Conformational Analysis of Flexible Compounds with Chemical Shift Simulation

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Abstract: Conformational analyses of flexible compounds with a chemical shift simulation method are described. It is known that NMR chemical shifts reflect the molecular structure, and hence, our method of analysis utilizes chemical shifts. Our newly developed chemical shift simulation method together with molecular dynamic calculation succeeded in the conformational analysis of the flexible compounds; cyclophanes, dicarboxylate complexes of Sn(IV) porphyrins and supramolecular complexes.

1. Introduction

Determination of significantly populated conformers in extremely flexible molecules is a matter of long-standing interest. It is not straightforward because these molecules have many conformational possibilities. However, for the successful prediction of the stereochemical outcome of some reactions of these compounds the knowledge about the significantly populated conformers plays an important role.¹ Hence, it is desirable to develop an efficient method for the conformational analysis of the flexible compounds. Conformations have been analyzed mainly with NMR spectroscopy by taking advantage of the torsion angle-dependent 3J coupling constants² and distance-dependent NOE.³ However, the method utilizing the 3J coupling constants cannot be applied if there is an intervention of a quaternary center or a divalent heteroatom. Moreover, it is difficult to determine exactly which conformer affords the NOE. Therefore, the structure analysis based on the NOE occasionally gives misleading results.⁴ By contrast, the chemical shift, which is the most fundamental data of NMR, is not extensively used for conformational analysis of flexible compounds, although the chemical shift gives invaluable information on the molecular structure. NMR chemical shifts reflect the molecular structure. Hence, variation in the local environment affects chemical shieldings, and the change in chemical shifts of nuclei caused by adjacent substituents provides valuable information about the relative arrangement of the nuclei under study with respect to these nearby substituents.⁵ The chemical shift changes caused by the nearby substituents can thus be applicable for conformational analysis. From this point of view, we have developed an efficient method for conformational analysis of flexible organic compounds by using chemical shift simulation technique.⁶

This account describes the conformational analysis of the flexible compounds; cyclophanes, dicarboxylate complexes of Sn(IV) porphyrins, supramolecular complexes, together with the methods of the chemical shift simulation by using shielding parameters of the aromatic rings and polar functional groups.

2. Shielding Effects of Functional Groups

Our method of conformational analysis utilizes a chemical shift simulation for all the plausible structures contribut-

ing to the conformational equilibrium. To obtain fruitful results one-to-one correspondence of the structure and the predicted chemical shift values is essential. Molecular orbital calculation can predict the chemical shift of the protons; however, the accuracy of the predicted values is still far from the level required for our purpose.⁷ Hence, we utilized the classical approach of the magnetic shielding effect of the functional groups.

To obtain reliable magnetic shielding parameters of a C-X single bond, a steroid skeleton was chosen because of its structural rigidity. We synthesized 4-hetero-androstane-17-one (**1**). The proton chemical shifts of this compound were compared to those of the parent compound, androstane-17-one (**2**). The observed substituent-induced shifts are the differences in the chemical shift of these compounds. The shielding parameters were obtained so as to reproduce the observed induced shifts. Shown in Figure 1 is the contour map of the induced shift values caused from the ether functionality (C-O-C).⁸ We have also succeeded in getting the magnetic shielding parameters for other functionalities; carbonyl,⁹ lactone,¹⁰ amine,¹¹ ammonium,¹¹ lactam and thioether.¹²

Figure 1. Contour map of the induced shift values caused from ether functionality (C-O-C).

One well-known magnetic shielding effect is the diamagnetic ring current of arene.¹³ When a magnetic field is applied to a cyclic conjugated π system, the π electrons are enforced

to flow around the conjugated ring. The resulting ring current gives a secondary induced magnetic field and shows pronounced diamagnetic anisotropy. The Johnson-Bovey type double currents model for the benzene ring^{13b} is well known to estimate the local anisotropic contribution to the chemical shift of protons of aromatic compounds. However, since this type of separated-current-loop model is known to be inappropriate to evaluate the induced chemical shift of out-of-plane protons,¹⁴ we have selected a line current approximation discussed originally by Salem.¹⁵ In this model the induced magnetic field is the sum of contribution from each edge of the current flowing polygon. The magnitude of the line current has been estimated to reproduce the ring-current-induced shifts of [2.2]cyclophanes (**3**, **4**). These compounds are so rigid that the structure found in the crystalline state should not change significantly in solution. We obtained a best fit value of the line current to reproduce the induced shifts of **3** and **4** (Table 1). Our ring current model is proven to give accurate induced shifts and have large versatility in chemical shift simulation of compounds carrying benzene ring(s).

