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# Template Effect of Tetrathiafulvalene in the Formation of Cyclobis(paraquat-*p*-phenylene)

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*Received February 9, 2005*

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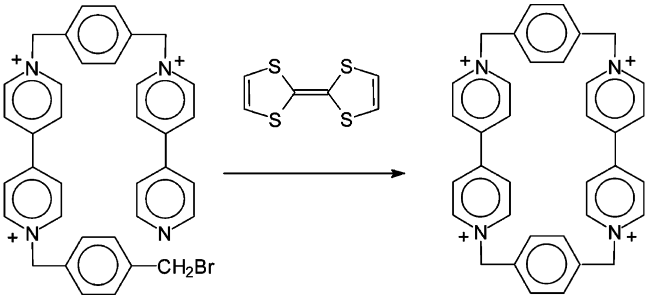

The template effect exerted by tetrathiafulvalene (TTF) in the ring-closure reaction of the trication **5**$^{3+}$ yielding cyclobis(paraquat-*p*-phenylene) has been quantitatively evaluated in acetonitrile at 62 °C with UV−vis spectrophotometry. The rate of ring closure of the trication **5**$^{3+}$ largely increases in the presence of the template (a maximum increase of ca. 80 times at [TTF] $\approx$ 0.14 M). The results are compared with those of other aromatic templates, **2** and **3**, that were provided with polyethereal sidearms and indicate that the template ability of tetrathiafulvalene is comparable or better than that of the others.

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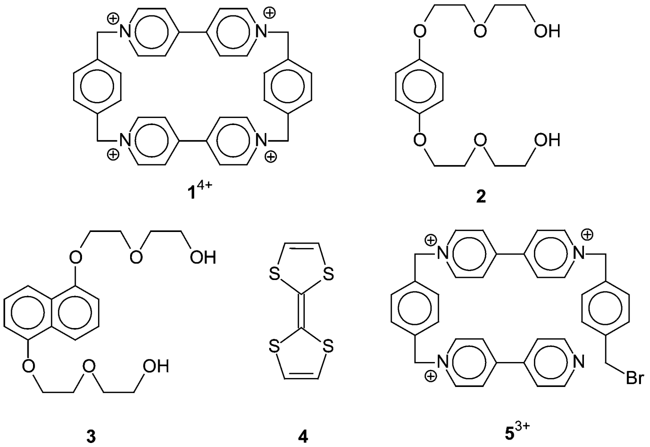
**CHART 1**



**1**$^{4+}$ **2** **3** **4** **5**$^{3+}$

The convergence of two areas of scientific endeavor, namely, the creation of machine-like molecular assemblies and molecular electronics, has attracted considerable attention in recent years because of potential applications in the field of information processing and technology.[1] Many key advances in the development of new nanoscale machines and devices have come from the outstanding contributions of Stoddart and co-workers, who have prepared a variety of catenanes, rotaxanes, pseudorotaxanes, molecular switches, and shuttles by exploiting the peculiar properties of the tetracationic host cyclobis(paraquat-*p*-phenylene), **1**$^{4+}$.[2] The synthesis of this host benefits from the template effects exerted by guests with $\pi$-electron-rich aromatic cores and poly(ethyleneoxy) sidearms.[2−4] Indeed, we have quantitatively investigated these effects in the cases in which the aromatic core is constituted of either 1,4-dioxybenzene or 1,5-dioxynaphthalene (e.g., guests **2** and **3**).[5] The polyethereal sidearms are very important for the binding of the aromatic guest to the cyclophane **1**$^{4+}$ because without them the binding affinities are generally very poor.[6] However, in some cases, as in the tetrathiafulvalene molecule **4**, the aromatic core does not need them to display a strong binding affinity for the cyclophane **1**$^{4+}$. Indeed, tetrathiafulvalene, derivatives of which were used in the self-assembly of a simple molecular-level device,[7,8] binds to cyclophane **1**$^{4+}$ with an

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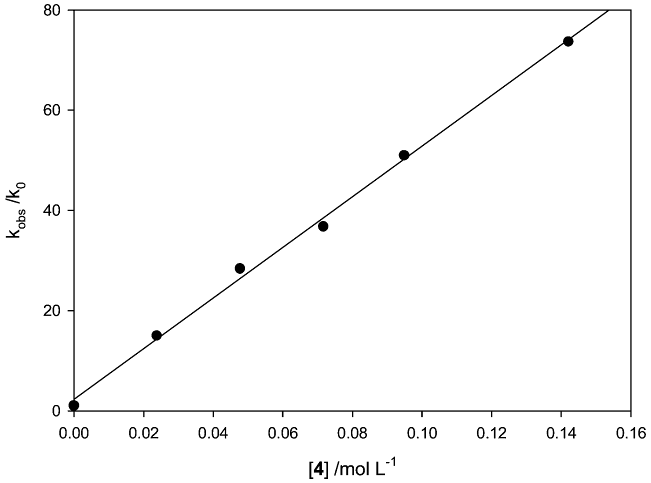


