($MgSO_4$) and evaporated to yield L-methyl phenylalaninate in a quantitative yield. The amide **3f** (0.745 g, 91%) was obtained as colorless crystals by addition of the amino ester in 20 mL of dry CH_2Cl_2 to a solution of 0.5 g (21.7 mmol) of (*S*)-naproxen as described above for the synthesis of **3d**: mp 108–109 °C; IR (KBr) ν (NH) 3268, (C=O) 1747, 1727, 1648 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (d, J = 8.6 Hz, 3 H, $COCHCH_3$), 2.95–3.05 (m, 2 H, CH_2CH), 3.63 (s, 3 H, OCH_3), 3.66 (q, J = 8.6 Hz, 1 H, $COCHCH_3$), 3.91 (s, 3 H, OCH_3), 4.75–4.8 (m, 1 H, $CHCH_2$), 5.76 (d, J = 7.3 Hz, 1 H, NH), 6.81 (d, J = 7.5 Hz, 2 H, 2′-H), 7.02 (t, J = 7.5 Hz, 2 H, 3′-H), 7.05–7.1 (m, 2 H, 4′-H, 5-H), 7.14 (dd, J = 8.8 and 2.5 Hz, 1 H, 7-H), 7.29 (dd, J = 8.4 and 1.8 Hz, 1 H, 3-H), 7.59 (bs, 1 H, 1-H), 7.67 (d, J = 8.8 Hz, 1 H, 8-H), 7.67 (d, J = 8.4 Hz, 1 H, 4-H); $[\alpha]^{24}_{589}$ = +23.2° (c 1.04, $CHCl_3$). Anal. Calcd for $C_{23}H_{25}NO_4$ (379.5): C, 72.80; H, 6.64; N, 3.69. Found: C, 73.12; H, 6.16; N, 3.67.

Acknowledgment. We thank BASF AG, Ludwigshafen, and the National Institutes of Health for the support of this work. Special thanks go to Professor C. E. Strouse (UCLA) and Dr. Paul N. Swepton (Molecular Structure Corporation) for technical assistance in the X-ray structure determination.

Registry No. 3 (R = COCl), 51091-84-0; **3a**, 22204-53-1; **3b**, 26159-35-3; **3c**, 123675-40-1; **3d**, 123675-42-3; **3e**, 123675-41-2; **3f**, 119991-61-6; (*R*)-**4**, 133043-27-3; (*S*)-**4**, 133043-28-4; (*R*)-**4** diiodide, 133043-29-5; (*S*)-**4** diiodide, 133043-32-0; (±)-**5**, 133043-12-6; (*R*)-**5**, 133160-35-7; (*S*)-**7**, 133160-34-6; (±)-**6**, 133043-13-7; (±)-**7**, 133043-14-8; (±)-**8**, 133043-15-9; (±)-**9**, 133043-16-0; (±)-**10**, 133043-17-1; (±)-**11**, 133043-18-2; (−)-**12**, 133160-36-8; (*R*)-**13**, 133043-30-8; (*S*)-**13**, 133043-19-3; (*R*)-**14**, 133043-20-6; (*S*)-**14**, 133043-31-9; (*R*)-**15**, 133043-21-7; (*S*)-**15**, 133043-22-8; (*R*)-**16**, 133043-23-9; (*S*)-**16**, 133043-24-0; (*R*)-**17**, 133043-25-1; (*S*)-**17**, 133043-26-2; EtOCHO, 109-94-4; $Cl(CH_2)_4Cl$, 110-56-5; EtI, 75-03-6; 2-bromo-6-methoxynaphthalene, 5111-65-9; *m*-anisaldehyde, 591-31-1; 1-acetyl-4,4-bis(4-hydroxy-3,5-dimethoxyphenyl)-piperidine, 133043-11-5; 4-aminopyridine, 504-24-5; methyl L-phenylalaninate hydrochloride, 7524-50-7; methyl L-phenylalaninate, 2577-90-4.