Table 1. Observed and calculated induced shifts ($\Delta\delta$) for [2.2]cyclophanes

position	$\Delta\delta$ (ppm) ^a	
	obs.	calc.
H ₈ (3)	2.62	2.63
H ₄ (3)	-0.06	-0.09
H ₅ (3)	-0.11	-0.07
H ₄ (4)	0.61	0.59

^a (-) denotes down-field shift.

In order to extend the applicability of the method of chemical shift simulation to polycyclic aromatic compounds, it is necessary to obtain the shielding parameters for other functionalities such as a naphthalene ring. For this purpose, the steroid skeleton and 7,8-dihydro-dibenzophenanthrene were chosen because they have rigid and well-defined structures. The induced shifts of protons caused by the diamagnetic anisotropy of the naphthalene rings can be obtained by the chemical shift differences of **5** and **6**. The chemical shift differences of protons between **5** and **6** can be successfully reproduced by assuming there are four individual benzene rings in **5**. Since we applied the line current model for the estimation of the ring current of benzene, the simple sum of the line current of the two fused six-membered rings exactly cancelled out the current through the fused bond. Thus the magnetic anisotropy of the naphthalene can be reasonably approximated by a loop current through the peripheral 10 π bonds.¹⁶

The porphyrin has an interesting π -system. Synthetic metalloporphyrins have received considerable attention in many fields of chemistry. The knowledge about the structure of the

metalloporphyrins plays an important role in understanding the structure-function relationship. Many models of the porphyrin ring current effect have been reported since the first report of the NMR spectra of porphyrins by Becker and Bradley.¹⁷ We developed a new model based on the classical line current approximation.¹⁵ In this simple model, the secondary magnetic field at a given proton is calculated on the assumption that the line current follows exactly the C-C and C-N bonds of the porphyrin ring. A current running along the two C-C bonds passing through a meso position separates into two (i_1 , i_2) at the α -position of a pyrrole ring (Figure 2). We can estimate the magnitude of the line current of outer and inner arcs of the pyrrole ring ($i_1 = 0.87i_B$, $i_2 = 0.41i_B$, where i_B is the line current of benzene ring⁶) to reproduce the complexation-induced shift values of dibenzoate complex Sn^{IV}(tpp) **7** and diadamantane-1-carboxylate complex of Sn^{IV}(tpp) **8**.¹⁸ The contour map of the induced shift values caused by the porphyrin ring current of the tetraphenyl porphyrin at the vertical section 3.0 Å is given (Figure 3). In order to examine the applicability of this ring current model, we calculated the complexation-induced shifts of quinones for the supramolecular complexes of cis-bis(2-hydroxy-1-naphthyl) porphyrin **9** reported by Ogoshi.¹⁹ The calculated complexation shifts of four protons of benzoquinone (BQ) in BQ·**9** complex are in between 4.55 and 5.02 ppm, the average value is 4.64 ppm that is close to the

Figure 2. Current loop model for porphyrin ring.

Figure 3. Contour maps of the induced shift values caused by tetraphenylporphyrin at the vertical section at 3.0 Å (ppm).

observed (4.86 ppm). The same procedure was repeated for the complexation shift of the methyl signal in duroquinone·9 complex to give a good reproduction ($\Delta\delta_{\text{calc}}$ 2.33 ppm) of the observed (2.22 ppm).¹⁸ The successful reproduction of the complexation shifts of these quinone protons supports the wide applicability of this simple model for porphyrin ring current effect.

