01	14 - 15	0.00
7 - 8	0.00		

4.2.3 Levofloxacin/ Levaquin: Crabit®



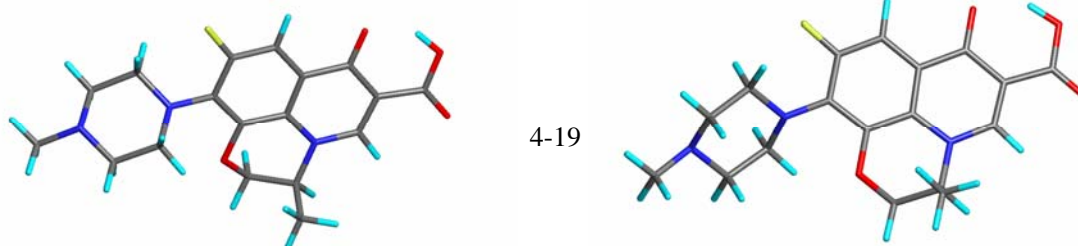
Levofloxacin is a new quinolone synthetic antimicrobial agent used antiseptically to inhibit gyrase activity of bacterial DNA. In addition, one optically active substance of ofloxacin (RS body

composite) exhibited approximately double the antimicrobial activity as ofloxacin. The microorganisms indicated are the following: Staphylococcus, Pneumococcus, Streptococcus pyogenes, Hemolytic streptococci, Peptostreptococcus, Gonococcus, Branhamella-catarrahalis, propionyl-Bacterium-acnes, Escherichia coli bacteria, Citrobacter, Salmonella, Shigella, Klebsiella, Enterobacter, Serratia, Proteus, Cholera bacilli, Pseudomonas aeruginosa, Haemophilus influenzae, Acinetobacter, Campylobacter, Chlamydia trachomatis, Anthrax bacteria, Pest bacillus, Francisella tularensis, brucella and Q fever rickettsia.

The flexibility of this chemical compound is thought to be particularly limited in the ring framework of the basic skeleton. However, factors contributing to the generation of many conformations are 2 sections: the piperazine sections and substantial amount of morpholine sections.

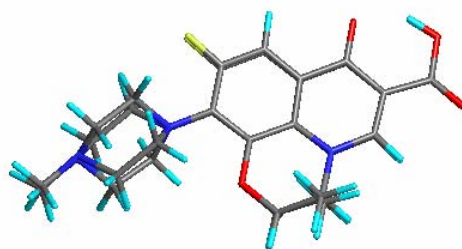
Conformational search results show the ring framework of the basic skeleton was hard, as the organic chemists presumed from experience. Carefully examining the conformations obtained showed 2 notable characteristics. The first characteristic is the hydrogen bond, which is exactly the same as the 5 dominant conformations, and exists between the hydrogen of the carboxylic group and the hydrogen bond from the carbonyl group, with a distance of 1.621Å and non-bonded interactive energy of 1.158 kcal/mol. On the other hand, the charge-charge interactive energy is -56.623 kcal/mol. This leads to the conclusion that a strong hydrogen bond exists in between. The second characteristic is how the piperidine segments preferentially take the chair form conformation, similar to cyclohexane of the 2 derivative substitutions seen in trans-1, 4-dimethylcyclohexane for example. The only difference between the most stable conformation and the 2nd most stable conformation is in the different inclination of the piperidine segment towards the ring skeletal framework, which takes the same chair form conformation. This difference alone generates 2 conformations that accounts for 83% of the total conformation.

Levofloxacin consists of 245 conformations. However, chemically significant conformational energy region is up to 2 kcal/mol. There are 5 chemically significant conformations that accounts for 96.7% of the total energy window, all of which is included within this energy window. Also, there are 2 conformations within the energy window of 0~1 kcal/mol, which accounts for 83.2% of the total conformation.