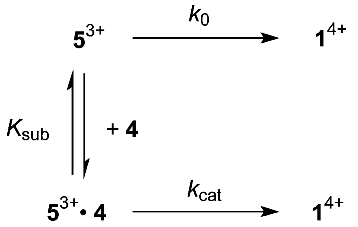
**FIGURE 1.** Rate enhancement produced by template **4** on the ring-closure reaction of trication $\mathbf{5}^{3+}$.

association constant ($K_a = 1 \times 10^4$ M$^{-1}$ at 27 °C in CH$_3$CN)[7] much higher than those of other electron-rich aromatic guests without polyethereal chains, such as hydroquinone ($K_a = 18$ M$^{-1}$ at 25 °C in CH$_3$CN)[6] or 1,5-naphthalenediol ($K_a = 768$ M$^{-1}$ at 25 °C in CH$_3$CN),[6] and it is comparable to those of guests with polyethereal chains, such as **2** ($K_a = 3.4 \times 10^3$ M$^{-1}$ at 25 °C in CH$_3$CN)[6] and **3** ($K_a = 5.7 \times 10^4$ M$^{-1}$ at 20 °C in CH$_3$CN).[9]

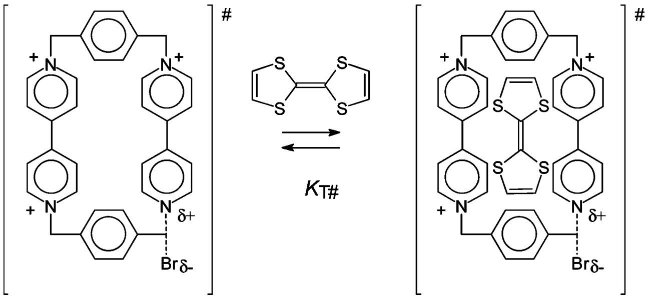
Following the above considerations, we were interested in investigating the template effect of tetrathiafulvalene, **4**, in the ring-closure reaction of precursor $\mathbf{5}^{3+}$ in order to determine if its behavior as template is qualitatively different from that of guests **2** and **3** which are provided with polyethereal sidearms. The results of this investigation are reported here.

In a previous work, we obtained, by $^1$H NMR in CD$_3$CN at 62 °C, the first-order rate constant ($k_0 = 8.3 \times 10^{-7}$ s$^{-1}$) for the cyclization of the trication $\mathbf{5}^{3+}$ to yield cyclobis(paraquat-*p*-phenylene) $\mathbf{1}^{4+}$ in the absence of any added template.[5a] In the present investigation, we have quantitatively studied the cyclization of the trication $\mathbf{5}^{3+}$ in the presence of tetrathiafulvalene **4**. The kinetics have been studied with UV−vis spectroscopy in acetonitrile at 62 °C by following the appearance of the charge-transfer band of the complex ($\mathbf{1}^{4+}\cdot\mathbf{4}$) at $\lambda = 855$ nm.[7] To avoid polymerization reactions, the concentration of the substrate $\mathbf{5}^{3+}$ has been kept as low as possible ($\sim 4 \times 10^{-4}$ M). The first-order rate constants ($k_{obs}$) were obtained in the presence of variable excess amounts of template **4** (up to ∼0.14 M). The ratio $k_{obs}/k_0$, plotted in Figure 1 against the concentration of **4**, provides a measurement of the rate enhancement produced by the presence of the template.

**SCHEME 1**



**SCHEME 2**



The data in Figure 1 show that the ring closure of the trication $\mathbf{5}^{3+}$ is strongly accelerated by the presence of template **4** (up to 80 times at the maximum concentration of **4**). The data can be interpreted on the basis of a simple kinetic scheme (Scheme 1).

