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Group Recognition by an Octamethoxy-Substituted Cyclophane Host As Studied by Electron Spin Resonance

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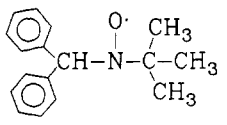
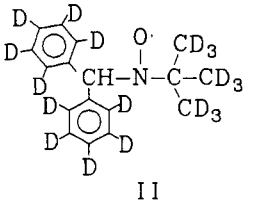
Summary: Inclusion complexation of α-substituted benzyl *tert*-butyl nitroxide spin probes is used to investigate the group recognition ability of a novel water-soluble octamethoxy-*p*-cyclophane by ESR spectroscopy. It is found that the phenyl or substituted-phenyl group is included but alkyl or cycloalkyl groups are not. Evidence for different spectra is obtained in the aggregated *p*-cyclophane at high concentration of the host.

Sir: Recent investigations have demonstrated that multiparameter nitroxide probes can provide information about bimodal inclusion in cyclodextrins. Thus for diphenylmethyl *tert*-butyl aminoxyl I, two different inclusion

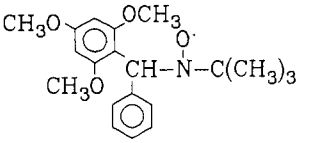


I

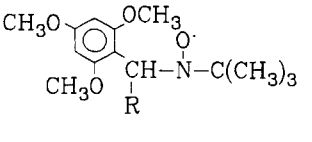


II

complexes of β-cyclodextrin in water can be detected by ESR spectroscopy.[1] These were assigned to "phenyl-in" and "*tert*-butyl-in" on the basis of the relative magnitudes of the nitrogen and β-hydrogen hyperfine splitting constants (N- and β-H hfsc's) and a comparison with the same parameters of the "free" spin probe. This assignment was confirmed by the finding that the phenyl-in complex actually consists of an equimolar mixture of two species as determined by ENDOR spectroscopy.[2] The components of this mixture are believed to be due to a diastereomeric pair of complexes since the β-cyclodextrin is pure D+. Similar results can be obtained with α-cyclodextrin but γ-cyclodextrin gives only one type of inclusion complex.[3] These observations are consistent with the larger aperture for the latter cyclodextrin. In these studies II was used for the first time, which is perdeuterated I except for the β-hydrogen. With this spin probe extremely sharp lines can be obtained that greatly facilitate analysis of multicomponent ESR spectra.[3] Another method for separating the component spectra more completely is to use a spin probe that gives a larger β-H hfsc. This occurs in spin adducts of *C*-(2,4,6-trimethoxyphenyl)-*N*-*tert*-butylnitrone.[4] Thus III also gives two spectra with β-cyclodextrin assigned to phenyl-in and *tert*-butyl-in since the trimethoxyphenyl group is assumed to be too large to be included. The complete separation found for the spectra



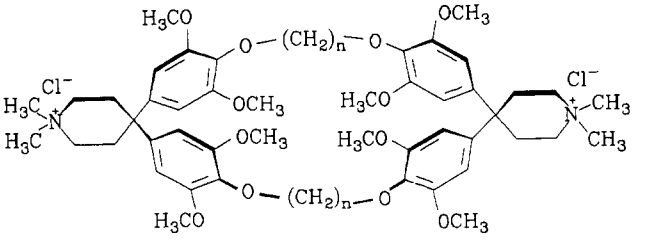
III



IV

of the two inclusion complexes of III has prompted a detailed study on the relative tendency of the alkyl group in IV to be included in γ-cyclodextrin.[5] The magnitudes of the association constants for inclusion increase in the sequence *n*-propyl, *n*-butyl, *n*-pentyl, and *n*-hexyl (K = 50, 60, 70, 150 M^{-1}). However, the largest values are found for cyclohexyl (K = 750 M^{-1}). Complexation with the methyl or ethyl group could not be detected.

In this communication we would like to report on a comparison of these results with a novel water-soluble synthetic cyclophane host,[6] V, named here octamethoxyparacyclophane-3, OMCP-3, in order to give emphasis to the portion of the molecule most influential in determining the hydrophobicity of the cavity. It has been shown by



n = 3

V

(1) (a) Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 3699–3701. For full paper, see: (b) Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1989**, *111*, 2066–2070. The single included species of cyclodextrin has been detected before by ESR spectroscopy. See references cited in above papers.

(2) Janzen, E. G.; Kotake, Y. *J. Am. Chem. Soc.* **1988**, *110*, 7912–7913.

(3) Kotake, Y.; Janzen, E. G. *Chem. Phys. Lett.* **1988**, *150*, 199–203.

(4) Kotake, Y.; Janzen, E. G. *Chem. Express* **1988**, *3*, 715–718.

(5) Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1989**, *111*, 5138–5140.

(6) Ferguson, S. B.; Seward, E. M.; Diederich, F.; Sanford, E. M.; Chou, A.; Inocencio-Szweda, P.; Knobler, C. B. *J. Org. Chem.* **1988**, *53*, 5593–5595.

0022-3263/89/1954-5421$01.50/0

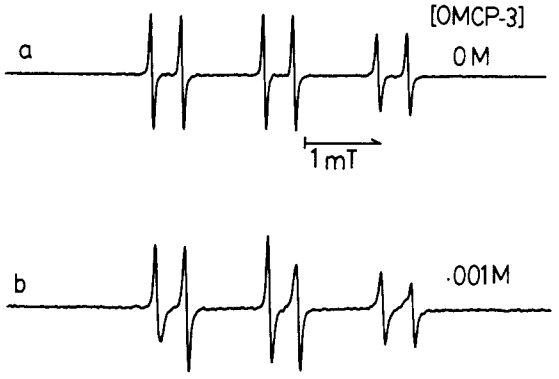


Figure 1. (a) ESR spectrum of probe I in water at 293 K. (b) ESR spectrum of probe I in water in the presence of 0.001 M OMCP-3 at 293 K. Observed hfsc's are the following: free probe, a_N = 1.595 mT, a_H = 0.425 mT; included probe, a_N = 1.581 mT, a_H = 0.378 mT.