Supplementary Material Available: Experimental details of the X-ray crystal structure analysis of (*S*)-(−)-**12**, tables of the atomic coordinates, equivalent isotropic thermal parameters, bond angles and bond lengths, intramolecular and intermolecular distances (23 pages); tables of observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

Redox-Controlled Chemical Switching of Cation Transport in Solid-Supported Membrane Systems

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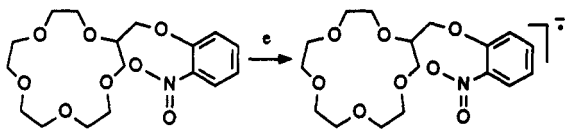
Redox-switchable anthraquinone-substituted crown ethers may be reduced by treatment with $NaBH_4$ to afford high-binding, water-stable, anion derivatives. These macrocycles, including 1-((9,10-dioxo-1-oxanthracenyl)-methyl-15-crown-5, **1**, transport Na^+ through a solid-supported, *o*-nitrophenyl octyl ether membrane with rates that depend on the charge state of the ligand and cooperation between reduction at the source phase and oxidation at the receiving phase.

The lariat ether program originated in part from our recognition that effective natural cation transport agents such as valinomycin are at once three-dimensionally enveloping and flexible.[1] This permits cation complexation and decomplexation to occur with reasonable rates while the equilibrium constant for complexation remains sufficiently high for transport. The paradox of membrane transport is that high binding strength and rapid complexation rates are required on one surface (the source phase) of the membrane while low complexation constants and rapid decomplexation rates are required at the other surface (receiving phase). The requirements make cryptands[2] ineffective as simple carriers in transport systems despite their high level of organization and three-dimensionality since their complexation and decomplexation rates, especially the latter, are relatively low.[3]

Most synthetic systems have relied upon a compromise in rates and complexation constants to achieve cation transport.[4] Our strategy from the beginning of this work was to use switching to make a weak but dynamic cation binder stronger and then to deactivate the binder after membrane transport had been accomplished.[5] The lariat ethers[6] designed for this purpose were simple crown ethers having nitrobenzene sidearms. The nitro group in nitrobenzene is a poor donor, even when appropriately placed in the ortho position. The first stage of this effort was to

Scheme I



(1) (a) Kaifer, A.; Echegoyen, L.; Gustowski, A.; Goli, D.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 7168.

(2) Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89.

(3) (a) Lamb, J. D.; Christensen, J. J.; Oscarson, J. L.; Nielsen, B. L.; Asay, B. W.; Izatt, R. M. *J. Am. Chem. Soc.* **1980**, *102*, 6820. (b) Lehn, L.-M. *Physical Chemistry of Transmembrane Ion Motions*; Spach, G., Ed.; Elsvier: Amsterdam, 1983; p 181. (c) Behr, J.-P.; Kirch, M.; Lehn, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 241. (d) Fyles, T. M. *Can. J. Chem.* **1987**, *65*, 884. (e) Castaing, M.; Lehn, J.-M. *J. Membr. Biol.* **1987**, *97*, 79.

(4) (a) See: *Progress in Macrocyclic Chemistry*; Izatt, R. M.; Christensen, J. J., Eds.; Wiley-Interscience: New York, 1979, 1981, and 1987; Vols. 1, 2, and 3. (b) Stolwijk, T. B.; Sudholter, E. J. R.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 7042. (c) Riddell, F. G.; Arumagam, S.; Brophy, P. J.; Cox, B. G.; Payne, M. C. H.; Southon, T. E. *J. Am. Chem. Soc.* **1988**, *110*, 743.

(5) Kaifer, A.; Echegoyen, L. Redox Control of Cation Binding in Macrocyclic Systems. In Inoue, Y.; Gokel, G. W., Eds. *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990; pp 363–395.

(6) (a) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *C. Chem. Soc., Chem. Commun.* **1980**, 1053. (b) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 1663. (c) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *Tetrahedron Lett.* **1981**, 2623.

0022-3263/91/1956-3369$02.50/0

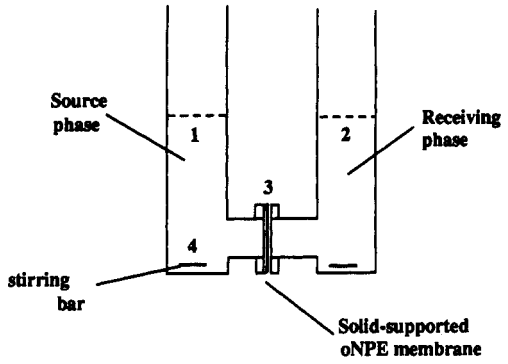


Figure 1. Apparatus for the chemically induced redox experiments.

demonstrate that electrochemical reduction of the sidearm, as represented in Scheme I, led to an intramolecular ion pair complex. We established this experimentally several years ago.[7]