With the assumption that the equilibrium of the formation of complex $\mathbf{5}^{3+}\cdot\mathbf{4}$ is fast with respect to the ring-closure reaction, the rate increase produced by the template, $k_{obs}/k_0$, is given by eq 1.

$$\frac{k_{obs}}{k_0} = \frac{1 + (k_{cat}/k_0)K_{sub}[\mathbf{4}]}{1 + K_{sub}[\mathbf{4}]} \tag{1}$$

It can easily be shown, by consideration of the transition-state theory, that the term $(k_{cat}/k_0)K_{sub}$ is the association constant ($K_{T\#}$) of the template with the cyclic transition state as illustrated in Scheme 2.[5] Accordingly, eq 1 reduces to eq 2 which shows that a rate enhancement will be observed when the template binds the transition state more strongly than it binds the reactants.[10,11]

$$\frac{k_{obs}}{k_0} = \frac{1 + K_{T\#}[\mathbf{4}]}{1 + K_{sub}[\mathbf{4}]} \tag{2}$$

Indeed, when the template concentration increases, eq 2 tends to a saturation value, given by the ratio $K_{T\#}/K_{sub}$, which is the maximum theoretical rate enhancement that would be attained when the substrate is completely bound to the template.

A maximally efficient catalyst will have a strong binding affinity for the transition state and a negligible binding affinity for the substrate. If the latter condition is met, $K_{sub}[\mathbf{4}] \ll 1$ and eq 2 reduces to eq 3.

$$\frac{k_{obs}}{k_0} = 1 + K_{T\#}[\mathbf{4}] \tag{3}$$

As shown in Figure 1, the experimental points do not show any appreciable tendency to saturation and are

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**TABLE 1. Association Constants in $CH_3CN$ at 62 °C**

| template | $K_{sub}$ ($M^{-1}$) | $K_{T\#}$ ($M^{-1}$) | $K_{T\#}/K_{sub}$ |
|---|---|---|---|
| **2**[a] | 1.9 ± 0.5 | 144 ± 7 | 76 ± 16 |
| **3**[b] | 8 ± 2 | 2900 ± 200 | 362 ± 70 |
| **4** | <1 | 506 ± 14 | >506 |

[a] Ref 5a. [b] Ref 5c.

**TABLE 2. Association Constants in $CH_3CN$**

| template | log $K_{T\#}$ at 62 °C | log $K_a$ |
|---|---|---|
| **2** | 2.2 | 3.5[a] |
| **3** | 3.5 | 4.8[b] |
| **4** | 2.7 | 4.0[c] |

[a] At 25 °C, ref 6. [b] At 20 °C, ref 9. [c] At 27 °C, ref 7.

nicely fitted by a straight line ($r^2 = 0.997$), the slope of which, according to eq 3, gives the constant $K_{T\#}$. The condition $K_{sub}[\mathbf{4}] \ll 1$ sets an upper limit for the constant $K_{sub}$ and a lower limit for the maximum catalytic effect given by the ratio $K_{T\#}/K_{sub}$. These data are reported in Table 1 along with the association constants previously obtained with guests **2** and **3**.[5a,c]

The preferential binding affinity of template **4** for the transition state rather than for the substrate $\mathbf{5}^{3+}$ is, mainly, the result of the preorganization of the cyclic transition state and, secondarily, the development of a further positive charge on the initially neutral nitrogen atom. In this respect, template **4** is more efficient as a catalyst than are templates **2** and **3**, which have a non-negligible affinity for the substrate. This is confirmed by the ratio $K_{T\#}/K_{sub}$ which increases in the order **2** < **3** < **4** despite the fact that the constant $K_{T\#}$ for **4** is not the largest. In a previous theoretical paper, we investigated the complexation of some aromatics devoid of polyethereal sidearms, **4** being among them, with the tetracationic cyclophane $\mathbf{1}^{4+}$ at the MP2/6-31G(d,p)//B3LYP/6-31G(d,p) level of theory and concluded that most of the driving force for complexation is from London dispersion forces.[12] A successive study by other authors, at a higher level of theory, confirmed our findings.[13] The lack of a significant complexation of **4** by $\mathbf{5}^{3+}$ indicates that London dispersion interactions require close packing of the $\pi$-surfaces of both the host and the guest, as found in the complexes of template **4** with both the transition state and cyclophane $\mathbf{1}^{4+}$, to be effective. The fact that templates **2** and **3** have a non-negligible affinity for the substrate can be ascribed to the presence of the polyethereal sidearms which apparently are less sensitive to the lack of preorganization of $\mathbf{5}^{3+}$, probably because the sidearms can effectively wrap even a single bipyridinium unit.

It is of interest to compare the affinities of guests **2**, **3**, and **4** for the transition state of the cyclization reaction, as expressed by the log $K_{T\#}$ values, with the affinities for the tetracationic cyclophane $\mathbf{1}^{4+}$, as expressed by the log $K_a$ values (Table 2).