3. Conformational Analysis of Macrocyclophanes

Bridged aromatic compounds are called "cyclophane".²⁰ Since Cram's first synthesis of [2.2]paracyclophane (4), the chemistry of cyclophanes has attracted much attention. Recently, cyclophanes play an important role in supramolecular chemistry.²¹ By contrast, conformational studies of highly flexible macrocyclophane are limited. We thought that our chemical shift simulation method can be applicable for rather elusive conformational study of highly flexible macrocyclophanes.

[4.4]Metacyclophanes were selected since they have a flexible 14-membered ring. Variable temperature NMR measurements disclosed that only one conformer is present in **10** and it interconverts to its mirror image by a ring-flipping of the two benzene rings. The relative orientation of the two benzene rings of this structure was determined so as to reproduce the ring-current-induced shifts of a benzene ring from the other ring. The position and orientation of one benzene ring with respect to the other thus obtained is identical to the structure obtained from the X-ray crystallographic analysis (Figure 4).⁶

Figure 4. Crystal structure of **10**.

The situation is not so simple in the conformational study of **11**. The chemical shifts of its aromatic protons change significantly with the temperature variation indicating multiple conformers contribute to the conformational equilibrium of **11**. Molecular mechanic calculations with the use of our in-house program, MMRS, gave 6 possible structures (Figure 5). The population of each conformer at various temperatures was obtained by using our chemical shift simulation technique (Table 2). The conformers A and C play an important role in the conformational equilibrium.²² The structure of **11** in the crystalline state is identical to conformer A (Figure 6), although it is a minor contributor at room temperature and the crystals were grown at that temperature.

Conformational studies for other cyclophanes were carried out. These include [2.2]orthocyclophanes (**12-17**),²³⁻²⁸

Figure 5. Conformers of **11** obtained by molecular mechanic calculations.

Table 2. Population of conformers of **11**

Temp.	Probability (%)					
	A	B	C	D	E	F
27	18	0	68	4	0	10
-30	31	0	63	1	0	5
-100	56	0	39	1	0	4

Figure 6. Crystal structure of **11**.

[3.3]orthocyclophanes (**18-19**),²⁹⁻³¹ [3.3]metacyclophanes (**20-21**),^{9,32-33} and [4.4]cyclophanes (**22-23**).³⁴⁻³⁵

Calix[n]arenes belong to the cyclophane family. Conformational problems of these compounds are an intensely interesting matter for many chemists. The smallest calixarene, calix[4]arene, has four conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate. The cyclic intramolecular hydrogen bondings of the four phenolic hydroxy groups stabilize the cone form and it is the exclusive conformer among the four. Depletion of one of the four hydroxy groups increases the flexibility of a calix[4]arene, and the resulting monodeoxycalix[4]arene is an interesting compound for conformational analysis. ¹H-nmr chemical shifts of **24** are concentration-dependent. Detailed analysis disclosed that the monomer of **24** is in equilibrium with the dimer. The equilibrium constant between the monomer and the dimer was obtained from the concentration-dependent change of the aromatic signal by a curve-fitting analysis.³⁶ The structure of the dimer has a cyclic hydrogen bonding array of 6 hydroxy groups and it was supported by the successful reproduction of the observed monomer-dimer shift change with our chemical shift simulation method (Figure 7). Cutting the hydrogen bonding of **24** with etherification of the hydroxyl groups further increases the flexibility and the conformational analysis of the resulting trimethylether **25** was carried out. A cone and two partial cones were the main contributors in the con-

Figure 7. Dimer of monodeoxy calix[4]arene.

formational equilibrium in this case. The relative populations of these conformers were obtained.³⁷

4. Structures of Dicarboxylate Complexes of Sn(IV) Porphyrins

Synthetic metalloporphyrins have received considerable attention in many fields of chemistry. The structures of metalloporphyrin complexes were studied mainly by X-ray crystallography. Although the X-ray crystallographic analysis is one of the most promising methods to know the precise structure, it provides only a limited number of structures in the solid state. Moreover, the structure obtained by this method is not always identical to that in solution. In order to know the solution geometry of the metalloporphyrin complexes it is found that the chemical shift simulation technique plays an important role.

