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Notes

Quantitative Evaluation of Template Effect in the Formation of Cyclobis(paraquat-*p*-phenylene)

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In the last decade there has been an increasing use of templates in synthesis which has enormously contributed to the development of supramolecular chemistry.[1]

Macrocyclization templates are the most exploited; they range from simple metal cations to structured organic guests. Countless examples of this type are found in literature; however the reported evidences are generally based on yield increases only.[2] A notable exception is due to Mandolini's group that carried out a thorough kinetic investigation on the template effect of alkali and alkaline-earth cations in the formation of benzo-crown ethers.[3] However in the case of template effects brought about by organic guests no kinetic study has been reported to date. This is due to the great difficulty in having a clean reaction in which macrocyclization is the only process, or at least the principal one. This in turn would require the, often not easy, preparation of the acyclic intermediate immediately preceding the macrocycle along the reaction path.

By using a different approach based on competitive experiments Stoddart *et al.* have recently assessed the *relative* template abilities of two different crown ethers in the formation of [2]catenanes.[4]

Among the literature examples of macrocycles whose formation is catalyzed by the presence of an organic molecule, no doubt, the most versatile system is cyclobis(paraquat-*p*-phenylene) (**4**), which has inspired most of the recent work of Stoddart and co-workers.[5] They reported, inter alia, that the yield of **4** is significantly increased by the presence of 1,4-bis[2-(2-hydroxyethoxy)ethoxy]benzene (**3**).[6] It was suggested that the reaction occurs in two steps, as shown in Scheme 1, and that only the second one, i.e., the ring closure reaction of the intermediate **5**, benefits from the template ability of the guest.[7] However compound **5** has never been observed. Recently, complexes containing a similar tricationic intermediate, bound to two different macrocyclic polyethers, have been detected by FAB mass spectrometry.[4]

In order to evaluate the template effect of the guest **3** on the formation of the cyclophane **4**, the synthesis of **5** is required. The preparation of **5** was carried out according to the route illustrated in Scheme 2. Equimolar amounts of the compound **6** and the salt **1** were allowed to react in acetonitrile at room temperature for 24 h affording, after column chromatography, the tricationic ester salt **7**$\cdot$3PF$_6$ in 14% yield. This low yield was reproducible. The ester **7**$\cdot$3PF$_6$ was converted to the hydrobromide of **5** by treatment with 48% HBr, at 85 °C for 2 days and was isolated as **5**H$\cdot$4PF$_6$ in 78% yield. Deprotonation of **5**H$\cdot$4Br in water afforded the trication **5** which was then precipitated as **5**$\cdot$3PF$_6$ in 89% yield.

The kinetics of cyclization of **5**$\cdot$3PF$_6$ was studied by both ^{1}H NMR spectroscopy in CD$_3$CN, by following the disappearance of the CH$_2$Br signal, and UV−vis spectroscopy in acetonitrile, by following the appearance of the charge-transfer band at λ 467 nm of the complex formed between **3** and **4**.[6] To avoid polymerization reactions the concentration of **5** was kept as low as possible ($3-5 \times 10^{-3}$ M in the ^{1}H NMR experiments, $6-7 \times 10^{-4}$ M in the UV−vis experiments). The kinetic measurements were carried out at 62 °C, since a preliminary kinetic investigation showed that the ring closure reaction is very slow at room temperature. First-order rate constants were obtained in the absence (k_0) and in the presence (k_{obs}) of variable excess amounts of guest **3**.[8] The ratios k_{obs}/k_0 (see Experimental Section), plotted in Figure 1 against the guest concentration, provide a measure of the extent of catalysis produced by the presence of the template.

It has long been recognized that catalysis is observed when the catalyst binds the transition state more strongly than the reactants.[9] The results here reported can be easily rationalized by eq 1 which is obtained from the distribution scheme in Figure 2, where K_{sub} and $K_T^{\#}$ are the association constants of the guest with the substrate and with the transition state, respectively.[3]

$$k_{obs}/k_0 = (1 + K_T^{\#}[\text{guest}])/(1 + K_{sub}[\text{guest}]) \quad (1)$$

Nonlinear least squares fit to eq 1 of the k_{obs}/k_0 ratios obtained by NMR and UV−vis, respectively, provided two

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(1) (a) Stoddart, J. F. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J.; Dürr, H., Eds.; VCH: Weinheim, 1991; pp 251−263. (b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469. (c) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375. (d) Busch, D. H.; Vance, A. L.; Kolchinski, A. G. In *Comprehensive Supramolecular Chemistry*, Vol. 9; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Chapter 1.

