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Supramolecular Control of a Fast and Reversible Diels−Alder Reaction

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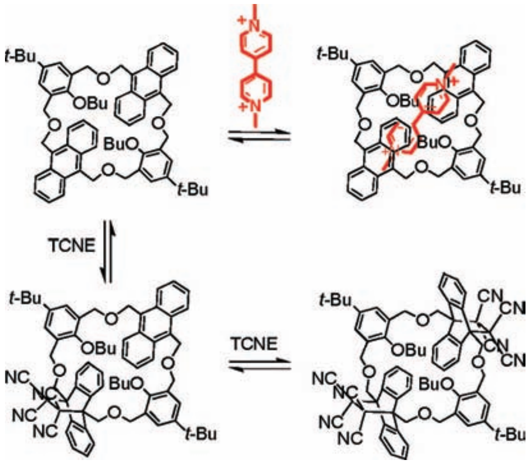
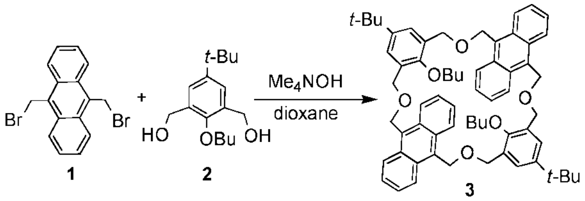
ABSTRACT



A new cyclophane featuring two opposite anthracene units linked in 9,10-positions has been synthesized thanks to the template effect of the Me_4N^+ ion. It forms pseudorotaxane complexes with alkylviologen ions and undergoes a fast and reversible reaction with tetracyanoethylene. A quantitative analysis has been carried out of the formation of Diels−Alder adducts, whose distribution can be controlled by host−guest complexation. These findings open interesting perspectives in the field of Dynamic Covalent Chemistry.

Anthracene units endow a cyclophane with potentially interesting physical and chemical properties that can be exploited in the development of synthetic receptors. Recent examples refer both to compounds featuring pendant anthracenyl groups[1] and to anthracenophane structures.[2] As an extension of our previous investigations on ether derivatives of octahomotetraoxacalixarenes,[3,4] we developed analogous cyclophanes featuring two opposite anthracene units linked in 9,10-positions. Here we report on the templated synthesis of **3** and on the Diels−Alder reactions undergone by its anthracene moieties. The synthesis of the ligand was carried out according to Scheme 1. The critical cyclization step could not be satisfactorily carried out using NaH base in DMF nor using powdered KOH base in dioxane that worked well in previous investigations.[3a,5] Thus, we tested the heterogeneous Me_4NOH−dioxane system to exploit the possible template

Scheme 1



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effect of the Me_4N^+ ion that was expected to be complexed by the final product. Satisfactory results were obtained, notwithstanding the fact that the exhaustive dehydration of the commercially available $Me_4NOH{\cdot}5H_2O$ could not be carried out.[6] To the best of our knowledge, this is the first report on a template effect of the Me_4N^+ ion in a kinetically controlled reaction.[7]

The lack of geminal coupling for the methylene ring protons in the spectrum of ligand **3** indicated that at room temperature fast conformational equilibration occurs with respect to the ^{1}H NMR time scale; moreover, the upfield shifts observed for the protons of the butyl chains indicated that in $CDCl_3$ solution the latter chains are partly included in the cavity. This feature is also observed in the single-crystal X-ray structure of **3** (Figure 1), that is centrosymmetric, with the opposed butyl chains sandwiched by the parallel anthracene units.

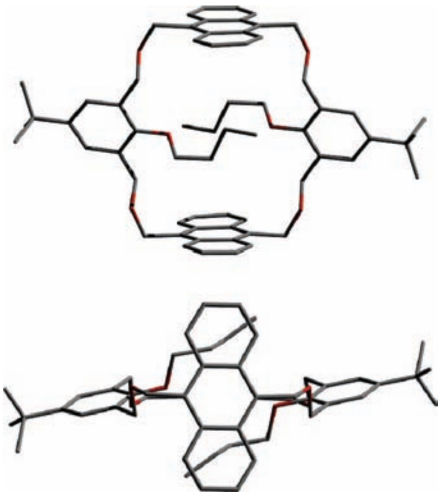

Figure 1. Two views of the single-crystal X-ray structure of compound **3**.