NMR that V exhibits specificity for aromatic ring inclusion and enthalpy-driven complexion with various para-substituted benzene derivatives. This suggests that aromatic binding is operative in arene complexes but not in complexes of aliphatic guests. It is of interest to verify whether these cyclophane hosts are able to recognize functional groups upon inclusion or whether they only recognize the substrate as a whole molecule.

When V is added to a solution of I in water, the observed ESR spectrum changes from the trace shown in Figure 1a to that in Figure 1b. It is clear from the asymmetry of the doublets in the spectrum that another species with very similar hfsc's is formed. Varying the concentration of V shows that only one type of inclusion complex is observed. However the difference in hfsc's is too small to calculate an association constant with any confidence. When the same trials are performed with III again only *one* new spectrum is produced, which is different from that of the free aminoxyl in aqueous solution (Figure 2). From these results the conclusion can be reached that only phenyl-in or *tert*-butyl-in complexes are formed with OMCP-3, but not both. When experiments with IV were performed where R = ethyl, *n*-hexyl, or cyclohexyl, *no new ESR spectra are obtained in the presence of OMCP-3*, indicating that this host accepts the phenyl group in I or III but not the alkyl or cycloalkyl group in IV. From this result we also conclude that no *tert*-butyl-in complexes are formed. The association constant for complexation based on spectrum simulation found for the phenyl group in III and OMCP-3 is 290 ± 40 M^{-1} at 293 K. On the basis of analysis of the temperature dependence 273–303 K), $\Delta H°$ and $\Delta S°$ are calculated to be −2.0 ± 0.7 kcal/M and 4 ± 4 cal/M·K, respectively. Though the error is large these numbers show that the complexation is mostly enthalpy driven. Since no inclusion with alkyl groups is found, association constants for these groups must be less than 1.[7] The value of 2.9 × 10^2 L mol^{-1} for III is comparable but slightly smaller than the association constant found for *p*-dimethoxybenzene and OCMP-3,[6] for example (namely 3.7 × 10^2 L mol^{-1}), indicating a weaker binding

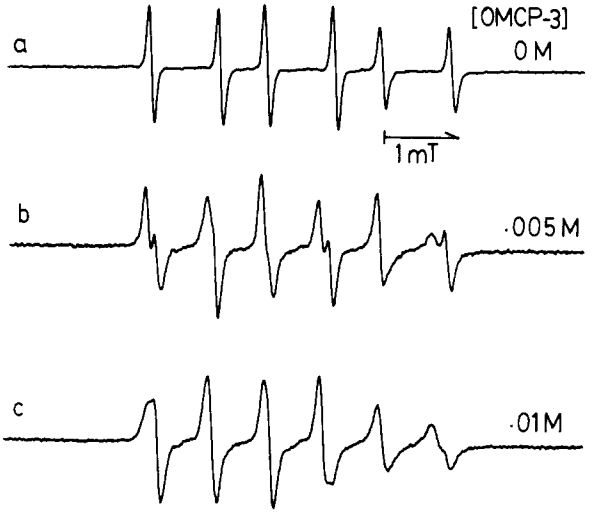


Figure 2. (a) ESR spectrum of probe III in water at 293 K. (b) Same as a in the presence of 0.005 M OMCP-3. (c) Same as a in the presence of 0.01 M OMCP-3. Observed hfsc's are the following: free probe, a_N = 1.642 mT, a_H = 0.978 mT; included probe, a_N = 1.602 mT, a_H = 0.752 mT.

for the spin probe III than for para-substituted benzene compounds. This difference may be due to incomplete insertion into the OCMP-3 cavity as a result of steric hindrance from the bulky substituent, 2,4,6-trimethoxyphenyl, or the lack of appropriate substituents at the para position of the included phenyl group.

OMCP-3 has a relatively high critical aggregate concentration (CAC) as compared to other similar cyclophane hosts. Information on cyclophane hosts and their binding ability above the CAC is desirable but virtually nonexistent.[8] When the concentration of OMCP-3 in a solution of probe I or III is increased, an almost pure spectrum of the complex is obtained around the CAC (~0.01 M) and an additional increase in concentration of OMCP-3 does not change the hfsc's of the probe. This means that the polarity of the environment of the probe is not influenced by aggregate formation because the probe stays in the cavity irrespective of the state of aggregation of OMCP-3. On the other hand probe IV when R = cyclopentyl shows no sign of complex formation; however, the N-hfsc starts to decrease above the CAC (1.62 mT at 0.01 M to 1.59 mT at 0.08 M). The smaller N-hfsc means that the probe experiences a more hydrophobic environment. Also the broadening of the high-field (M_I = 1) line of N-hfs is observed indicating that the molecular tumbling motion is restricted above CAC. This shows that the probe starts to be sequestered into the OMCP-3 aggregate at the CAC and the decrease of the N-hfsc continues until all probes are in the aggregate.[9]

The aminoxyl probes were prepared from spin traps and organomagnesium halide compounds as described elsewhere.[1b] The conditions of ESR measurement are also the same as reported previously.[1b]

Acknowledgment. Support from the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

(7) Estimated from the error of determination of the association constant.

(8) See, for example: Diederich, F. *Angew. Chem.* **1988**, *100*, 372–396: *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386.

(9) Kotake, Y.; Janzen, E. G. *Can. J. Chem.* **1988**, *66*, 1895–1900.