

We find that incubation of **1** with 0.2 M DSCH₂CO₂CH₃ in both 9:1 CD₃OD:CD₃CO₂D and 9:1 CH₃OD:CH₃CO₂D, as described above, leads to >80% incorporation of deuterium at C-2 and C-6 in isolated **2**.²⁴ These observations provide strong support for the biradical intermediate of Scheme I. Its formation from the cumulene-ene of Scheme I, as compared with the Bergman reaction²⁵ postulated to occur in the calichecin²⁶ and esperamicin²⁷ antibiotics, represents a new molecular rearrangement and a distinct strategy for the spontaneous generation of carbon-centered free radicals at or below ambient temperature.

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Supplementary Material Available: A tabulation of complete and assigned ¹H NMR spectral data for **2** and **3** and the 2-D COSY spectrum of **2** and chemical shift comparisons for (*R*)- and (*S*)-Mosher ester derivatives of **2**, **5**, and **6** (3 pages). Ordering information is given on any current masthead page.

(24) Goldberg et al. report that incubation of **1** with DSCH₂CO₂CH₃ (concentration not specified) in 0.1 M CD₃CO₂D in CH₃OD leads to production of a monoadduct displaying signals at δ 7.83 (s) and δ 7.01 (d) "at reduced intensity" with "incomplete deuterium incorporation from deuteriothioglycolate".⁵

(25) (a) Bergman, R. G.; Jones, R. R. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

(26) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

(27) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

NMR Determination of Association Constants for Calixarene Complexes. Evidence for the Formation of a 1:2 Complex with Calix[8]arene

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Calixarenes are cyclic oligomers made up of benzene units just as cyclodextrins are made up of glucose units. A variety of calixarenes may now be synthesized in good yields,¹ and they are now useful as a basic skeleton in the design of new functionalized host molecules.²⁻⁸ Beginning in 1984 we synthesized and studied

(1) For comprehensive reviews of Gutsche's work, see: (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. (b) Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1.

(2) Shinkai, S. *Pure. Appl. Chem.* **1986**, *58*, 1523.

(3) Ungaro, R.; Pochini, A.; Andreotti, G. D.; Domiano, P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 197.

(4) Coruzzi, M.; Andreotti, G. D.; Bocchi, V.; Pochini, A.; Ungaro, R. *J. Soc., Perkin Trans. 2* **1982**, 1133.

(5) Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 1709.

(6) McKervery, M. A.; Seward, E. M.; Ferguson, G.; Rubl, B. L. *J. Org. Chem.* **1986**, *51*, 3581.

(7) Olmstead, M. M.; Sigel, G.; Hope, H.; Xu, X.; Power, P. P. *J. Am. Chem. Soc.* **1985**, *107*, 8087.

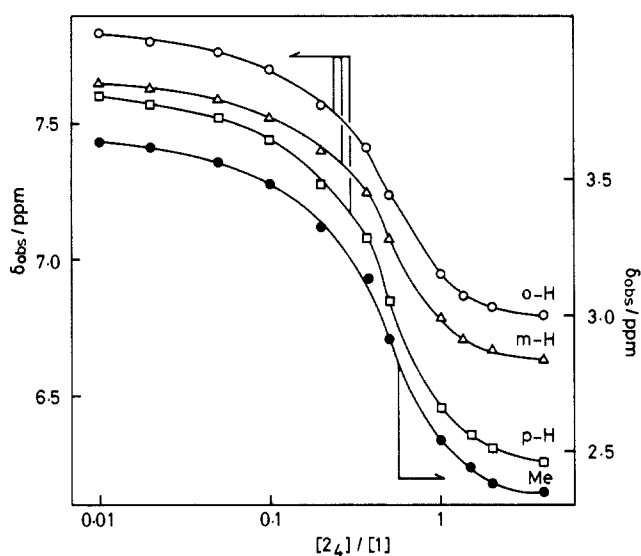


Figure 1. Plots of δ_{obsd} versus $[2_4]/[1]$. The concentration of **2₄** was maintained constant (1.00 mM) while that of **1** was varied (0.25–100 mM): D₂O, 25 °C, pD 7.3 with 0.1 M phosphate buffer, internal standard DSS.

Table I. Association Constants and Thermodynamic Parameters

parameter	2₄	2₆	2₈	
			1:1	1:2
$10^{-2}K$ (M ⁻¹ , at 25 °C)	56.0 ± 2.5	5.5 ± 0.4	52.0 ± 0.5	46.0 ± 0.5
ΔG (kcal mol ⁻¹ , at 25 °C)	-5.1 ± 0.5	-3.7 ± 0.2	-5.1 ± 0.2	-5.0 ± 0.1
ΔH (kcal mol ⁻¹)	-6.2 ± 0.3	-0.25 ± 0.10	0.0 ± 0.10	0.0 ± 0.10
ΔS (cal mol ⁻¹ deg ⁻¹)	-3.6 ± 0.8	11.7 ± 0.3	17.0 ± 0.3	16.7 ± 0.1

sulfonatocalixarenes, the first example for water-soluble calixarenes.⁹⁻¹⁴ However, the question on molecular recognition in solution remained unresolved. We report here the NMR method,¹⁵ which is more complicated but applicable to a variety of guest molecules. We have determined the association constants (*K*), ΔH , and ΔS for the complexation of trimethylanilinium chloride (**1**) and *p*-sulfonatocalix[*n*]arene (*n* = 4, 6, and 8; **2_n**). During this study we unexpectedly found unequivocal evidence for the formation of the 1:2 complex with **2₈**.