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(3) (a) Mandolini, L. *Pure Appl. Chem.* **1986**, *58*, 1485. (b) Cacciapaglia, R.; Mandolini, L. *Chem. Soc. Rev.* **1993**, *22*, 221.

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(5) (a) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154.

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(7) Brown, C. L.; Philp, D.; Spencer, N.; Stoddart, J. F. *Isr. J. Chem.* **1992**, *32*, 61.

(8) (a) It is not possible to evaluate k_0 by UV−vis spectroscopy because in the absence of **3**, of course, the charge-transfer band is absent. (b) The upper limit of the concentration of **3** was imposed by its solubility in acetonitrile.

(9) Kraut, J. *Science* **1988**, *242*, 533 and references therein.

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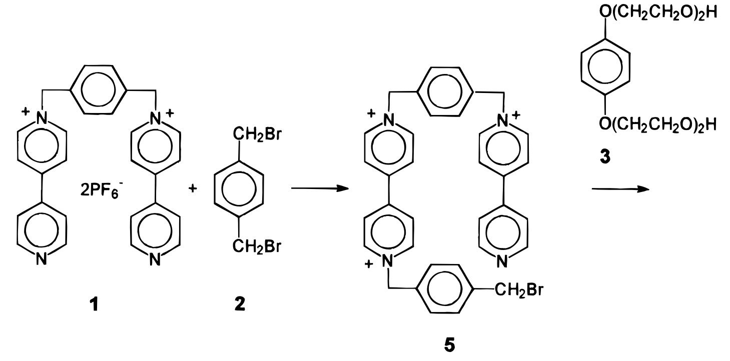
Scheme 1



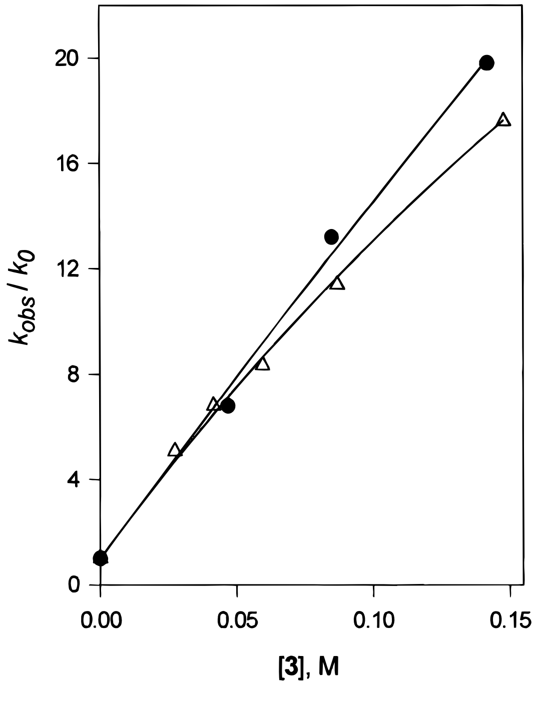


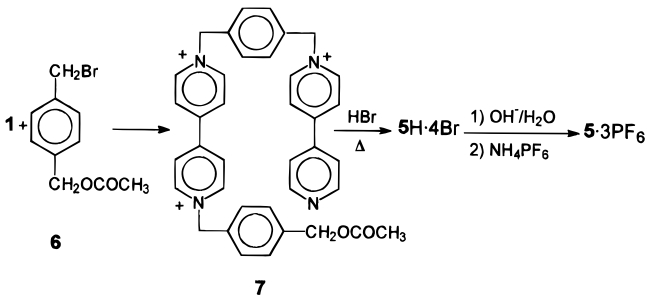
Figure 1. Catalytic effects of guest **3** on the ring closure of **5** as measured by ^{1}H NMR (●) and UV−vis (△) techniques. The points are experimental and the curves are calculated.

sets of association constants. By the NMR data we obtained $K_T{}^{\#} = 140 \pm 17$ M^{-1} and $K_{sub} \approx 0$ M^{-1}, by the UV−vis data we obtained $K_T{}^{\#} = 144 \pm 7$ M^{-1} and $K_{sub} = 1.9 \pm 0.5$ M^{-1}. The two sets of constants are quite consistent; however the UV−vis data should be held as more reliable because of the lower substrate concentration, the better temperature control, and the inherent greater sensitivity and accuracy of the UV−vis technique. Interestingly the plot in Figure 1 obtained by the UV−vis technique shows an undeniable tendency to saturation which is absent in the NMR plot. The saturation value $K_T{}^{\#}/K_{sub}$ is the maximum theoretical catalytic effect which would be attained when the host is completely bound to the guest.[3] This value indicates that the complexed form of **5** is 76(±24) times more reactive than the free one.

