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Conformational Behaviors of Tetra-*O*-methylsulfinylcalix[4]arenes—An Approach to Control the Conformation of Thiacalix[4]arenes by Oxidizing Sulfur Bridges

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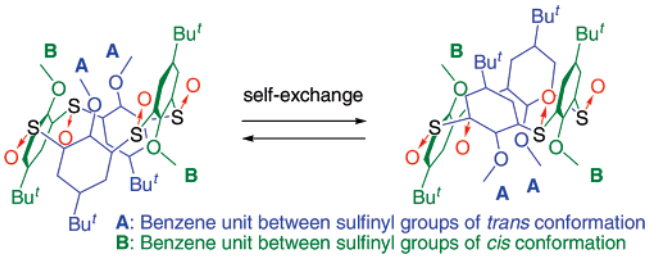
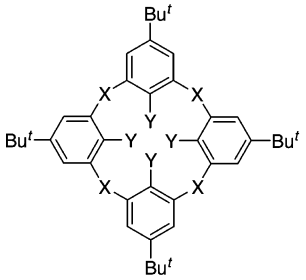


The conformational behaviors of all four stereoisomers [**5**(*rctt*), **5**(*rcct*), **5**(*rtct*), and **5**(*rccc*)] of tetra-*O*-methylsulfinylcalix[4]arene were studied by the ^{1}H NMR spectroscopic method. Variable-temperature (VT) NMR experiments of **5**(*rctt*), **5**(*rcct*), and **5**(*rtct*) revealed that each compound adopted the same conformation as that in the crystals at low temperatures and exhibited a self-exchange between the two equivalent species of this conformation at elevated temperatures. The values of the activation enthalpy $\Delta H^{\ddagger}$ for the self-exchange were similar (~70 kJ mol^{-1}). Further, the activation entropy $\Delta S^{\ddagger}$ was more important for **5**(*rtct*) (−40 J mol^{-1} K^{-1}) than for **5**(*rctt*) (−5 J mol^{-1} K^{-1}) and **5**(*rcct*) (−7 J mol^{-1} K^{-1}); consequently, the exchange rate of **5**(*rtct*) was 150−180 times less than that of the other isomers at 273 K. On the other hand, **5**(*rccc*) was in an equilibrium state between cone and partial-cone conformers at 253 K with the molar ratio being 85:15, which was in reasonable agreement with the relative stability between the two conformers calculated by the ab initio molecular orbital method.

Introduction

Calixarenes (e.g., **1**) are one of the most important molecular scaffolds in host−guest supramolecular chemistry.[1] Among such entities, thiacalix[4]arene **2**[2] and its sulfur-oxidized analogues **3** and **4**[3] have attracted much interest[4] because they have been found to exhibit useful properties either unknown or very different from the chemistry of conventional methylene-bridged calixarenes.



1 X=CH_2, Y=OH
2 X=S, Y=OH
3 X=SO_2, Y=OH
4 X=SO, Y=OH
5 X=SO, Y=OMe

For example, in solvent extraction experiments, thiacalixarene **2** and sulfonylcalixarene **3** selectively extract soft and hard metal ions, respectively,[5] while methylene-bridged calixarene **1** exhibits almost no extractability with regard to metal ions. Both

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(1) (a) Gutsche, C. D. Calixarenes. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989. (b) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 1991. (c) Gutsche, C. D. *Calixarenes Revisited.* In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998.

(2) Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kameyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971.

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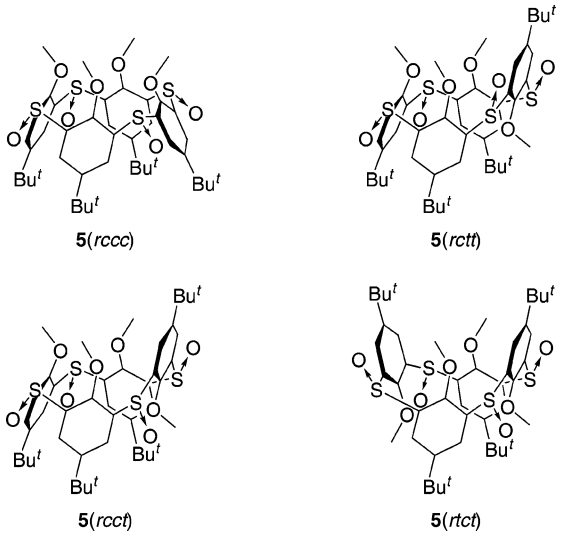