Complexation experiments of **3** with tetramethylammonium and alkylviologen salts were carried out through both ^{1}H NMR and UV−vis techniques. High association constants were observed; in particular, $K = (3.3 \pm 0.2) \times 10^4$ M^{-1} was determined with methylviologen dihexafluorophosphate in $CHCl_3/CH_3CN$ 1:1 at 298 K by monitoring variations in the UV−vis spectra, including the formation of a charge transfer band at about 500 nm.[8] Other determined K values were as follows: with tetramethylammonium picrate in $CDCl_3$, $K = (8.7 \pm 0.5) \times 10^3$ M^{-1} (^{1}H NMR); with propylviologen dihexafluorophosphate in $CDCl_3/CD_3CN$ 1:1, $K = (1.4 \pm 0.1) \times 10^4$ M^{-1} (^{1}H NMR) and $(1.5 \pm 0.1) \times 10^4$ M^{-1} (UV−vis). In the ^{1}H NMR spectra, marked shielding effects are experienced by the protons of the included guest cations,[9] while the signals of the butyl protons of the host, that appeared to be shielded in the free ligand, are shifted back to the values observed in simple model compounds. A single-crystal X-ray structural investigation failed in the case of the complex **4a** with a methylviologen dihexafluorophosphate guest but could be successfully performed in the case of the complex **4b** with a propylviologen dihexafluorophosphate guest (Figure 2). The observed pseudorotaxane structure is still centrosymmetric, but when the wheel is compared to the free ligand, the butyl chains are found to exit the cavity, and the planes of the benzenoid units are markedly rotated

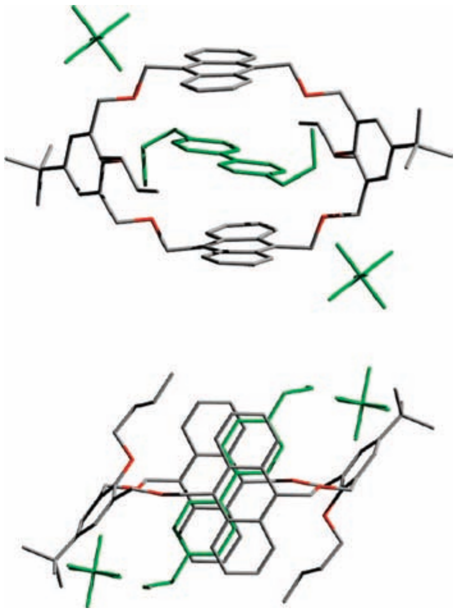

Figure 2. Two views of the single-crystal X-ray structure of the pseudorotaxane complex **4b**, between **3** and propylviologen dihexafluorophosphate.

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(1) (a) Schaefer, C.; Eckel, R.; Ros, R.; Mattay, J.; Anselmetti, D. *J. Am. Chem. Soc.* **2007**, *129*, 1488–1489. (b) Tamayo, A.; Pedras, B.; Lodeiro, C.; Escriche, L.; Casabo, J.; Capelo, J. L.; Covelo, B.; Kivekas, R.; Sillanpaa, R. *Inorg. Chem.* **2007**, *46*, 7818–7826. (c) Moore, E. G.; Bernhardt, P. V.; Fuerstenberg, A.; Riley, M. J.; Vauthey, E. *J. Phys. Chem. A* **2005**, *109*, 11715–11723.

(2) (a) Ishikawa, T.; Shimasaki, T.; Akashi, H.; Toyota, S. *Org. Lett.* **2008**, *10*, 417–420. (b) Hirose, K.; Shiba, Y.; Ishibashi, K.; Doi, Y.; Tobe, Y. *Chem.−Eur. J.* **2008**, *14*, 981–986. (c) Gassensmith, J. J.; Arunkumar, E.; Barr, L.; Baumes, J. M.; Di Vittorio, K. M.; Johnson, J. R.; Noll, B. C.; Smith, B. D. *J. Am. Chem. Soc.* **2007**, *129*, 15054–15059. (d) Kuwabara, J.; Stern, C. L.; Mirkin, C. A. *J. Am. Chem. Soc.* **2007**, *129*, 10074–10075. (e) Kutsumizu, R.; Shinmori, H. Takeuchi. *Tetrahedron Lett.* **2007**, *48*, 3225–3228. (f) Das, N.; Ghosh, A.; Singh, O. M.; Stang, P. J. *Org. Lett.* **2006**, *8*, 1701–1704. (g) Qin, D.-B.; Xu, F.-B.; Wan, X.-J.; Zhang, Z.-Z. *Tetrahedron Lett.* **2006**, *47*, 5641–5643.