Overall, these results indicate that, while the acyclic precursor **5** does not appreciably associate, the cyclic transition state shows a significant ligand affinity toward the guest **3**. This is mainly due to the preorganization of the cyclic transition state and, secondarily, to the developing positive charge on the nucleophilic nitrogen.

One may note that the association constant of the transition state is more than 1 order of magnitude lower than that of the reaction product **4** (2220 M^{-1} at 25 °C).[6] The major factors responsible for this behavior should be searched among the different structural features of the transition state and the cyclophane **4**. Although the interactions between the guest and the transition state should be of the same nature of those existing between the guest and the host **4**,[6,10] the transition state differs

Scheme 2



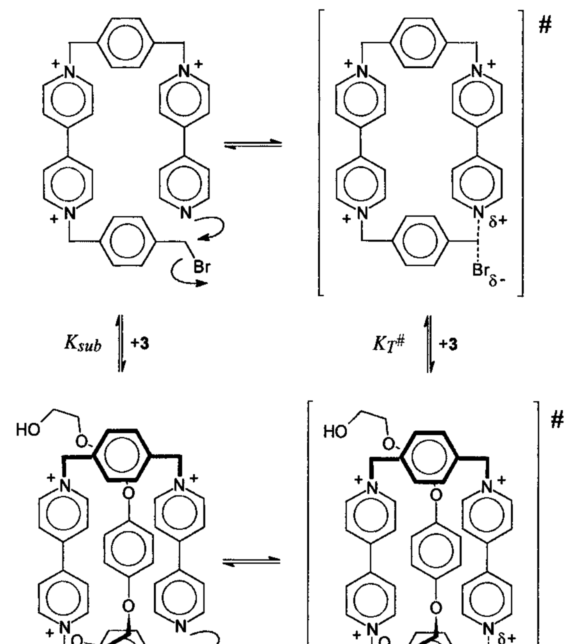


Figure 2. Distribution scheme, derived from transition state theory, considering the association equilibria of the guest **3** with the substrate **5** and with the transition state.

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(10) Asakawa, M.; Dehaen, W.; L'abbé, G.; Menzer, S.; Nouwen, J.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 9591 and references therein.

from the cyclophane **4** in two respects: (i) the nucleophilic nitrogen should bear only a partial positive charge against the net charge in **4**; (ii) the cavity should be less tight and more irregular than that of **4** since the N−C bond is not completely formed. Both these features would weaken the ligand affinity of the transition state with respect to **4**.

It should be noted that the availability of the trication **5** opens up new fronts regarding the study of template effects in the formation of more exotic systems such as the rotaxanes and catenanes already synthesized by Stoddart and co-workers.[5,6]

Experimental Section

General and Instrumentation. Thin-layer chromatographies (TLC) were carried out on 5 × 20 plates coated with silica gel 60 F_{254} (Merck 1.05714). Column chromatographies were performed on silica gel 60 70−230 mesh (Merck 1.07734). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC 300 instrument. ES mass spectra were obtained on a Fison Instruments VG-Platform benchtop mass spectrometer. The spectrophotometric measurements were carried out on a Varian Cary1 instrument.

4-(Bromomethyl)benzyl acetate (6) was prepared by reacting 1,4-bis(bromomethyl)benzene (10.5 g, 39.8 mmol) with 1 equiv of potassium acetate in 100 mL of DMF (Fluka puriss. over molecular sieve) at 80 °C for 22 h. The solvent was removed in vacuo and the solid extracted with ethyl ether (4 × 50 mL). The four fractions were combined and dried (Na_2SO_4), and the solvent was removed in vacuo. Column chromatography (silica gel, benzene) afforded **6** (3.76 g, 39% yield) as a white solid (≥95% pure by ^{1}H NMR). Since **6** slowly decomposes (in about a month) on standing at room temperature, it must be stored under argon at −20 °C: ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 4.49 (2H, s), 5.10 (2H, s), 7.37 (4H, m); ES-MS m/z 266 (M + Na)$^+$.