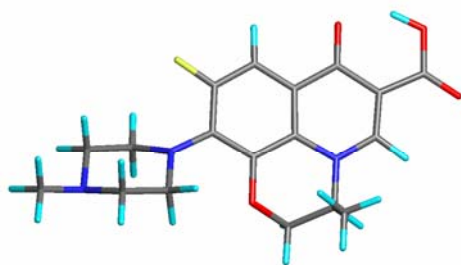


The most stable conformation

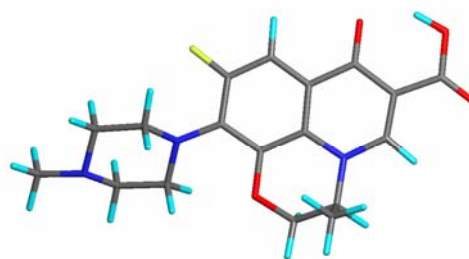
The second stable conformation



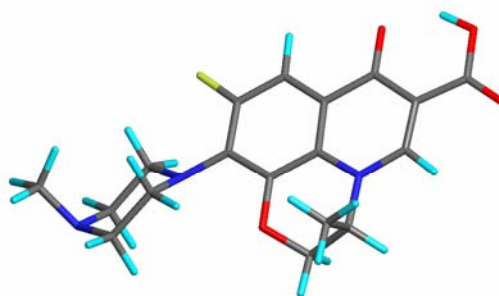
The two conformations superimposed



The third stable conformation



The fourth stable conformation



The fifth stable conformation

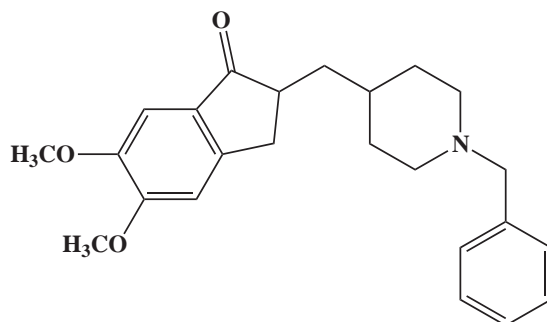
Conformational search results 1 for Levofloxacin

Energy Range of Conformers (kcal/mol)	No. of Conformers	Energy Range of Conformers (kcal/mol)	No. of Conformers
0 - 1	2	9 - 10	20(117)
1 - 2	3(5)	10 - 11	25(142)
2 - 3	4(9)	11 - 12	20(162)
3 - 4	4(13)	12 - 13	22(184)
4 - 5	11(24)	13 - 14	25(209)
5 - 6	11(35)	14 - 15	14(223)
6 - 7	18(53)	15 - 16	7(230)
7 - 8	13(68)	16 - 17	9(239)
8 - 9	29(97)	17 - 18	6(245)

Conformational search results 2 for Levofloxacin

Energy Range of Conformers (kcal/mol)	Pop. of Conformers (%)	Energy Range of Conformers (kcal/mol)	Pop. of Conformers (%)
0 - 1	83.19	9 - 10	0.00
1 - 2	13.52	10 - 11	0.00
2 - 3	2.29	11 - 12	0.00
3 - 4	0.60	12 - 13	0.00
4 - 5	0.34	13 - 14	0.00
5 - 6	0.04	14 - 15	0.00
6 - 7	0.02	15 - 16	0.00
7 - 8	0.00	16 - 17	0.00
8 - 9	0.00	17 - 18	0.00

4.2.4 Donepezil: Aricept®



Donepezil is the first curative drug approved in Japan to treat dementia of the Alzheimer type. In Alzheimer's dementia, the reduction of acetylcholine concentration within the brain is seen due to disorder of the cholinergic agonist nervous system. By reversibly inhibiting acetylcholine esterase, Donepezil is presumed to exhibit its effect by raising the concentration of acetylcholine by suppressing its decomposition. The effectiveness of Donepezil on other forms of dementia besides Alzheimer's is not confirmed. Moreover, it is important to stress that Donepezil is used merely as a symptomatic drug and by no means effective in treating the fundamental causes of Alzheimer's dementia itself.

The characteristic of Donepezil is the 2 substituents of piperidine constituting the basic skeleton. The 2 substituents of Piperidine is presumed to be important in considering the distance and interaction necessary to reversibly inhibit the acetylcholine esterase. Moreover, this chemical compound is appropriately used as examples when learning about conformational search using CONFLEX, in order to point out the importance of the straight chain parts and the flexibility of the ring. Also, it is important for those specializing in organic chemistry to understand that not all targeted atoms or chemical compounds can be analyzed.

Conformational search results of Donepezil up to 5 kcal/mol including geometry optimization resulted in a total of 2,447 conformations. This is a clear indication of conformational eruption. However, chemically significant conformational energy window is up to 3 kcal/mol. This energy window accounts for 97.6% of the total conformation, with 135 chemically significant conformations. All chemically significant conformations are thought to be included within this energy window. As this targeted compound Donepezil shows, not all atoms can be targeted and conformationally analyzed completely.

Especially organic chemists must be cautious of an intermediate step specific to

conformational search. In other words, the most stable conformation presumed by organic chemists to possess the most stable energy might not always be the most stable conformation after all. The initial conformation of this example Donepezil ranked 622 in the conformational search, and it is 7.76 kcal/mol higher in comparison to the most stable conformation. In this manner, the importance of understanding the conformational search results cannot be stressed enough.

In the conformational search results of Donepezil and its search window up to 5kcal/mol, there are two factors contributing to the explosion of conformational eruption: first, the positional relationship of the interaction between 2 methoxy groups; and second, the conformational oscillation of piperazine's 2 derivative substitution parts. It is unlikely for the first factor to generate many conformational eruptions, but the second factor is presumed to be contributing to many conformational eruptions due to the reflecting characteristic and substitute group of the nitrogen atomic lone pair.