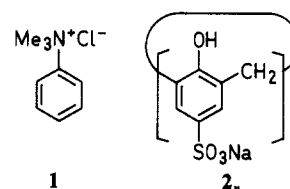


Figure 1 shows the chemical shift of **1** in the presence of **2₄** in D₂O at 25 °C.¹⁶ It is seen from **Figure 1** that all peaks shift to

(8) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6063. (9) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315.

(10) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, *108*, 2409.

(11) Shinkai, S.; Mori, S.; Araki, T.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3679.

(12) Shinkai, S.; Arimura, T.; Sotoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495.

(13) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, M. *Chem. Lett.* **1987**, 2269.

(14) A water soluble calixarene (*p*-*tert*-butylcalix[4]arene tetracarboxylic acid) was also reported by the Italian group, but the water solubility is not enough, especially, in the presence of salts: Arduini, A.; Pochini, A.; Verberber, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.

(15) JEOL GX-400 NMR apparatus. Schürmann and Diederich used the similar NMR method for the determination of binding constants for cyclodextrins, but the measurements were carried out only at the constant temperature: Schürmann, G.; Diederich, F. *Tetrahedron Lett.* **1986**, *27*, 4249.

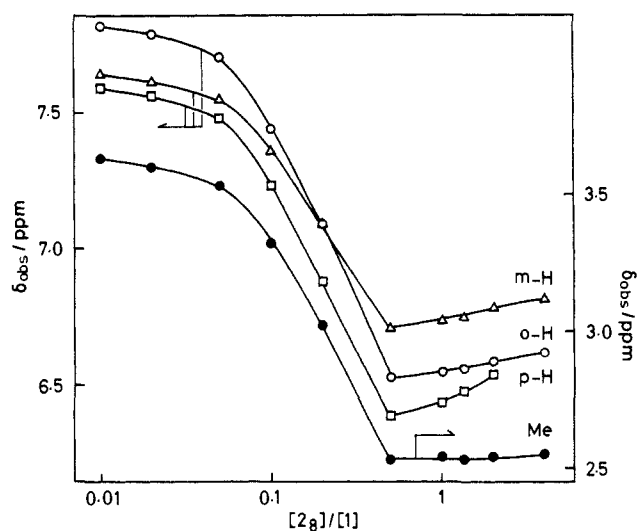
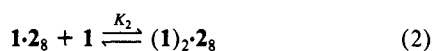


Figure 2. Plots of δ_{obsd} versus $[2_8]/[1]$. The concentration of 2_8 was maintained constant (1.10 mM) while that of 1 was varied (0.25–100 mM): D_2O 25 °C, pD 7.3 with 0.1 M phosphate buffer, internal standard DSS.

higher magnetic field with increasing $[2_4]/[1]$ ratio. This indicates that 1 is included in the cavity of 2_4 and undergoes the effect of the ring current of the benzene components. The observed chemical shift (δ_{obsd}) appears as an average of the free 1 (δ_{free}) and the complexed 1 (δ_{complex}).¹⁶ We thus determined that K at 25 °C assuming the formation of a 1:1 complex: $K = 5.39 \times 10^3 \text{ M}^{-1}$.¹⁷ The similar plots of δ_{obsd} versus $[2_4]/[1]$ were made at 0, 40, 60, and 80 °C in addition to 25 °C, and the K values were determined at each temperature. The plot of $\ln K$ versus T^{-1} shows a good linear relationship with $r = 0.99$. This indicates the formation of the 1:1 complex. The ΔH and ΔS were determined from the slope ($-\Delta H/R$) and the intercept ($\Delta S/R$) by the least-squares procedure: $\Delta H = -6.2 \text{ kcal mol}^{-1}$ and $\Delta S = -3.6 \text{ cal mol}^{-1} \text{ deg}^{-1}$. From these thermodynamic parameters we obtained the most reliable binding constant at 25 °C (Table I).¹⁸

The NMR peaks for 2_6 also shifted to higher magnetic field with increasing $[2_6]/[1]$ ratio, and the plot of $\ln K$ versus T^{-1} showed a good linear relationship. Thus, we could determine the K for the 1:1 complex with 2_6 (Table I). In contrast, the plot for 2_8 showed an unusual biphasic dependence (Figure 2): the NMR peaks shifted to higher magnetic field at $[2_8]/[1] < 0.5$, while the slight downfield shift occurred at $[2_8]/[1] > 0.5$. The biphasic dependence with a break point at $[2_8]/[1] = 0.5$ supports the formation of a 1:2 $2_8/1$ complex. We thus assumed the following two-step association scheme and estimated K_1 and K_2 independently. The results are summarized in Table I.