Two conformations, 'vertical' and 'horizontal', were proposed for the structure of an aromatic carboxylate complex of Sn^{IV}(tetraphenylporphyrin).³⁸ The former is based on the structure of the dibenzoate complex in which benzoates bound with their aromatic rings perpendicular to the porphyrin plane. An attractive π - π or donor-acceptor interaction between the anthracene and the porphyrin rings was claimed as the main cause for the horizontal conformation of anthracene-9-carboxylate complex of Sn^{IV}(tpp) in which the anthracene ring is roughly coplanar to the porphyrin ring.³⁸ In order to elucidate the structure in solution, **26** was subjected to NMR measurement at various temperatures. The chemical shifts of the aromatic protons of **26** showed temperature dependence. This suggested that at least two conformers are in equilibrium in solution; however, it is difficult to identify how many conformers are contributing to the equilibrium because neither signal separation nor extensive signal broadening was detected. DFT calculation disclosed that two con-

formers (*exo*, *endo*) are possible for **26** (Figure 8). Calculation of the complexation-induced chemical shift changes of the naphthalene protons was then estimated to these two conformers with use of the secondary induced magnetic fields due to the porphyrin ring current. Using these theoretical induced shift values, the relative ratio of the two conformers in solution was estimated at various temperatures (Table 3).³⁹ Repeating the same analytical procedure to **27** ended up with a successful conformational analysis in solution.⁴⁰

Figure 8. Molecular structures of **26** obtained from DFT calculations.

Table 3. Relative ratio (%) of two conformers of **26** in CDCl₃

Temperature (°C)	<i>exo</i>	<i>endo</i>
25	63.8	36.2
0	67.5	32.5
-20	71.0	29.0
-40	74.5	25.5
-60	78.5	21.5

5. Configurational Assignment of Secondary Alcohols

Our chemical shift simulation technique can be applied to the assignment of absolute configurations of secondary alcohols. Besides the classical reagents, methoxytrifluoromethylphenyl acetic acid (MTPA) and methoxyphenyl acetic acid (MPA) proposed originally by Mosher⁴¹ and Trost,⁴² a wide variety of chiral auxiliaries have been developed. The method of the assignment of configuration is based on the derivatization of the alcohols with (*R*)- and (*S*)-chiral auxiliary followed by comparison of the chemical shifts of the resulting diastereomers. The chemical shifts of the L₁ and L₂ substituents at the asymmetric center reflect the diamagnetic ring current of the aryl ring of the chiral auxiliary. The L₁ group should have a large aryl-induced shift influence if (*S*)-MTPA was used. Thus the absolute configuration of a secondary alcohol can be assigned. The mechanism of the assignment stems from the syn preferred conformation of the diastereomeric ester in which two groups, carbonyl oxygen and methoxy groups, are in an eclipsed arrangement. Since both MTPA and MPA have rotational freedom of movement around the chiral center to the aryl substituent many conformational options should be taken into account. In order to reduce the rotational freedom of movement a condensed ring system was employed. Our new reagents for the chiral auxiliary that can be applied to assign the absolute configuration of secondary alcohols are 1-methoxyindane-1-carboxylic acid **28** and 1-methoxy-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-1-carboxylic acid **29**.

As a chiral alcohol, naturally occurring (–)-menthol was selected and esterified with racemic **28** and **29**, respectively. The resulting diastereomeric esters were separated with HPLC on silica gel. Esterification shifts of (–)-menthol can be estimated from comparison of the chemical shift of the diastereomeric ester and a reference compound, (–)-menthyl acetate.

In order to predict the aryl-induced shifts correctly with our chemical shift simulation technique, information about conformers of the esters and their populations is necessary. Of course, molecular mechanics or molecular orbital calculations can give many plausible structures though they correspond to the motionless frozen form at 0 K. At room temperature where the NMR spectra were given, many conformers of the ester molecule are in dynamic equilibrium. To simulate the conformational equilibrium of the ester, molecular dynamic (MD) calculations with stochastic dynamic (SD) simulation⁴³ was applied. While molecular or stochastic dynamics will cover all conformational space in the limit, energy barriers significantly greater than RT slow the exploration of conformational space substantially. Hence, the Metropolis Monte Carlo (MC) algorithm is applied so as to explore all the conformational space of the compound effectively, since the ester has many rotatable bonds. The MD calculation of the (–)-menthyl-(*R*)-**29** ester with the MC/SD mixed mode for 1000 ps simulation was carried out. A snapshot of the structure was monitored at every 0.5 ps. A total of 2000 structures were obtained. Esterification shifts of (–)-menthol in each structure can be estimated by using the naphthalene ring current and shielding parameter of the OMe group. Averaging these 2000 esterification shifts gave the predicted value of the esterification shift of each proton of (–)-menthol. The predicted esterification shifts are very close to the observed as shown in Figure 9.⁴⁴ A comparison