Unfortunately, carriers which rely upon the nitrobenzene redox switch are of limited utility because the radical anion rapidly decomposes at any aqueous interface. We thus prepared analogues of these carriers incorporating the anthraquinone residue as a substitute for nitrobenzene in the appropriate lariat ether sidearm. We have successfully demonstrated cation binding and switching based on anthraquinone redox chemistry in previous reports,[8] enhanced cation transport ability,[9] and, recently, the first example of electrochemically switched "on/off" activation/deactivation of transport.[10] We now report that cation transport through a solid-supported liquid membrane system can be effected by chemical redox switching. We believe this is especially timely in light of several reports that have recently appeared concerning cation and electron transport in several membrane systems.[11]

Experimental Section

All reactions were conducted under dry N_2 unless otherwise noted. All reagents were the best grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate.

1-((9,10-Dioxo-1-oxanthracenyl)methyl)-15-crown-5, 1, was prepared from 2-(hydroxymethyl)-15-crown-5 and 1-chloroanthraquinone as previously described, mp 86–88 °C (lit.[8] mp 86–88 °C).

Solid-Supported Membranes. The solid-supported membranes used for these studies were made of microporous polypropylene film (CelGard 2500) with an effective pore size of 0.04 μm. The membranes were 25 μm in thickness and 45% by volume porosity. *o*-Nitrophenyl octyl ether (*o*-NPE) was purchased commercially and used as received as the membrane plasticizer

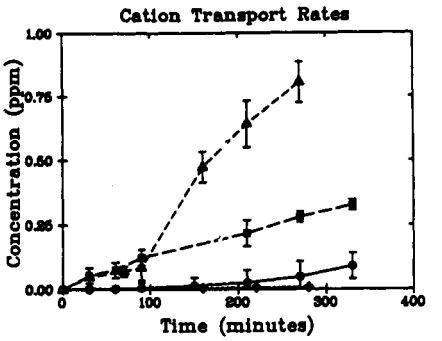
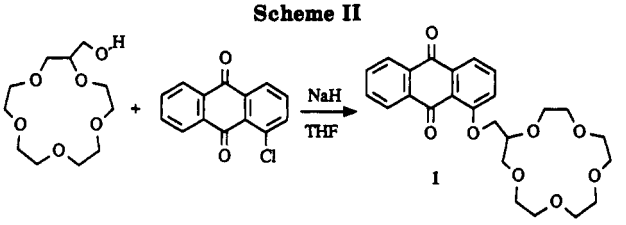


Figure 2. Plot of Na^+ concentration in the receiving phase (ppm) as a function of time for: diamonds = no ligand in the membrane phase but $NaBH_4$ in the donor phase and $K_3Fe(CN)_6$ in the receiving phase; circles = ligand present in the membrane phase and NaCl present in the donor phase; squares = ligand present in the membrane phase and $NaBH_4$ in the donor phase; triangles = ligand present in the membrane phase, $NaBH_4$ in the donor phase, and $K_3Fe(CN)_6$ in the receiving phase.

Scheme II



(liquid support). Sodium borohydride and potassium hexacyanoferrate (ferricyanide) were obtained commercially and used without further purification. The water used was distilled and then deionized using a Barnstead Nanopure system until its resistance was ≥18 MΩ.

Transport experiments were conducted using an H-type cell (shown in Figure 1 to which the parenthetical numbers refer), which was completely immersed in a thermostatted circulating bath held at 25 ± 1.0 °C. A 25-mm diameter polypropylene film (3) was immersed in a 10 mM ligand solution in *o*-NPE. The impregnation procedure took 5 min. After removal from this solution, the membrane was carefully wiped with filter paper to remove excess solution. The resulting membrane was then fixed between the two arms of the glass cell using two rubber O rings. The exposed area of the membrane was determined to be 0.79 cm^2. Equal volumes (10 mL) of aqueous source (1) and receiving phases (2) were simultaneously placed in the tube compartments. Both water phases were continuously stirred magnetically (4) at a controlled rate of 500 rpm throughout the complete cation transport experiment. Two milliliters of the aqueous receiving phase were sampled at regular intervals and immediately replaced by 2 mL of deionized water. Cation transport was monitored by measuring the concentration in the receiving phase using a Varian SpectrAA 300 atomic absorption spectrometer. Each experiment was repeated at least three times and each value reported is the average.