(3) (a) Masci, B.; Saccheo, S. *Tetrahedron* **1993**, *49*, 10739–10748. (b) Masci, B.; Finelli, M.; Varrone, M. *Chem.−Eur. J.* **1998**, *4*, 2018–2030.

(4) For reviews on homooxacalixarenes see: (a) Masci, B. *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; Chapter 12. (b) Shokova, E. A.; Kovalev, V. V. *Russ. J. Org. Chem.* **2004**, *40*, 607–643, and 1547−1571.

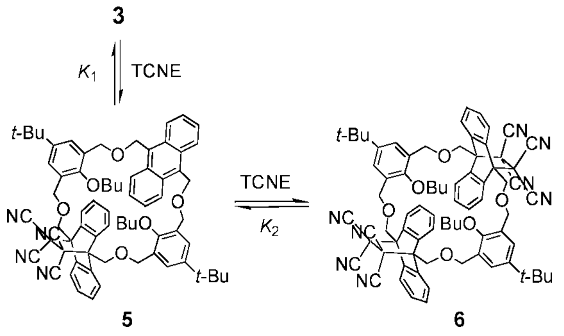
(5) (a) Masci, B.; De Iasi, G. *Tetrahedron Lett.* **1993**, *41*, 6635–6638. (b) Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115–1121.

(6) Powdered, partially dried $Me_4NOH{\cdot}5H_2O$ (900 mg, 4.97 mmol) in dioxane (50 mL) was added to a stirred mixture of **1** (400 mg, 1.10 mmol) and **2** (292 mg, 1.10 mmol) heated at 50 °C. After 22 h reaction and chloroform−water work-up, recrystallization from acetone afforded pure **3** (100 mg, 19% yield). Yields obtained using the commercially available $Me_4NOH{\cdot}5H_2O$ base were lower, in the order of 10%. Yields obtained with NaH in DMF were in the order of 5%, while no product could be isolated using powdered KOH in dioxane.

with respect to the mean plane of the macrocycle (dihedral angle of 49.46(4)° instead of 26.64(8)° in **3**) to make room to the axle. Moreover, the two facing anthracene units are closer (distance between centroids 7.26 Å instead of 9.07 Å in **3**) and somewhat distorted, with contact distances indicative of parallel-displaced π-stacking between each of the pyridinium rings in the guest and two rings in one anthracene unit and one in the other (centroid$\cdots$centroid distances 3.73−3.87 Å, dihedral angles 4.5−9.2°, offset displacements 1.04−1.47 Å). In both structures, the anthracene units are nearly perpendicular to the mean plane of the macrocycle (dihedral angles 89.56(4)° in **3** and 80.23(4)° in **4b**), and intermolecular π-stacking interactions are present in the packing.

The anthracene moieties in **3** are suitable for further transformations and have been tested to undergo Diels−Alder reaction with several dienophiles. Notwithstanding the importance of the Diels−Alder reaction, the stability of the adducts has seldom been assessed, and even in the case of the archetypical anthracene−TCNE pair, only a lower limit value of the formation constant could be estimated.[10] In the case of compound **3**, a number of adducts can be expected that can be reduced to only one monoadduct and one diadduct in the case of 9,10-addition of a symmetric dienophile and of low barriers for conformational equilibration. Here we report on the reaction with tetracyanoethylene (TCNE) which was found to fulfill the latter requirements and to undergo fast and reversible reaction at room temperature.[11] Integration of the areas of suitable signals in the ^{1}H NMR spectra allowed the stability of the adducts to be assessed, in spite of the difficulties arising from the large values of both K_1 and K_2 (Scheme 2) and from the absence of signals for the dienophile. The distribution of the three species **3**, **5**, and **6** at fixed overall concentration of the cyclophanes and at varying TCNE concentration is shown in Figure 3.