Figure 9. Observed (upper) and calculated (lower) chemical induced shifts ($\Delta\delta$) of (–)-menthyl-(*R*)-**29**. A + sign denotes up-field shift.

Figure 10. Plot of observed and calculated SIS values of (-)-menthyl-(R)-29.

of the observed and calculated values gave a high correlation value ($R^2 = 0.989$) (Figure 10). This analysis clearly shows that our chemical shift simulation method can be applied for the chemical shift prediction of a highly flexible compound such as the (-)-menthyl-(R)-29 ester.

6. Structures of Supramolecular Complexes

There has been intense activity in the investigation of supramolecular complexes. Synthetic receptors capable of binding small guest compounds are reported extensively. The essential aspect of molecular recognition is understanding the nature of the interaction of one molecule with another. There should be a specific arrangement of the two for which the energy is lower than that of other possible orientations. It is thus important to identify the exact arrangement of the two in solution. From that, detailed understanding is obtained of the factors that affect the way the molecules arrange. However, it is not easy to determine the precise arrangement of the two molecules of a complex in solution. Our chemical shift simulation technique is one of the most efficient methods to obtain the precise structure of supramolecular complexes.

One of the most challenging targets for the structure elucidation is the supramolecular complex in which non-directional forces (van der Waals, CH- π , π - π interactions, etc.) play an important role in binding the two components in solution. The restriction of the guest motion imposed by the host cavity wall is usually not so severe in such complexes. The guest can move or rotate in the host cavity. How can we determine the precise structure of such a complex in solution? To address this important issue, we selected MD simulation combined with our chemical shift simulation method.

We selected supramolecular complexes of **30** and dihalomethanes as the challenging targets for the structure elucidation. A crystallographic analysis of the inclusion complex of **30** and CH_2Cl_2 gave the structure in the solid state (Figure 11). In this complex, the host changes its structure to control the orientation of the guest; an induced-fit type adjustment of the host cavity for the guest shape is seen. The other structural feature worthy to note is the positional disorder of the guest. The disorder in this case was found to be not static but dynamic in nature. The analysis of the temperature-dependent NMR spectral patterns of the crystalline complex of **30** and deuterated dichloromethane suggested a dynamic multiple site jump of the guest is operative in the host cavity in the crystalline state. The dynamic movement of

the guest in the host cavity should be more extensive in solution because the forces that keep the shape of the host as tight as in the crystalline state (such as packing forces) do not work effectively in solution. In order to analyze the dynamic motion of the complex, MD simulation study on the complex was carried out with a stochastic dynamic treatment using AMBER* force-field at 300 K. The calculation showed that the guest moves rapidly within the host cavity. The MD simulation also gave a large number of structures of the complex during the thermal motions which were monitored at constant time intervals. The theoretical complexation-induced shift (CIS) value of the guest proton for each monitored structure can be estimated with our chemical shift simulation method and the time-averaged induced shift of the guest proton reproduced the observed CIS quite satisfactorily (Table 4).⁴⁵

Figure 11. Crystal structure of **30**· CH_2Cl_2 .