Results and Discussion

The ligand used in the studies reported here, 1-((9,10-dioxo-1-oxanthracenyl)methyl)-15-crown-5, 1, was prepared from 2-(hydroxymethyl)-15-crown-5 and 1-chloroanthraquinone. The reaction involves direct nucleophilic aromatic substitution, a process we have recently reported separately and is presented in Scheme II.[8a,c]

The transport studies described here were conducted using the H-cell illustrated in the Experimental Section. This system is somewhat unusual in that the membrane was *o*-nitrophenyl octyl ether supported on polypropylene film. The switchable carrier was 1-((9,10-dioxa-1-oxanthracenyl)methyl)-15-crown-5, 1, illustrated above. Cation transport was monitored by measuring (atomic absorption) the cation concentration in the receiving phase.

(7) (a) Gustowski, D.; Echegoyen, L.; Goli, D. M.; Kaifer, A.; Schultz, R. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 1633. (b) Kaifer, A.; Gustowski, D. A.; Echegoyen, L.; Gatto, V. J.; Schultz, R. A.; Cleary, T. P.; Morgan, C. R.; Goli, D. M.; Rios, A. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 1958.

(8) (a) Gustowski, D. A.; Delgado, M.; Gato, V. J.; Echegoyen, L.; Gokel, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 7533. (b) Delgado, M.; Gustowski, D. A.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1988**, *110*, 119. (c) Lu, T.; Yoo, H. K.; Zhang, H.; Bott, S.; Atwood, J. L.; Echegoyen, L.; Gokel, G. W. *J. Org. Chem.* **1990**, *55*, 2269.

(9) Echeverria, L.; Delgado, M.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1986**, *108*, 6825.

(10) Echegoyen, L. E.; Yoo, H. K.; Gatto, V. J.; Gokel, G. W.; Echegoyen, L. *J. Am. Chem. Soc.* **1989**, *111*, 2440.

(11) (a) Ozeki, E.; Kimura, S.; Imanishi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1353. (b) Patterson, B.; Thompson, D. H.; Hurst, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 3656. (c) Leidner, C.; Liu, M. D. *J. Am. Chem. Soc.* **1989**, *111*, 6859. (d) Kobuke, Y.; Hamachi, I.; *J. Chem. Soc., Chem. Commun.* **1989**, 1300.

Table I. Redox-Switched Transport for 1 in a Solid-Supported Membrane[a]

reductant (source)	oxidant (recvng)	type of switching	rate (h^{-1})	rel rate
NaCl	none	none	$(6.4 \pm 0.3) \times 10^{-5}$	1
$NaBH_4$	none	chemical reduction	$(2.5 \pm 0.1) \times 10^{-4}$	4
$NaBH_4$	$K_3Fe(CN)_6$	chemical pumping	$(1.0 \pm 0.2) \times 10^{-3}$	16
electrode	electrode	electrochem pumping	(3.4×10^{-1})	(5)[a,b]

[a] Chemically switched experiments were conducted in a solid-supported ligand membrane (see text). The electrochemically switched systems utilized a bulk liquid membrane. [b] The values in parentheses are for a liquid membrane system; the relative rate value compares the values at its left with the value determined for the same system and previously published.[10]

Several control experiments were conducted, and a summary of the results for Na^+ cation transport are depicted graphically in Figure 2. Membrane integrity was demonstrated for the case in which no ligand was present in the membrane phase, 0.5 M $NaBH_4$ was present in the donor phase, and 10 mM $K_3Fe(CN)_6$ was present in the receiving phase. In this case, no transport was observed (diamonds). When 1 was present in the membrane and NaCl was present in the donor phase, modest Na^+ transport was observed (circles), $k_{transport} = 6.4 \times 10^{-5}$ h^{-1}. When 1 was present in the membrane and $NaBH_4$ was present in the source phase but no oxidant was present in the receiving phase, a Na^+-transport rate of 2.5×10^{-4} h^{-1} was observed (squares). As shown in previous work using electrochemical reduction,[9,10] this leads to a nearly 4-fold increase in transport rate. Using the electrochemical method,[10] we observed a rate enhancement with this ligand of about 2-fold.

When a trans-membrane redox couple existed (triangles), enhanced but nonlinear transport was observed. We refer to such a trans-membrane redox couple as a "pumped" system to distinguish it from a reduced cation binder that is "switched" off by oxidation or a neutral binder that is "switched" off by oxidation. An induction period of about 90 min was evident, during which time the transport rate was similar to that observed in the $NaBH_4$ case in which oxidant was absent. After the induction period, the rate increased and was nearly linear, $k = 1.0 \times 10^{-3}$ h^{-1}, a 4-fold rate increase over the system in which ligand was reduced at the source phase but not oxidized at the receiving phase. The analogous experiment conducted under electrochemical conditions[10] gave a rate enhancement of 2.6. The nonlinearity of the redox-switched system appears to result from a leveling effect, probably due to partitioning of the fairly hydrophilic ligand into the aqueous phase(s). The results are summarized in Table I.