FIGURE 1. Schematic views of the X-ray structures of the stereoisomers of compound **5**. The aromatic rings are depicted as hexagons for clarity. The dispositions of the sulfinyl oxygen atoms are denoted by the term *cis* (*c*) or *trans* (*t*) relative to the reference sulfinyl oxygen atom (*r*) with respect to the mean plane defined by the macrocycle as suggested by Böhmer.[4a] The notation proceeds around the system in a direction from the reference oxygen, which is chosen in order to prioritize *cis* over *trans* and maximize the number of *cis*.

the extractability and selectivity were attributed to the cooperative coordination of a soft sulfur or hard sulfonyl oxygen atom with two neighboring phenoxide anions toward the metal center.[6] On the other hand, the sulfinylcalixarene with the *rtct* configuration, **4**(*rtct*) (refer to Figure 1 for the configurational notations of sulfinylcalixarenes), can extract both types of metal ions by switching the ligating atom between the oxygen and sulfur of the sulfinyl function, depending on the type of metal ions to be extracted.

Thiacalixarenes also exhibit higher conformational flexibility as compared to the corresponding methylene-bridged analogues. As in the case of calixarene **1**, thiacalixarene **2** adopts cone conformation in crystals by virtue of intramolecular cyclic hydrogen bonding among the hydroxy groups;[7] further, in solution, it exhibits rapid interconversion between two cone conformations via the oxygen-through-the-annulus rotation.[8] However, the activation energy of the interconversion of **2** was reported to be 8.4 kJ mol^{-1} lower than that of **1**,[9] which was attributed to the larger ring size of the former macrocycle, owing to the difference in the bond length between the Ar−S and Ar−C bonds, and, as a result, to weaker strength of the hydrogen bonding of **2** as compared with that of **1**.[10]

In addition to the difference in the mobility, the difference in conformational preferences has also been observed in etherified derivatives. It has been reported that the tetraethyl ether of de-*tert*-butylated thiacalix[4]arene is in the equilibrium state of all the four possible conformers in $CDCl_2CDCl_2$ at 303 K; the conformer distribution at this temperature was 56:trace: 17:26 (partial cone:1,2-alternate:cone:1,3-alternate).[11] On the other hand, the tetraethyl ether of conventional calixarene **1** does not undergo conformational change at room temperature but becomes mobile with increasing temperature; in this case, the conformer distribution reaches 47:43:7:3 at 405 K.[12]

Sulfinylcalix[4]arene **4** has four stereoisomers originating from the disposition of the four sulfinyl functions (Figure 1). Recently, we succeeded in preparing all the four stereoisomers by the direct oxidation of **2** or the stereocontrolled oxidation of its *tetra-O*-benzyl derivatives, followed by debenzylation.[3c] During our study, we noticed that stereoisomeric *tetra-O*-methyl derivatives **5** exhibit different conformational behaviors in solution. This suggests that the conformation of thiacalixarenes can be controlled by oxidizing the sulfur bridges, which is a notable feature not attainable by the methylene-bridged analogues of thiacalixarenes. In this study, we wish to report on the conformational behaviors of all the four stereoisomers of **5** in solution as studied by ^{1}H NMR spectroscopy. The conformational calculation of **5**(*rccc*) was also conducted by the ab initio molecular orbital method to estimate the effect of the orientation of the sulfinyl groups on the relative stability of its four conformers.