Table 4. Observed and Calculated CIS (ppm)

	CH_2Cl_2	CH_2Br_2	CH_2ClCN	CH_2BrCN
obsd.	3.97 ± 0.25	3.90 ± 0.12	4.15 ± 0.05	3.85 ± 0.06
calc.	3.72 ± 1.09	3.27 ± 1.27	4.12 ± 0.85	3.92 ± 1.04

Recognition of planar molecules based on non-covalent interactions is of current interest in host-guest chemistry. A molecular tweezers host containing two aromatic chromophores connected by a spacer is a suitable receptor for planar guests. We prepared the receptors (**31**, **32**) having two units of dioxo[2.2]orthocyclophane. These receptors bind electron acceptor guests such as tetracyanoquinodimethane (TCNQ) and pyromellitic dianhydride (PDA). While the structure of the receptor in the supramolecular complex of TCNQ and **32** in the crystalline state has the tweezers form, that in the supramolecular complex of TCNQ and **31** is an L-

character form and two molecules of the receptor bind the one guest in the crystalline state to form a 2:1 complex (Figure 12).⁴⁶ Simple aromatic guests such as benzene or naphthalene showed no propensity towards these receptors, but the π -electron acceptor guests were complexed with these hosts in solution. Hence, the electron donor-acceptor interaction plays an important role in the complex formation. A 1:1 stoichiometry of the complex was determined by a continuous variation method using the CT-absorption band in all cases.

Figure 12. Crystal structures of **32**·TCNQ (left) and **31**·TCNQ·**31** (right).

In order to know the structure of the complex in solution, a modeling study of the supramolecular complex (PDA·**32**) was carried out with AMBER* force field using GB/SA chloroform solvation in the program of MacroModel V6.5. With the use of the low mode search algorithm two structures (**C1**, **C2**) of the complex were obtained (Figure 13). The most stable structure (**C1**) predicted by this calculation is almost identical to that found in the crystalline state. The second structure (**C2**) has a different orientation of the guest from **C1** in the cleft host. The complexation-induced shift value for the guest (1.30 ppm) obtained from the ¹H-nmr titration experiment suggested that the structure of the complex is very close to **C2** because our chemical shift simulation method predicted that the calculated induced shift of **C1** and **C2** is 3.67 and 1.68 ppm, respectively.⁴⁷

Figure 13. Calculated structures of PDA·**32**.

In the course of our study for the analysis of the guest binding behavior of the tweezers hosts, we had an interesting finding that alkyl chains directly connected to the tweezers host can alter the conformation of the host molecule. The two terminal aromatic chromophores of our tweezers are dif-

ferent from each other. We could not prepare the tweezers having the same polycyclic rings as the terminal aromatic chromophore because of the solubility problem. Hence, we introduced alkyl chains into the tweezers. Compound **33** has two hexyloxy substituents and **34** has a 1,14-dioxo[14]paracyclophane structure at the central part of the tweezers. To our surprise, **34** did not show any propensity to bind TCNQ in CDCl₃, although **34** can adopt an empty cleft conformation (**34x**) with an alkyl bridge situated outside of it. This clearly indicated that the alkyl bridge of paracyclophane obstructs the guest binding.

The failure of the guest binding for **34** suggested that the alkyl bridge should be situated above the naphthalene ring(s) so that there is no room for electron acceptor guest in the cavity. This was supported by the ¹H NMR chemical shift of the alkyl bridge.

The cleft conformation of **34** carrying a nested alkyl ring is found in the crystalline state (Figure 14). The CH/ π attractive interaction between the alkyl moiety and terminal naphthalene rings plays an important role in stabilizing this conformation. By contrast, the molecular structure of **33** in the crystalline state has a stepped anti arrangement of the three aromatic rings. The stepped anti conformation clearly shows that the intramolecular alkyl-arene interaction is not operative effectively in this molecule. The entropic cost to have a folded conformation of the alkyl chain suitable for the CH/ π attractive interaction is higher than the energy gain due to the attractive interaction between the alkyl chain and the terminal naphthalene rings.⁴⁸

Figure 14. Crystal structures of **34** (left) and **33** (right).

Fullerene C₆₀ and its family represent an intriguing class of molecules due to their unique physical and chemical properties. Their applications have been directed to many research areas such as chemistry, material science, biology, etc. Developing specific containers for fullerenes is of great interest in

constructing fullerene-based functional materials. We have found that calix[5]arenes are appropriate receptors for not only fullerene C60 but also C70. Simple calix[5]arene host **35** binds more preferentially to C60 than C70. The structure of the supramolecular complex of C60·**35** was obtained by an X-ray crystallographic analysis. Our chemical shift simulation method with a complexation-induced ^{13}C shift value of the guest disclosed that the structure of the complex in solution is almost identical to that found in the crystalline state.⁴⁹ The same simulation method clarified that the structure of the supramolecular complex of C70 and **35** in solution has an oblique arrangement of the guest with respect to the principal axis of the host.⁵⁰

Figure 15. Stereoview of calculated structure of C60·**36**.