Scheme 2



The K_1/K_2 ratio is independent of [TCNE] and could be easily determined in a suitable concentration range: $K_1/K_2 = [\mathbf{5}]^2/[\mathbf{3}][\mathbf{6}] = 21.7 \pm 0.5$ in $CD_3CN-CDCl_3$ 1:1 at 298 K. On the other hand, in independent experiments carried out on suitably diluted solutions of crystals of preformed **6**, [**3**] was found to be negligible, while the small area of the signal of **5** could be safely integrated. So we assumed [TCNE] = [**5**] and obtained $K_2 = (1.5 \pm 0.1) \times 10^5$ M^{-1} and then $K_1 = (3.2 \pm 0.6) \times 10^6$ M^{-1}. The latter values have been used to calculate the solid lines in Figure 3 that fairly match with the experimental points. While **6** can be considered to be a practically stable species in solution (in concentrated enough solution or in excess TCNE),[12] **5**is a labile species that within even a few seconds is partially converted into **3** and **6**.

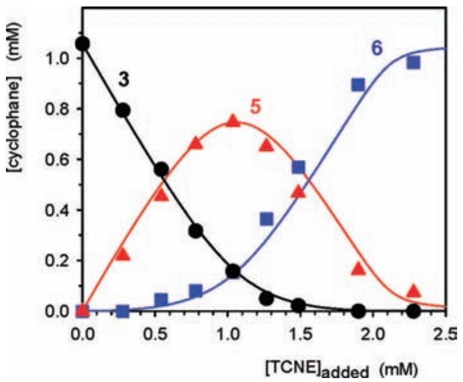


Figure 3. Cyclophane distribution at varying added [TCNE] and at fixed 1.03 mM overall cyclophane concentration. Points are experimental, and curves are calculated.

In a further experiment, we added increasing amounts of TCNE to a solution prepared from crystals of **4a**, namely, the complex of **3** with methylviologen dihexafluorophosphate. Three sets of signals were apparent in the ^{1}H NMR spectra that could be attributed to the three cyclophanes. The chemical shifts of the cyclophanes were markedly affected by the presence of the salt in the case of **3**, slightly affected in the case of **5**, and unaffected in the case of **6**, so that the equilibria involved are apparently those reported in Scheme 3, with $K_3 < K$. The distribution of the three cyclophanes at fixed overall concentration and at increasing [TCNE] is given in Figure 4.[13] Marked differences appear with respect to the picture given in Figure 3, with cyclophanes **3** and **6** being significantly amplified by the guest in wide $[\mathrm{TCNE}]_{\mathrm{added}}$ ranges at the expenses of the monoadduct **5** that is reduced to a minor component. The salt can thus be viewed as a tuner of the Diels−Alder equilibria, while TCNE promotes the exit of the axle from the wheel in the rotaxane structure.

In the search for suitable systems for the development of dynamic combinatorial libraries, Lehn and co-workers[14] investigated some rapidly reversible Diels−Alder reactions

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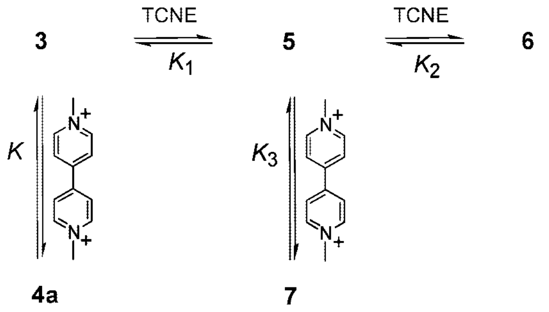
(7) For template effects of tetraalkylammonium ions on reversible systems, see, for instance: (a) Lam, R. T. S.; Belenguer, A.; Roberts, S. L.; Naumann, C.; Jarrosson, T.; Otto, S.; Sanders, J. K. M. *Science* **2005**, *308*, 667–669. (b) Roberts, S. L.; Furlan, R. L. E.; Cousins, G. R. L.; Sanders, J. K. M. *Chem. Commun.* **2002**, 938–939. (c) Cousins, G. R. L.; Furlan, R. L. E.; Ng, Y.-F.; Redman, J. E.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 423–428.

(8) A light reddish color was apparent upon mixing alkylviologen salts and **3** in diluted solution, and a red color was observed in the crystals of the complexes.

(9) Namely, 3.3 ppm in the case of tetramethylammonium picrate and 0.2−1.9 ppm in the case of propylviologen dihexafluorophosphate.