The formation of the 1:2 complex with 2_8 is primarily attributed to the large ring size. Therefore, the flexibility also plays an important role in the binding of the second guest molecule. It is shown that β - and γ -cyclodextrins can include two guest molecules in the cavity.¹⁹⁻²¹ In these 1:2 complexes the K_1 is

usually smaller than the K_2 .¹⁹⁻²¹ It is seen from Table I, on the other hand, that the K_1 is almost equal to the K_2 . This implies that the two "pinched" half-cavities¹ in 2_8 can interact with 1 flexibly in an "induced-fit" manner (eq. 3).²²



In conclusion, the present study demonstrated that the association properties of water-soluble calixarenes are conveniently estimated by the NMR measurements and that only 2_8 can form the 1:2 complex with 1 . This suggests that calixarene cavities are capable of molecular recognition.

(19) Ueno, A.; Takahashi, K.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 921.

(20) Hamai, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2721.

(21) Kano, K.; Takenoshita, I.; Ogawa, T. *Chem. Lett.* **1982**, 321.

(22) The referee of this paper suggested that 2_8 may adopt a "pleated loop" conformation and two guest molecules may be face-to-face in a large 2_8 cavity. This idea may explain the upfield shift at $[2_8]/[1] = 0.5$ (Figure 2). At present, we cannot further specify the binding manner only on a basis of the NMR data.

Oxygen-Atom Transfer from Nitrous Oxide. Synthesis and Structure of a Zirconocene Oxametallacyclobutene Complex

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Interactions between nitrous oxide and oxophilic, early-metal d^0 systems (where oxidation at the metal center is formally precluded) can produce interesting reactivity at the ligand sites. We recently reported examples of reactions between nitrous oxide and transition-metal complexes that result in addition of the oxygen atom of N_2O to coordinated ligands instead of formation of metal oxides.¹ While studying the reaction of N_2O with $Cp^*_2Hf(D)(Ph)$ (1 ; $Cp^* = \eta^5-C_5Me_5$), we observed that the deuterium label in 1 scrambles into the phenyl hydrogen positions (at about 40 °C) well before the onset of the reaction between N_2O and 1 (that gives $Cp^*_2Hf(OH)(Ph)$ and $Cp^*_2Hf(H)(OPh)$ at about 80 °C).¹ In the light of related zirconocene² and tantalocene³ chemistry, an intermediate benzene complex is strongly implicated in the scrambling process.⁴ Moreover, we have found that the reaction

(16) The 1H NMR studies and the conductance measurements indicated that 2_4 , 2_6 , and 2_8 do not form the micelle-like aggregate under the experimental conditions.

(17) For the complexation process $1 + 2_n \rightleftharpoons 1 \cdot 2_n$, $\delta_{\text{obsd}} = \delta_{\text{free}} \left(\frac{[2_n]_0 - [1 \cdot 2_n]}{[2_n]_0} + \delta_{\text{complex}} \left(\frac{[1 \cdot 2_n]}{[2_n]_0} \right) \right)$ where $[2_n]_0$ is the initial concentration of 2_n . Thus, $\delta_{\text{obsd}} = [2_n]_0 + [1]_0 + K^{-1} \pm \left(([2_n]_0 + [1]_0 + K^{-1})^2 - 4[2_n]_0[1]_0 \right)^{1/2} (2[1]_0)^{-1} (\delta_{\text{complex}} - \delta_{\text{free}}) + \delta_{\text{free}}$ where $[1]_0$ is the initial concentration of 1 . The K was determined from this relationship by the computer-assisted nonlinear least-squares procedure.

(18) The T_c values of 2_4 (9 °C: $1.10 \times 10^{-2} \text{ M}$) were enhanced in the presence of 4.60 M LiCl (26 °C), 4.70 M NaCl (25 °C), 2.30 M KCl (20 °C), and 3.80 M CsCl (17 °C), but the effect of 1 (T_c 65 °C) was incomparably greater than that of these alkali metal cations.

(1) Vaughan, G. A.; Rupert, P. B.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1987**, *109*, 5538.

(2) (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7411. (b) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *Ibid.* **1987**, *109*, 7137. (c) Erker, G. *J. Organomet. Chem.* **1977**, *134*, 189. (d) Erker, G.; Kropp, K. *J. Am. Chem. Soc.* **1979**, *101*, 3629. (e) Kropp, K.; Erker, G. *Organometallics* **1982**, *1*, 1246.

(3) (a) McLain, S. J.; Schrock, R. R.; Sharp, P. R.; Churchill, M. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1979**, *101*, 263. (b) Parkin, G.; Bunel, E.; Burger, B. J.; Trimmer, M. S.; van Asselt, A.; Bercaw, J. E. *J. Mol. Catal.* **1987**, *41*, 21.

(4) Similar observations of H/D scrambling were recently reported for the Zr analogue of 1 : Miller, F. D.; Sanner, R. D. *Organometallics* **1988**, *7*, 818.