Results and Discussion

Before describing the conformational behaviors of the stereoisomers of compound **5**, we would like to briefly summarize their X-ray structures reported previously (Figure 1).[3c] In the crystals, **5**(*rccc*) adopts a cone conformation in which all the methoxy groups are in the direction opposite to that of the sulfinyl oxygen atoms with respect to the mean plane defined by the macrocycle. On the other hand, **5**(*rctt*) and **5**(*rcct*) adopt a partial-cone conformation, in which the methoxy group(s) between the two adjacent sulfinyl groups of the *cis* conformation are in the direction opposite to that of the sulfinyl oxygen atoms, and **5**(*rtct*) adopts a 1,3-alternate conformation defined univocally. These X-ray structures obey the following two rules, which are attributable to the minimization of the electrostatic repulsion between the sulfinyl and methoxy groups (Figure 2): (*a*) at least one of the two methoxy groups adjacent to a sulfinyl group is in the direction opposite to that of the sulfinyl oxygen atom; and (*b*) the methoxy group on the benzene ring between the two adjacent sulfinyl groups of the *cis* conformation is in the direction opposite to that of the sulfinyl oxygen atoms. We denote hereafter such a *p-tert*-butylmethoxybenzene unit between the two neighboring sulfinyl groups of a *cis* conformation by a *cis*-benzene unit and that between the two neighboring sulfinyl groups of a *trans* conformation by a *trans*-benzene unit.

(3) (a) Mislin, G.; Graf, E.; Hosseini, M. W.; Cian, A. D.; Fischer, J. *Chem. Commun.* **1998**, 1345. (b) Iki, N.; Kumagai, H.; Morohashi, N.; Ejima, K.; Hasegawa, M.; Miyanari, S.; Miyano, S. *Tetrahedron Lett.* **1998**, *39*, 7559. (c) Morohashi, N.; Katagiri, H.; Iki, N.; Yamane, Y.; Kabuto, C.; Hattori, T.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2324.

(4) Review: (a) Iki, N.; Miyano, S. *J. Inclusion Phenom.* **2001**, *41*, 99. (b) Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675. (c) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291.

(5) Iki, N.; Morohashi, N.; Narumi, F.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1597.

(6) Morohashi, N.; Iki, N.; Sugawara, A.; Miyano, S. *Tetrahedron* **2001**, *57*, 5557.

(7) Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, G.; Pansanel, J.; Cian, A. D.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 2311.

(8) Araki, K.; Iwamoto, K.; Shinkai, S. *Chem. Lett.* **1989**, 1747.

(9) (a) Sone, T.; Ohba, Y.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **1997**, *53*, 10689. (b) Ito, K.; Ohba, Y.; Sone, T. *Nippon Kagaku Kaishi* **1999**, 217.

(10) Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437.

(11) Lang, J.; Dvořáková, H.; Bartošová, I.; Lhoták, P.; Stibor, I.; Hrabal, R. *Tetrahedron Lett.* **1999**, *40*, 373.

(12) Groenen, L. C.; Loon, J.-D.; Verboom, W.; Harkema, S.; Casnati, A.; Ungaro, R.; Pochini, A.; Ugozzoli, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 2385.

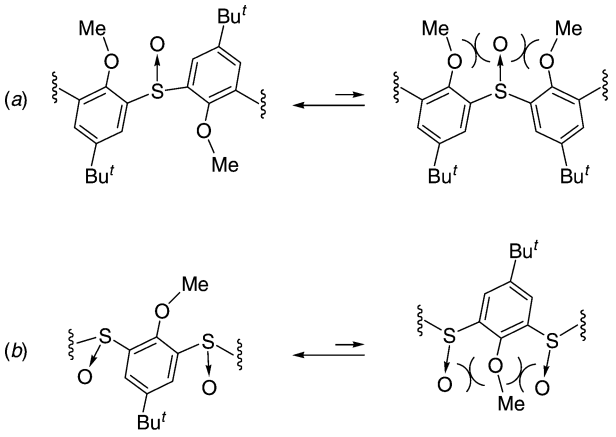


FIGURE 2. Two rules followed by the X-ray structures of the stereoisomers of compound **5**.

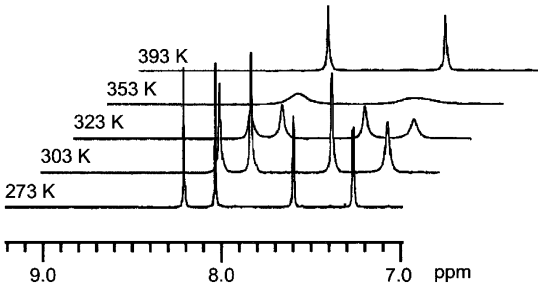
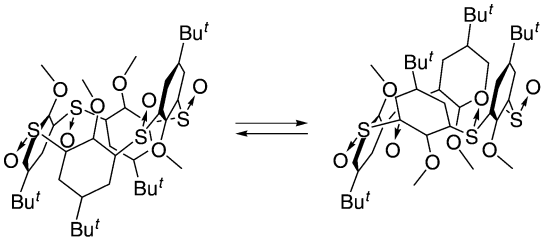


FIGURE 3. Expanded VT NMR spectra of the aryl region of **5**(*rctt*).

