Frozen 1,3-Alternate Conformation of Exhaustively Methylated Azacalix[4]arene in Solution: Successful Immobilization by Small but yet Sufficiently Bulky *O*-Methyl Group

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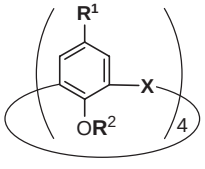
Conformational flexibility of exhaustively methylated azacalix[4]arene in solution has been investigated. Relaxation time measurements revealed that its 1,3-alternate conformation was inflexible even in solution. Intramolecular small annulus plays a central role in suppressing the conformational inversion by the small but yet sufficiently bulky *O*-methyl groups. Without regard to the small anulus, the azacalix[4]arene has a room to selectively accommodate potassium ion in the cavity.

Heteroatom-bridged calixarenes attract much interests as a new class of calixarene family because of the intriguing properties distinct from those of the original calixarenes.[1,2] Recently, Tanaka et al.,[3] Yamamoto et al.,[4] and Wang et al.[5] independently succeeded in preparing nitrogen-bridged calixarenes, which exhibited interesting structure–property relationships reflecting the introduction of nitrogen atoms as bridging units. In the course of our study aiming at developing a functional material with a host ability, we very recently reported the preparation of exhaustively methylated azacalix[4]arene **1** with a 1,3-alternate conformation (Chart 1).[6] However, a rational conclusion of the conformational flexibility of **1** in solution had not been derived from the ^{1}H NMR spectra because of the lack of temperature dependence (Figure S1).[6,7] This unsettled question has to be solved, when considering the fact that host ability of calix[4]arenes **2** and **3** is strongly dependent on the conformational flexibility in solution.[8] In the present study, to establish a firm basis for applying **1** as a host molecule, its conformational flexibility in solution has been investigated by means of relaxation time measurements. As an eventual outcome, it was found that the 1,3-alternate conformation of **1** was inflexible even in solution. Here, we report the successful conformational immobilization of **1** by small *O*-methyl group, which does not suffice to suppress the conformational inversion of carbocyclic analogue **2** in solution.[9] Host-ability of **1** based on the frozen 1,3-conformation is also described.

^{1}H NMR relaxation time (T_1) is sensitive to molecular motion, and T_1 measurement was successfully applied for studying the conformatioal flexibility of thiacalix[4]arene **4**, which was reported to be flexible in $CDCl_3$.[10] It was also reported that $\Delta G^{\ddagger}$ for the conformational inversion of thiacalix[4]arene derivatives correlated closely with the T_1 values of the aromatic protons.[10] T_1 value of the corresponding resonance of **1** in $CDCl_3$ was determined at 270 MHz and 21 °C by using the inversion recovery method (Figure 1).[11] That of calix[4]arene **5**, which retained a frozen 1,3-alternate conformation in solution due to the *O*-propyl groups,[9] was also estimated as a reference. A much smaller T_1 value of 0.81 s was obtained for conformationally inflexible **5**, as compared with 2.51 s reported for flexible **4**.[10] Azacalix[4]arene **1** exhibited almost the same T_1 value of 1.03 s as **5**, implying that the molecular framework of **1** was as rigid as **5**. This result is consistent with our previous two experimental facts. First, ^{1}H NMR spectra of **1** was temperature independent in the range of −80 to 80 °C (Figure S1).[6,7] Second, NOE correlations were explained properly by considering a sole contribution of an inflexible 1,3-alternate conformation of **1**.[6] Accordingly, it is reasonable to conclude from the above three experimental results that the 1,3-alternate conformation of **1** is frozen in solution, at least, up to the examined temperature of 80 °C.

To explore a reason for the observed conformational stability of **1** in solution, its crystal structure[6] was compared with that of the carbocyclic analogue **2**.[12] As shown in Figure S3,[7] interatomic distances between the bridging nitrogens of **1** are in the range of 4.84 to 4.93 Å, whereas the corresponding distances of **2** are 5.07 to 5.11 Å. It was reported that *O*-methyl group was not sufficiently large to curtail the conformational inversion of **2** via the "lower rim through the annulus" pathway.[8] However, the intramolecular annulus of **1** (23.9 Å^2) is reduced by ca. 9% in area, as compared with that of **2** (26.0 Å^2). As a result, it is likely that the small annulus of **1** suppresses the passage of even the *O*-methyl groups and thereby hinders the conformational inversion of **1** in solution.[13]

Complexation behavior of calix[4]arenes **2** and **3** for alkali-metal ions was reported to be dependent on the conformational freedom; conformationally flexible tetramethyl ether **2** revealed no selectivity for these cations, whereas tetrapropyl ether **3** with



1: R^1 = *t*-Bu, R^2 = Me, **X** = NMe
2: R^1 = *t*-Bu, R^2 = Me, **X** = CH_2
3: R^1 = H, R^2 = *n*-Pr, **X** = CH_2
4: R^1 = *t*-Bu, R^2 = H, **X** = S
5: R^1 = *t*-Bu, R^2 = *n*-Pr, **X** = CH_2

Chart 1.