Even though it appears that the electrochemically pumped system gives much faster transport, this and the chemically pumped systems are not directly comparable for a variety of reasons. The most basic difference aside from the technique used for redox is the membrane itself. The electrochemical studies were conducted using a bulk liquid membrane system. The chemical redox studies were carried out using a solid-supported *o*-nitrophenyl octyl ether membrane. Other factors which influence these systems are: cell geometry, membrane phase stirring (liquid) vs diffusion in the solid-supported membrane, and the presence of a substantial concentration of supporting electrolyte in the bulk liquid phase (electrochemical reactions). Even so, a comparison of the two systems is inevitable. For these cases, the change from neutral to

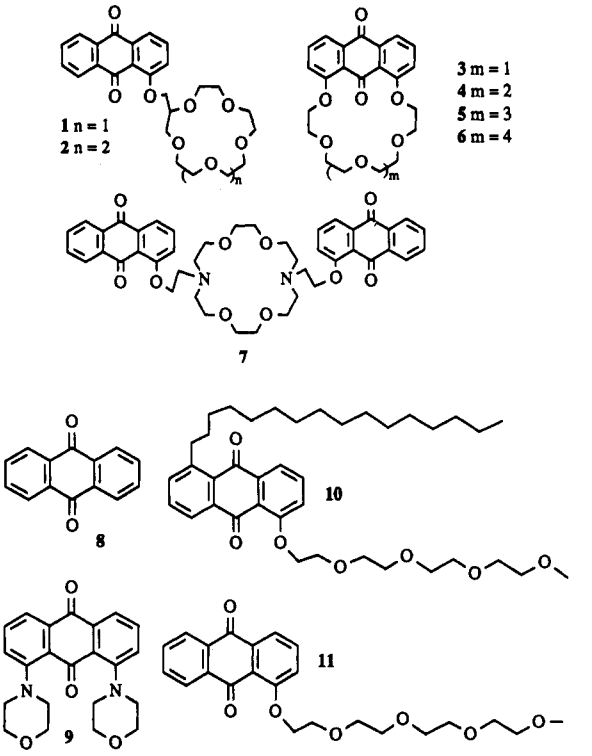


Figure 3. Structures of alternate carriers studied.

reduced to pumped gives approximate relative rates of 1:2:5, respectively. The corresponding ratios are 1:4:16 for the chemically pumped system. In a single, isolated experiment we combined the chemical redox system with the bulk liquid membrane. In this case, the concentration of ferricyanide was monitored in the receiving phase by UV–vis absorption. No change in the ferricyanide concentration was observed over time when no reducing agent was present. When $NaBH_4$ was present in the source phase, the decrease in ferricyanide concentration was linear with a rate of 5.6×10^{-2} h^{-1}. These results show clearly that when sodium cation is transported, electrons are co-transported.

In the search for an optimal system, reduction of several other ligands was attempted in a H_2O/CH_2Cl_2 system since reduction was visible in this two-phase mixture. The corresponding experiment could not be done in the solid-supported liquid membrane system since color changes were obscured by the solid-supported membrane due to its physical arrangement. Twelve potential ligand structures were examined (shown in Figure 3). Of these, only the crown ethers proved to be readily reducible. A possible explanation for this phenomenon is that Na^+ complexation renders the crown more hydrophilic, thus making it more accessible to the aqueous reducing agent. The podand derivatives could be reduced, but only in a DMF/H_2O system. The two-phase experiments involved water and dichloromethane in the presence of $NaBH_4$. Small increments of solvents such as dimethylformamide, 1,2-dimethoxyethane, tetrahydrofuran, and acetonitrile were added to the CH_2Cl_2/H_2O mixture to see if electron transfer efficiency could be improved. Although electron transfer was indeed facilitated, loss of the reduced ligand to the aqueous phase became an acute problem.