The plot of the log $K_{T\#}$ values against the corresponding log $K_a$ values (Figure 2) shows a perfect linear correlation with a slope = 1.0 and an intercept = −1.3. This linear relationship strongly suggests that the same factors that dictate the order of the affinities for $\mathbf{1}^{4+}$ are responsible for the order of the affinities for the cyclic transition state. However, the cyclic transition state is not as good a ligand as the tetracationic cyclophane because the $K_{T\#}$ constants are about 20 times lower than the $K_a$ constants. Several factors may be responsible for this behavior. The most obvious one is that the $K_{T\#}$ constants were obtained from kinetic data at 62 °C, whereas the $K_a$ constants were measured at room temperature. Since a temperature increase unfavorably affects 1 + 1 association equilibria, this can justify, at least in part, the lower values of $K_{T\#}$. However, at least two structural features of the transition state should weaken its ligand affinity with respect to cyclophane $\mathbf{1}^{4+}$: (i) its cavity should be less tight and symmetric than that of $\mathbf{1}^{4+}$ since the N−C bond is not completely formed and (ii) the nucleophilic nitrogen atom bears only a partial positive charge instead of the net charge present in $\mathbf{1}^{4+}$.

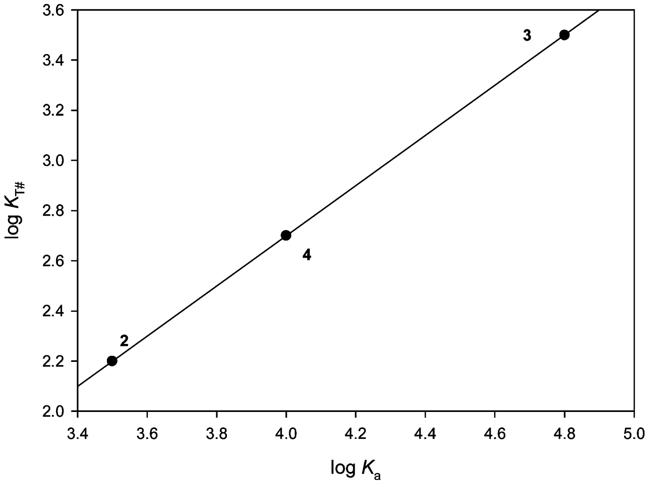

**FIGURE 2.** Plot of log $K_{T\#}$ vs log $K_a$ (data in Table 2).

It is interesting to note that the correlation shown in Figure 2 allows us to predict the $K_{T\#}$ constant of a template on the basis of its association constant with the cyclophane $\mathbf{1}^{4+}$. However, as pointed out above, this may be insufficient to predict the goodness of a template in all of the available concentration range because the constant $K_{sub}$ also plays an important role. However, it is worth noting that the value of $K_{T\#}$ is especially important at the lower template concentrations since it determines the initial slope.

In conclusion, the results presented here are the first quantitative evaluation of the template effect, exerted by an electron-rich molecule, such as tetrathiafulvalene, devoid of polyethereal side chains, in the formation of the tetracationic cyclophane $\mathbf{1}^{4+}$. They indicate that the template ability of tetrathiafulvalene is comparable to or better than that of other electron-rich aromatic molecules, such as **2** and **3**, which have been provided with polyethereal side chains.

## Experimental Section

**Materials and Methods.** 1-(4-Bromomethylbenzyl)-1′-{4-[(4-pyridin-4-ylpyridinium-1-yl)methyl]benzyl}-4,4′-bipyridinium tris(hexafluorophosphate) ($\mathbf{5}^{3+}\cdot 3PF_6^-$) was from our previous

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work.[5] Commercially available tetrathiafulvalene, **4**, and HPLC grade acetonitrile were used in the kinetic experiments without further purification.

**Kinetic Measurements.** Kinetic measurements were carried out at 62 °C in acetonitrile in a 3 mL cuvette (optical path 1 cm) kept in the thermostated cell compartment of the spectrophotometer. In a typical run, 100 $\mu$L of a 0.010 $L^{-1}$ mol solution of $\mathbf{5}^{3+}\cdot 3PF_6^-$ was added to a 2.5 mL solution of template **4** at the appropriate concentration (see below). The appearance of the charge-transfer band of the complex ($\mathbf{1}^{4+}\cdot\mathbf{4}$) was followed at $\lambda$ = 855 nm. In all cases, a clean first-order behavior was observed. The relative kinetic constants ($k_{obs}/k_0$, where $k_0 = 8.3 \times 10^{-7}$ $s^{-1}$) at the various template concentrations (corrected for the volume increase at 62 °C and given in parentheses in M) were as follows:1 (0), 15.0 ($2.38 \times 10^{-2}$), 28.4 ($4.77 \times 10^{-2}$), 36.8 ($7.16 \times 10^{-2}$), 51.0 ($9.49 \times 10^{-2}$), 73.7 ($1.42 \times 10^{-1}$). Data plotted in Figure 1.

JO050263H