Rule (*a*) is obeyed by all the crystal structures and rule (*b*) by **5**(*rccc*), **5**(*rctt*), and **5**(*rcct*).

The conformational behaviors of the stereoisomers of compound **5** were examined by VT NMR spectroscopy. We will describe the spectral pattern and the corresponding temperature dependence only in the aryl region; however, we have confirmed that the results obtained in the other regions support the discussion presented herein. The ^{1}H NMR spectrum of **5**(*rctt*) measured in $CDCl_2CDCl_2$ at 273 K exhibited two singlets [δ 7.26 and 7.60 (2H each)] and two doublets [δ 8.03 and 8.20 (2H each)] for the aryl protons (Figure 3), indicating that the compound has a symmetric structure with a σ-plane. Assuming that rule (*b*) stated above is applicable to the conformation of **5**(*rctt*) in the solution, the same structure as that in the crystals can be unambiguously deduced from the spectral pattern. As the temperature was increased, both the singlets (δ 8.03 and 8.20) and doublets (δ 7.26 and 7.60) assigned to the *cis*- and *trans*-benzene units, respectively, coalesced to yield two singlets. This temperature-dependent behavior derived from the spectra can be explained by the self-exchange between the two equivalent species of the partial-cone conformation that emerged from the fast inversion of the *trans*-benzene units on the NMR time scale (eq 1).



(1)

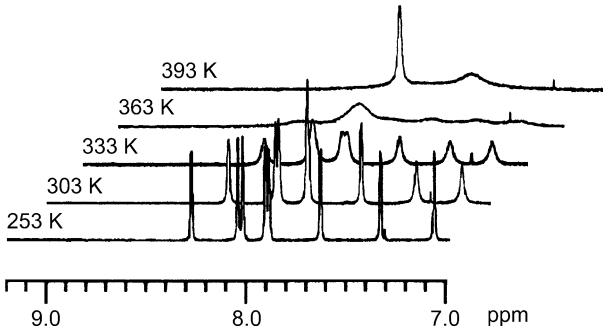


FIGURE 4. Expanded VT NMR spectra of the aryl region of **5**(*rcct*).

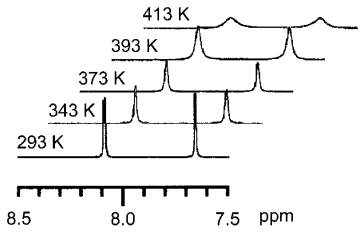
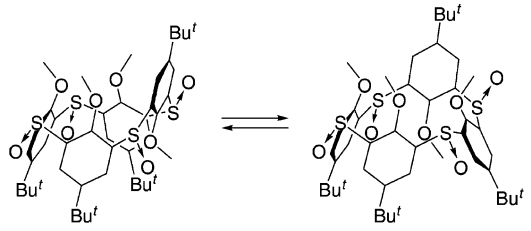


FIGURE 5. Expanded VT NMR spectra of the aryl region of **5**(*rtct*).

The ^{1}H NMR spectrum of **5**(*rcct*) measured at 253 K exhibited eight doublets [δ 7.07, 7.34, 7.64, 7.90, 7.91, 8.03, 8.05, and 8.28 (1H each)] for the aryl protons (Figure 4), indicating that the compound has an unsymmetrical structure. The application of rule (*b*) to the spectral pattern leads to a sole conformation, which is consistent with rule (*a*) and identical to that in the crystals. Although the conformational behavior of this species obtained from the VT NMR spectrum was ambiguous because of the severe peak broadening, a ROESY spectrum of **5**(*rcct*) measured at room temperature revealed the existence of four couples of exchanging protons, which corresponds to the equilibrium between the two equivalent species of the partial-cone conformation attributed to the inversion of the *trans*-benzene units (eq 2) (refer to the Supporting Information).