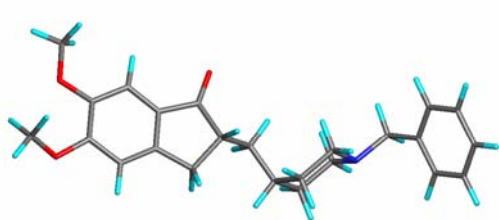
Intermediate step of Donepezil's conformational search

Energy Range of Conformers (kcal/mol)	No. of Conformers	Pop. of Conformers (%)
0 - 1	22	76.73
1 - 2	37(59)	15.10
2 - 3	76(135)	5.73
3 - 4	123(258)	2.02
4 - 5	98(356)	0.34
5 -	2091(2447)	0.08

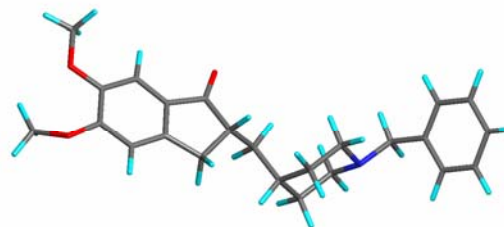
Specific intermediate step of Donepezil's conformational search by CONFLEX

No.	Conformational ID	Original Streric E (kcal/mol)	E (kcal/mol)	Distribution (%)
1	65	81.0618	0.0000	7.0609
2	61	81.0654	0.0036	7.0185
3	72	81.0767	0.0149	6.8859

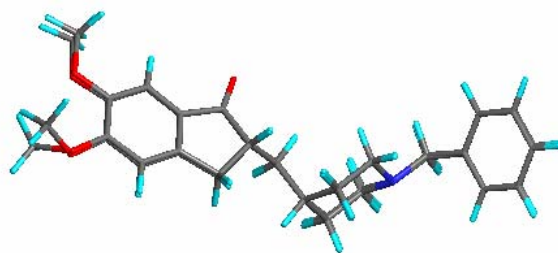
4	85	81.0919	0.0301	6.7114
5	79	81.1288	0.0670	6.3058
6	64	81.1320	0.0702	6.2722
7	105	81.1525	0.0907	6.0589
8	93	81.1599	0.0981	5.9832
9	321	81.6918	0.6300	2.4384
10	308	81.7256	0.6638	2.3031
11	306	81.7672	0.7054	2.1470
12	295	81.7793	0.7174	2.1037
13	333	81.8328	0.7710	1.9219
14	319	81.8653	0.8035	1.8194
15	345	81.8970	0.8352	1.7244
16	304	81.9346	0.8728	1.6184
17	66	81.9993	0.9375	1.4511
18	170	82.0171	0.9552	1.4082
19	183	82.0187	0.9569	1.4044
20	94	82.0191	0.9573	1.4034
21	188	82.0360	0.9742	1.3638
22	200	82.0532	0.9914	1.3248
622	1	88.8240	7.7622	0.0000



The most stable conformation



The second stable conformation



The two conformations superimposed

4.2.5 Pravastatin/ Pravachol: Mevalotin(

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Pravastatin inhibits HMG-CoA reductase, the rate-controlling enzyme of cholesterol biosynthesis series in a particularly antagonizing manner. This mechanism will improve the serum lipids by promptly and forcefully lowering the serum cholesterol count of selected major organs for cholesterol synthesis such as the liver and small intestines. Adaptation to both hyperlipemia and hypercholesterolemia takes place.

The flexibility of this chemical compound is extremely high in comparison to previous samples. For beginners specializing in organic chemistry, there is usually the desire to analyze all target chemical compounds. However, not all targeted chemical compounds can be analyzed. While taking the flexibility of the chemical compounds and computational capacity of the calculator into consideration, calculations are done

purposely without modeling operations, due to the intention of having decisions whether or not to modelize the target compounds are made carefully.

When the conformational search for Pravastatin was conducted within the search window of up to 5kcal/mol including geometry optimization, a total of 7,022 conformations were found as a result. This is a clear indication of conformational eruption. However, the energy window of chemically significant conformation is up to 3kcal/mol. This energy window accounts for 97.7% of the total conformation, and 167 chemically significant conformations were all found within this energy window. As this targeted chemical compound Pravastatin shows, not all atoms can be completely analyzed conformationally.

In the most energetically stable conformation within the search window of 5kcal/mol, 2 hydrogen bonds exist. Of these 2 hydrogen bonds, 1 exists between the hydrogen derived from carboxylate ester and the other side chain of the alcohol oxygen, where another hydrogen derived from the side chain of the alcohol is bonded with the oxygen derived from the carbonyl group of the carboxylate ester. Thus, Pravastatin relatively minimizes the flexibility of the side chain parts of hydrogen bonds. Also, these hydrogen bonds serve as the key, or foothold to the joining of the acceptor, thus the loss of the positional relationship of this functional group must be prevented according to results obtained from this conformational search.

Intermediate step of Pravastatin conformational search

Energy Range of Conformers (kcal/mol)	No. of Conformers	Pop. of Conformers (%)
0 - 1	34	66.59
1 - 2	58(92)	24.25
2 - 3	75(167)	6.87
3 - 4	97(264)	1.43
4 - 5	239(503)	0.64
5 -	6519(7022)	0.22