Conclusion

We have demonstrated that crown-ether based, redox-switchable ligands can be used to enhance cation transport in chemically controlled systems as well as the previously demonstrated electrochemically controlled ones. In the

present case, higher transport rate enhancements are observed which may be due to chemical redox but may also result from use of the little-studied solid-supported, liquid membrane system. In our experience, the solid-supported system permits better control of experimental parameters. Previous electrochemical results reported from our laboratories necessitated the use of bulk liquid membrane models for the experiments to succeed. These are plagued with stirring and convection problems as well as interfacial disruptions.

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^{13}C NMR Chemical Shifts. A Single Rule To Determine the Conformation of Calix[4]arenes

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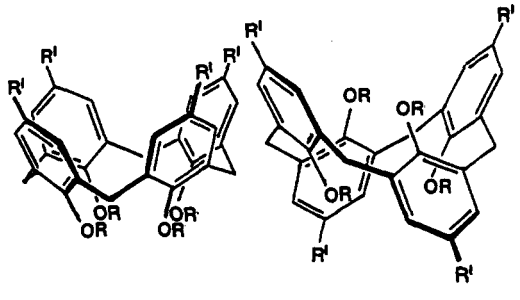
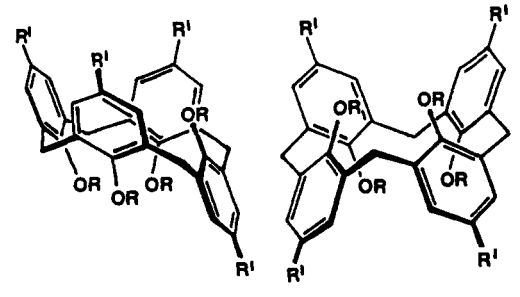
The conformations of calix[4]arenes can be deduced from the ^{13}C NMR chemical shift of the methylene groups connecting each pair of aromatic rings. Inspection of 24 cases revealed that when the phenol rings beside each methylene are in a syn orientation (i.e., in cone conformations), the methylene signals appear around δ 31, whereas they appear around δ 37 when both phenol rings are anti oriented (i.e., in 1,3-alternate conformations). Steric effects are believed to be the main cause of such large differences.

The conformations of calix[4]arenes in solution have long been studied since the pioneering work of Gutsche.[1] Among the number of methods that can be used,[2] those based on the ^1H NMR methylene or aromatic signals and their multiplicities have been shown to be the most useful to distinguish the four main conformations of these cyclic tetramers of phenols.[3] For calix[4]arenes with the same substituent at each para position, an AB system is usually observed below the coalescence temperature for the methylene protons in the cone (A) conformation, whereas



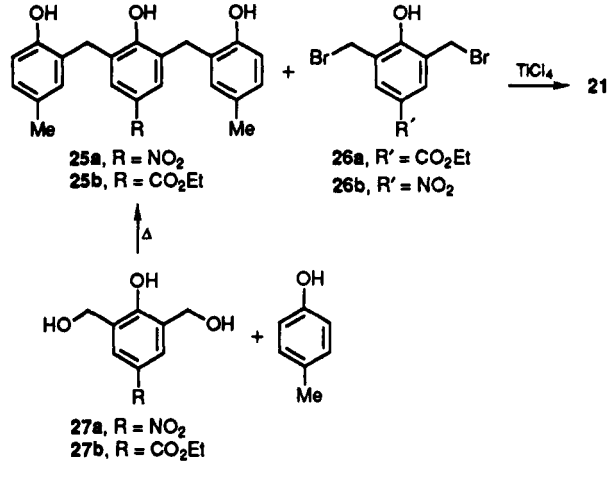
(A) (B)



(C) (D)

a singlet is observed in the 1,3-alternate (B) conformation.

Scheme I



Both singlet and AB systems should be present in partial cone (C) or in 1,2-alternate (D) conformations, and the number and multiplicity of aromatic signals could be used to differentiate them. Since most calix[4]arenes coalesce above room temperature in a broad range of solvents, these observations are usually enough to ascertain the preferred

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(1) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.
(2) (a) NOE experiments: Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335. (b) Dipole moments measurement: Elguero, J.; Fayet, J. P.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Sánchez, C.; Vertut, M. C. To be published. (c) For X-Ray crystal structures, see ref 3.
(3) Gutsche, C. D. In "Calixarenes"; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry; London, 1989; Vol. 1.
(4) (a) Gutsche, C. D.; Lin, L. G. *Tetrahedron* **1986**, *42*, 1633. (b) Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1979.
(5) Iqbal, H.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, *43*, 4917.
(6) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

0022-3263/91/1956-3372$02.50/0