(2)

The ^{1}H NMR spectrum of **5**(*rtct*) measured at 293 K exhibited two doublets [δ 7.65 and 8.09 (4H each)] for the aryl protons (Figure 5). This indicates the magnetic equivalence of all the benzene units, which is satisfied by the 1,3-alternate conformation with S_4 symmetry as well as the cone conformation with C_{2v} symmetry; both were defined univocally. The former conformation is identical to that in the crystals and feasible considering the fact that it follows rule (*a*); however, the latter conformation does not. The two aryl signals did not coalesce, even at 413 K, but exhibited significant peak broadening, which was attributed to a slow self-exchange of the 1,3-alternate conformer resulting from the inversion of the *trans*-benzene units (eq 3). A ROESY spectrum of **5**(*rtct*) measured at room temperature revealed that no exchange signal existed between

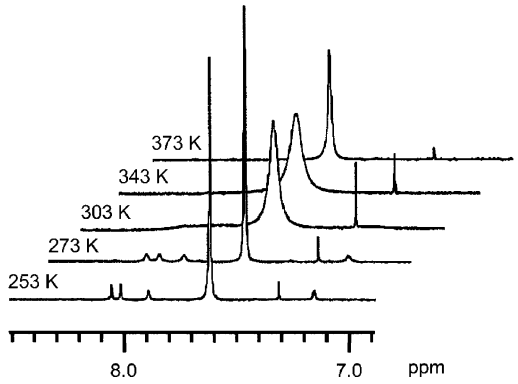
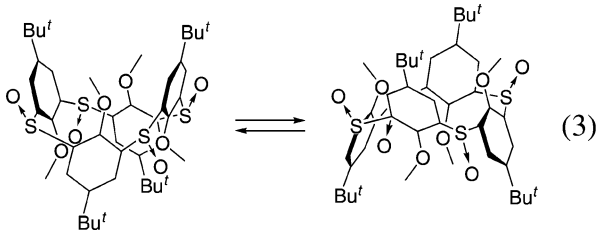
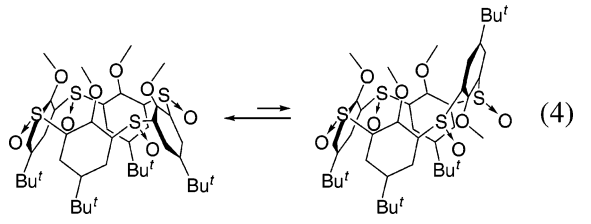


FIGURE 6. Expanded VT NMR spectra of the aryl region of **5**(*rccc*).

the aryl protons, which supports the dynamic behavior (refer to the Supporting Information).



The dynamic behaviors of these three stereoisomers share a common characteristic. Thus, all the *trans*-benzene units experienced a flip-flop motion, while the *cis*-benzene units did not. This resulted in the self-exchange between the two equivalent species. On the other hand, **5**(*rccc*) exhibited different dynamic behavior. The ^{1}H NMR spectrum of **5**(*rccc*) measured at 253 K exhibited an 85:15 mixture of two conformers (Figure 6). The major isomer exhibited one singlet for aromatic protons [δ 7.62 (8H)]; on the application of rule (*a*) to this observation, a cone conformation identical to the X-ray structure was obtained. On the other hand, the minor isomer exhibited two doublets [δ 7.16 and 7.90 (2H each)] and two singlets [δ 8.02 and 8.06 (2H each)] for the aryl protons. In this case, the magnetic equivalences corresponded to a partial-cone conformation, though it did not obey rule (*b*). The signals of the two species coalesced at an elevated temperature to form a spectral pattern, thereby suggesting a C_4-symmetric structure. These observations should indicate that the partial-cone conformer is the one formed by flipping a benzene ring of the cone conformer, and that a fast flip-flop motion of the four benzene rings was responsible for the appearance of the apparently C_4-symmetric spectral pattern at the elevated temperature (eq 4).