1,1″-[1,4-Phenylenebis(methylene)]-1′-(4-(acetoxymethyl)benzyl)-bis(4,4′-bipyridinium) Tris(hexafluorophosphate) (7·3PF$_6$). The tricationic ester **7** was prepared by adding dropwise, to a 20 mL solution of **1**·2PF$_6$ (2.00 g, 2.83 mmol) in acetonitrile (Carlo Erba, HPLC grade), 15 mL of an acetonitrile solution containing **6** (0.688 g, 2.83 mmol). The solution was kept at room temperature for 24 h. In order to complete the precipitation of the salts as bromides, a saturated solution of Et_4NBr in acetonitrile was added to the reaction mixture until no further precipitation was observed. The yellow precipitate was filtered off, washed with acetonitrile, and subjected to several column chromatographic runs (silica gel, CH_3OH/CH_3NO_2/2 N aqueous NH_4Cl solution 7:2:1). The fractions containing **7** were combined, and the solvent was removed in vacuo. The residue was dissolved in water, and a saturated aqueous solution of NH_4PF_6 was added until no further precipitation was observed. After filtration **7**·3PF$_6$ was obtained as a white solid (0.414 g, yield 14%, ≥95% pure by ^{1}H NMR): ^{1}H NMR (CD_3CN) δ 2.06 (3H, s), 5.11 (2H, s), 5.82−5.85 (6H, m), 7.50 (4H, s), 7.60 (4H, s), 8.01−8.04 (2H, m), 8.36−8.40 (6H, m), 8.87−8.98 (8H, m); ES-MS m/z 870 (M − PF$_6$)$^+$.

1,1″-[1,4-Phenylenebis(methylene)]-1′-(4-(bromomethyl)benzyl)-bis(4,4′-bipyridinium) Tris(hexafluorophosphate) (5·3PF$_6$). The salt **7**·3PF$_6$ (0.414 g, 0.408 mmol) in 30 mL of 48% HBr was heated at 85 °C, for 2 days. The reaction mixture was diluted to 100 mL with water, and a saturated aqueous solution of NH_4PF_6 was added until no further precipitation of **5**H·4PF$_6$ was observed (0.373 g, yield 78%). **5**H·4PF$_6$ was then converted to **5**H·4Br by anion exchange[11] with Et_4NBr in $MeNO_2$. **5**H·4Br was dissolved in 100 mL of water and deprotonated by adjusting the pH to 6 with 0.2 N NaOH, and then precipitated as **5**·3PF$_6$ (0.291 g, yield 89%, ≥95% pure by ^{1}H NMR). A TLC analysis (silica gel, CH_3OH/CH_3NO_2/2 N aqueous NH_4Cl solution 7:2:1) of **5**·3PF$_6$ confirmed the absence of other products: ^{1}H NMR (CD_3CN) δ 4.61 (2H, s), 5.80−5.86 (6H, m), 7.47−7.60 (8H, m), 7.91−7.93 (2H, m), 8.34−8.40 (6H, m), 8.85−8.98 (8H, m); ES-MS m/z 890 (M − PF$_6$)$^+$.

Kinetic Measurements. The ^{1}H NMR kinetic measurements were carried out as follows. A 5 mm NMR tube containing a CD_3CN solution of **5**·3PF$_6$ and the guest **3** in the appropriate concentrations was kept in a thermostatic bath at 62 °C. At regular intervals an ^{1}H NMR spectrum was recorded at room temperature. The integral of the CH_2Br signal was taken relatively to an internal standard (1,3,5-tri-*tert*-butylbenzene).

The spectrophotometric kinetic measurements were carried out, at 62 °C, in acetonitrile (Carlo Erba, HPLC grade), in a 3 mL cuvette (optical path 1 cm) kept in the thermostatted cell compartment of a Varian Cary1 instrument. In a typical run, 100 μL of a solution 0.0193 M of **5**·3PF$_6$ were added to a 2.5 mL solution of **3** at the appropriate concentration (see below). The appearance of the charge-transfer band of the complex formed between **3** and **4** was followed at λ 467 nm. In all of the cases first-order behavior was observed. Relative kinetic constants (k_{obs}/k_0, where $k_0 = 8.3 \times 10^{-7}$ s^{-1}) at the various guest concentrations, corrected for the volume increase at 62 °C, given in parentheses in M were as follows:

^{1}H NMR rates, 1 (0), 6.8 (0.047), 13.2 (0.085), 19.8 (0.142); UV−vis rates, 1 (0), 5.1 (0.0274), 6.8 (0.0416), 8.34 (0.0596), 11.4 (0.0870), 17.8 (0.148).

Supporting Information Available: ^{1}H NMR of compounds **6**, **7**, and **5** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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