The fullerenes were bound more strongly within the cavity of bis-calix[5]arene host **36**. The binding selectivity of the bis-calix[5]arene host towards the fullerenes is reversed when compared to that of **35**. The bis-calix[5]arene host binds more strongly to C70 than to C60. Although the C70 guest is fully encapsulated (Figure 15), it should have freedom of movement within the host cavity since the principal factor of the guest binding is the van der Waals force in nature. To simulate the dynamic character of the supramolecular complex, molecular dynamic calculation was carried out. The calculation showed that the guest moves rapidly within the host cavity. The MD simulation also gave the structures of the complex during the thermal motions. The theoretical complexation-induced shift (CIS) values of the guest for each monitored structure can be estimated with our chemical shift simulation method and the time-averaged induced shifts of the guest reproduced the observed CIS values quite satisfactorily.⁵¹

In order to elucidate the role of solvent molecules in the supramolecular complex formation in solution we tied the

host and guest with an oxyethylene chain as in compounds **37a-37c**. The ratios of the intramolecular complex formation are shown in Table 5. The complexation ratio is larger in all compounds than that of the intermolecular complex at the same concentration. The ratio is dependent on the chain length and the temperature. A remarkable solvent effect was observed in CHCl_3 and in toluene. In CHCl_3 , the complexation ratios increased with decrease of the temperature. On the other hand, in toluene, the completely reverse binding behavior was observed; the ratio increased with the increase of the temperature. The inclusion ratio is found to be independent of the concentration of **37** at micro- to millimolar concentrations. This result rules out the formation of the intermolecular dimer. In toluene, the entropy changes in the intramolecular complex formation are all positive, but the enthalpy changes are also positive. Apparently, the intramolecular complex formation of these compounds is a typical entropy-driven and enthalpy-opposed process (Table 6).⁵²

Table 5. Inclusion ratios (%) of **37_{a-37c}**

Temp(K)	CHCl_3			Toluene		
	37_a	37_b	37_c	37_a	37_b	37_c
320	62	43	26	78	63	40
303	80	58	35	66	53	35
282	90	68	44	50	41	23

Table 6. Thermodynamic parameters of intramolecular complex formation process of **37_{a-c}**

	CHCl_3		Toluene	
	$\Delta H(\text{kcal}\cdot\text{mol}^{-1})$	$\Delta S(\text{cal}\cdot\text{K}^{-1}\cdot\text{mol}^{-1})$	$\Delta H(\text{kcal}\cdot\text{mol}^{-1})$	$\Delta S(\text{cal}\cdot\text{K}^{-1}\cdot\text{mol}^{-1})$
37_a	-8.03	-24.0	5.16	18.4
37_b	-4.87	-15.7	3.89	13.1
37_c	-3.79	-13.8	3.34	9.6

The extensive desolvation from the fullerene moiety of these compounds plays an important role in the guest inclusion process. Net positive enthalpy suggested that the energy gain due to the formation of the intramolecular complex was less than the energy loss due to the desolvation around the guest moiety. In chloroform, on the other hand, both the entropy and enthalpy changes in the complex formation process gave negative values in all cases. Thus, this is the typical enthalpy-driven and entropy-opposed process.⁵² From this experiments, it is found that the desolvation from the guest and host plays an important role in the formation of supramolecular complexes.

7. Conclusion

We have developed a method for the determination of significantly populated conformers in highly flexible molecules. The method utilizes NMR chemical shifts of the compounds since those reflect molecular structures. The chemical shift changes caused by the nearby substituents were successfully reproduced by our chemical shift simulation method. In

order to widen the applicability of the method, the magnetic shielding parameters for several arenes and polar functional groups were developed. Combination of the chemical shift simulation method and molecular dynamic calculation was found to be an efficient method to analyze conformational equilibrium in highly flexible molecules.

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