It has been reported that the ^{1}H NMR spectrum of the tetraethyl ether of de-*tert*-butylated thiacalix[4]arene measured in $CDCl_2CDCl_2$ exhibits the presence of all four conformers in an equilibrium state, and the corresponding molar ratio at 303 K is 56:trace:17:26 (partial cone:1,2-alternate:cone:1,3-alternate).[11] In the case of the tetramethyl ether of thiacalixarene **2**, the ^{1}H NMR spectrum exhibited a C_4-symmetric spectral pattern at room temperature caused by the fast chemical exchange among these conformers.[3a,13] Therefore, the difference in the free energy among the four conformers of these thiacalixarenes appears to be small, as compared to that among the stereoisomers of sulfinylcalixarene **5**, which only exhibited self-exchange or the interconversion between two specific conformers. The conformational calculation of **5**(*rccc*) was carried out by the ab initio molecular orbital method at the HF/6-31G* level to estimate the effect of the orientation of the sulfinyl groups on the relative stability of its four conformers. This calculation revealed that the cone conformer was most stable, and that the energies of the partial cone, 1,3-alternate, and 1,2-alternate were 4.22, 15.53, and 67.05 kJ mol^{-1} higher than that of the cone conformer, respectively (Table 1). The distribution of the conformers calculated from the energy differences was cone:partial cone:1,3-alternate = 88:12:$\sim$0 at 253 K, which is in reasonable agreement with the experimental value of cone:partial cone = 85:15 derived from the ^{1}H NMR analysis (vide supra). The order of the relative stability of the four conformers differs from that of the deoxidized structure (i.e., partial cone > 1,3-alternate > cone > 1,2-alternate), as can be judged from the equilibrium composition of the tetraethyl ether of de-*tert*-butylated thiacalix[4]arene in $CDCl_2CDCl_2$ (vide supra). Further, this order can be qualitatively rationalized by applying the conformational rules (*a*) and (*b*). Thus, the cone conformer that fulfills both the rules completely is most stable. The partial cone with one substructure disobeying rule (*b*), the 1,3-alternate with two such irregular substructures, and the 1,2-alternate with a substructure disobeying rule (*a*) in addition to two substructures disobeying rule (*b*) are less stable than the cone conformer in the given order. Therefore, it is concluded that the conformations of sulfinylcalixarenes **5** are strongly controlled by the electrostatic repulsion between the sulfinyl and methoxy groups, although the conformational preferences of the deoxidized thiacalixarene skeleton would also affect the conformational outcome.

TABLE 1. Total and Relative Energies for the Conformers of 5(*rccc*)[a]

conformer	E	ΔE^b
cone	−10 206 493.48	
partial cone	−10 206 489.26	4.22
1,3-alternate	−10 206 477.95	15.53
1,2-alternate	−10 206 426.43	67.05

[a] Units: kJ mol^{-1}. [b] Energy relative to E(cone).

The VT NMR spectra of **5**(*rctt*), **5**(*rcct*), and **5**(*rtct*) possessed shapes that were suitable for determining the rate constants for the exchange process by using the complete line-shape method. In each case, the simulation was in reasonable agreement with the measured spectrum (Figure 7). The Eyring plots allowed us to determine the activation parameters from the temperature dependence of the rate constant (Table 2). The $\Delta H^{\ddagger}$ values were similar ($\sim$70 kJ mol^{-1}) and approximately 10 kJ mol^{-1} higher than those reported for the conformational exchanges between the partial cone and the other three conformers of the tetramethyl ether of conventional calixarene **1**.[14] The increase in activation enthalpy can be attributed partly to the loss, in the transition

(13) Lhoták, P.; Himl, M.; Stibor, I.; Sýkora, J.; Dvořáková, H.; Lang, J.; Petříčková, H. *Tetrahedron* **2003**, *59*, 7581.
(14) Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1994**, *116*, 11957.

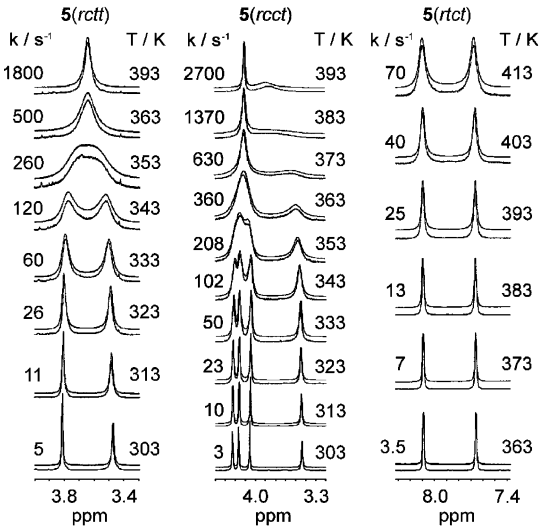


FIGURE 7. Experimental (lower) and simulated (upper) ^{1}H NMR signals as functions of temperature.