(10) $K = 1 \times 10^5$ M^{-1} for addition in 9,10-positions. See: Handoo, K. L.; Lu, Y.; Parker, V. D. *J. Am. Chem. Soc.* **2003**, *125*, 9381–9387.

Scheme 3



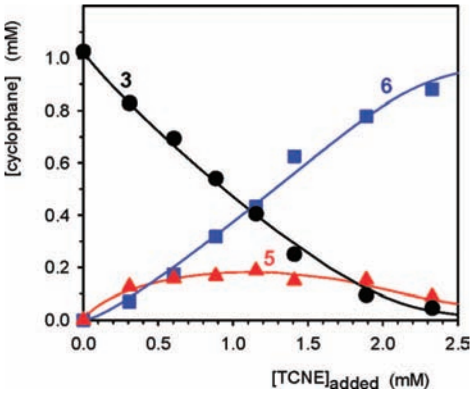


Figure 4. Cyclophane distribution at varying added [TCNE] and at fixed 1.03 mM overall cyclophane concentration, as affected by the presence of 1.03 mM methylviologen dihexafluorophosphate. The notations "**3**", "**5**", and "**6**" indicate the points and the lines corresponding to the total concentrations of these species. Points are experimental, and solid lines merely interpolate them.

and determined formation constants in the range 40−2300 M^{-1} for structurally simple systems. On the other hand, no example has been reported, to the best of our knowledge, of easily reversible Diels−Alder reactions involving the macrocyclic receptor itself as either the diene or the dienophile.[15] Actually, the set of compounds arising from **3** and TCNE can be viewed as a small library in the frame of Dynamic Combinatorial Chemistry.[16] Interestingly, the template that amplifies **3** also causes the amplification of the poor ligand **6**.

Larger libraries can be conceived, also including, for instance, analogues featuring different substituents or modified ring systems. The present dynamic system based on the Diels−Alder reaction suffers from the lack of a chemical quencher; it is nevertheless suitable to be investigated in detail and to undergo supramolecular control. An extension to less reactive dienophiles will allow an effective thermal quenching and the isolation of kinetically stable compounds formed in equilibrating systems at high temperatures.

Supporting Information Available: General methods for the experimental procedures, synthesis, ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, **6**, **4a**, and **4b**, figures, and treatment of experimental data for salt complexation and Diels−Alder adducts formation; crystal data, displacement ellipsoid plots, and crystallographic files in CIF format for compounds **3** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In typical experiments run at 1 mM **3** and 0.1−2 mM TCNE, the equilibration was apparently complete well within 15 min at 298 K.

(12) Unfortunately, the obtained single crystals of **6** were not suitable for X-ray diffraction analysis.

(13) Solid lines in Figure 4 simply interpolate the experimental points. Due to peak superimposition in the ^{1}H NMR spectra, deconvolution procedures were adopted in the integration of the areas. Although substantially reproducible results were obtained, the complexity of the system and the uncertainty in the values of the areas of the ^{1}H NMR signals hampered a fully quantitative treatment.

(14) Boul, P. J.; Reutenauer, P.; Lehn, J.-M. *Org. Lett.* **2005**, *7*, 15–18.

(15) Important examples of supramolecular catalysis in Diels−Alder reactions have been reported for inclusion of both reactants in capsules or macrocyclic cavities. See, for instance: (a) Kang, J.; Hilmersson, G.; Santamaria, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3650–3656. (b) Walter, C. J.; Anderson, H. L.; Sanders, J. K. M. *Chem. Commun.* **1993**, 458–460. (c) Nakash, M.; Clyde-Watson, Z.; Freeder, N.; Davies, J. E.; Teat, S.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 5286–5293. (d) Nakash, M.; Sanders, J. K. M. *J. Org. Chem.* **2000**, *65*, 7266–7271. (e) Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1270–1273.

(16) For recent reviews on Dynamic Covalent Chemistry and Dynamic Combinatorial Chemistry, see: (a) Corbett, P. T.; Leclaire, J.; Vial, L.; West, K. R.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711. (b) De Bruin, B.; Hauwert, P.; Reek, J. N. H. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2660–2663. (c) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 1705–1723. (d) Ladame, S. *Org. Biomol. Chem.* **2008**, *6*, 219–226.