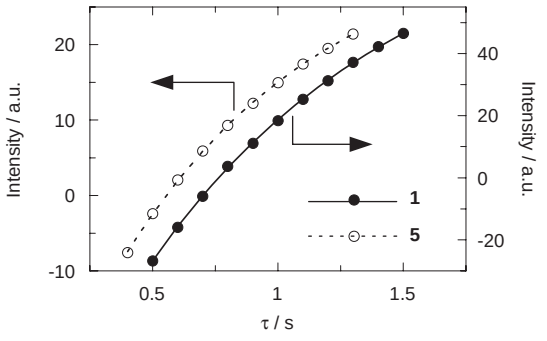


Figure 1. Inversion recovery curves for the aromatic protons of azacalix[4]arene **1** and calix[4]arene **5** in $CDCl_3$ at 21 °C and 270 MHz.

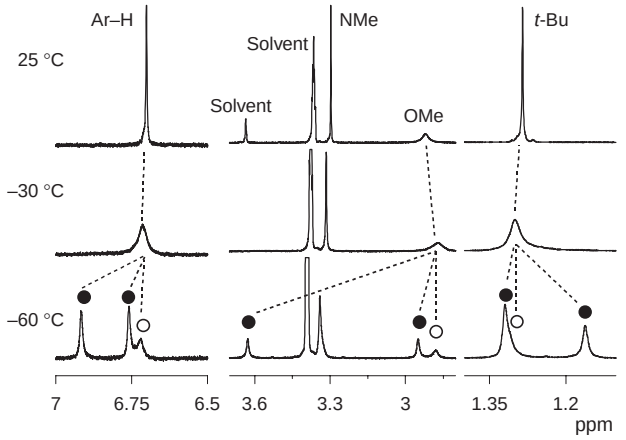


Figure 2. Partial ^{1}H NMR spectra of azacalix[4]arene **1** (0.50 mM) in the presence of potassium picrate (0.50 mM) in $CDCl_3/CD_3OD$ (4:1, v/v). Solid and open circles represent the NMR signals for the **1**·K^+ complex and those of uncomplexed **1**, respectively.

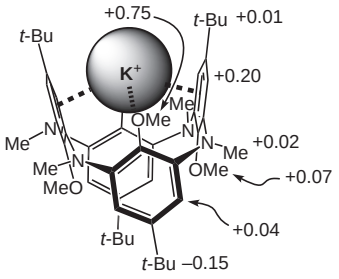


Figure 3. The structure of the **1**·K^+ complex deduced from the ^{1}H NMR spectra. Numbers indicate the observed changes in the chemical shifts upon complexation with K^+ ion at −60 °C. Plus and minus signs represent downfield and upfield shifts, respectively, as compared to the chemical shifts of **1**. Dashed and dotted lines indicate cation/π and ion–dipole interactions, respectively.

a frozen 1,3-alternate conformation exhibited selective complexation for K^+ ion.[8] Thus, it is conceivable that azacalix[4]arene **1** will selectively form a complex with K^+ ion. Complexation of **1** with alkali-metal ions was examined according to the described procedure.[8] As shown in Figure 2, NMR signals of **1** were drastically changed upon complexation with K^+ ion. Signal broadening was observed for the methoxy groups at 25 °C, and the resonances of the aromatic and *tert*-butyl protons were also broadened at −30 °C. Upon further decreasing the temperature to −60 °C, each of the broadened NMR signals was split into three, one of which corresponded to uncomplexed **1** and the remaining two were assigned to a 1:1 potassium complex schematically illustrated in Figure 3. The depicted structure of **1**·K^+, which was essentially identical with that reported for **3**·K^+,[8] was deduced from the observed spectral changes; the resonance of the *N*-methyl groups was not altered over the examined temperature range, indicating that the aromatic rings and methoxy groups rather than the bridging nitrogens contributed to the formation of **1**·K^+, probably due to the steric hindrance around the nitrogen atoms. Na^+ and Li^+ ions were similarly examined, but no appreciable spectral changes were observed (Figure S2).[7]

Table 1. Binding constants (K_{ass}) for alkali-matel ions

Compound	log K_{ass}		
	Li^+	Na^+	K^+
1	<1[a,b]	<1[a,b]	3.4[a,b]
2[9]	2.2[c]	3.0[c]	2.6[c]
3[9]	<1[c]	<1[c]	4.7[c]

[a]Perchlorate salts for Li^+ and Na^+, and picrate salt for K^+ were used. [b][**1**] = [alkali-metal ion] = 0.50 mM, $CDCl_3/CD_3OD$ (4:1, v/v), −60 °C. [c]Cited from Ref. 9.

As was expected above, azacalix[4]arene **1** exhibited selective complexation for K^+ ion, as summarized in Table 1. It was found from the host–guest study that **1** left a room to accommodate K^+ ion with an ionic radius of 1.33 Å, though the intramolecular annulus of **1** was smaller than that of **2**.

In summary, we have demonstrated that the 1,3-alternate conformation of azacalix[4]arene **1** is inflexible even in solution. Intramolecular small annulus of **1** would be responsible for the observed conformational immobilization by the small *O*-methyl groups. Without regard to the small annulus, azacalix[4]arene **1** formed a potassium complex on the basis of the frozen 1,3-alternate conformation.

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13 To evaluate electronic effect, NBO analysis at a B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p) level was performed. It was found that ca. 0.24 electrons of each nitrogen lone pair migrated equally to the two adjacent benzene rings. In other words, the bridging nitrogen atoms partially conjugate with the benzene rings, suggesting that electronic effect also contributes to the stabilization of the 1,3-conformation of **1**.

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