TABLE 2. Activation Parameters for the Conformational Exchange of the Stereoisomers of Compound 5 in $CDCl_2CDCl_2$

stereoisomer	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	k_{273}[a] (s^{-1})
5(*rctt*)	68.9	−5	0.20
5(*rcct*)	68.9	−7	0.16
5(*rtct*)	71.2	−40	0.0011

[a] Calculated from $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

state, of the stabilization energy provided by the conjugation between a benzene ring and adjacent sulfinyl groups. On the other hand, the $\Delta S^{\ddagger}$ value for the 1,3-alternate−1,3-alternate exchange of **5**(*rtct*) was smaller than the $\Delta S^{\ddagger}$ values for the partial cone−partial cone exchanges of **5**(*rctt*) and **5**(*rcct*), which yielded a rate constant 150−180 times smaller than that of the others at 273 K. The structure of **5**(*rtct*) with the 1,3-alternate conformation is the one with the smallest dipole moment. Therefore, the interconversion necessarily passes through a transition state with a larger dipole moment, which will result in the more significant organization of solvent molecules around the calixarene to decrease the activation entropy.

Conclusion

The conformational behaviors of the four stereoisomers of tetra-*O*-methylsulfinylcalix[4]arene have been examined by ^{1}H NMR and computational methods. Their conformations were found to be controlled by the disposition of the sulfinyl groups, which could be rationalized by the electrostatic repulsion between the sulfinyl and methoxy groups. The activation parameters for the conformational exchanges were determined by Eyring plots. The conformation of calixarenes has thus far been controlled dynamically by the hydrogen bonding between the hydroxy groups and statically by introducing bulky substituents at the lower rim. The oxidation of the epithio linkages adds another method to realize the dynamic controlling of calixarene conformations and will be useful not only for the development of sophisticated molecular hosts with thiacalixarene skeletons but also for the regioselective and stereoselective modification of thiacalixarenes. A regioselective methoxy displacement reaction of **5** with lithium benzylamide taking advantage of this conformational control will be reported in due course.[15]

Experimental Section

General. The stereoisomers of compound **5** were prepared according to our previously reported procedures.[3c]

VT NMR Measurement. The VT NMR spectra were recorded on a 400 MHz spectrometer using tetramethylsilane as an internal standard and $CDCl_2CDCl_2$ as solvent. The samples were prepared with a concentration of 1.5×10^{-2} mol dm^{-1}.

Computational Method. The conformational search of **5**(*rccc*) was performed by employing the MM2* force field using MacroModel[16] to yield conformers, the geometries of which were optimized at the HF/6-31G* level using Gaussian98.[17] The computer simulations of the NMR spectra were performed using the DNMR71 program.[18]

Acknowledgment. A part of the experimental results in this research was obtained using the supercomputing resources at the Information Synergy Center, Tohoku University. We are grateful to Dr. Fumitaka Narumi, Ishinomaki Senshu University, for the ROESY measurements.

Supporting Information Available: ^{1}H NMR data for the stereoisomers of compound **5**, photocopies of the complete VT NMR spectra of the stereoisomers of compound **5**, photocopies of the ROESY spectra of **5**(*rcct*) and **5**(*rtct*), Eyring plots for the conformational exchanges of **5**(*rctt*), **5**(*rcct*), and **5**(*rtct*), and *z*-matrixes of the calculated structures of **5**(*rccc*). This material is available free of charge via the Internet at http://pubs.acs.org.

JO701381H

(15) Katagiri, H.; Iki, N.; Hattori, T.; Kabuto, C.; Miyano, S. *J. Am. Chem. Soc.* **2001**, *123*, 779.

(16) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still. W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.10; Gaussian Inc.: Pittsburgh, PA, 2001.

(18) Reich, H. J. *J. Chem. Educ. Software* **1996**, *3D*, 2.