JOC*Note*

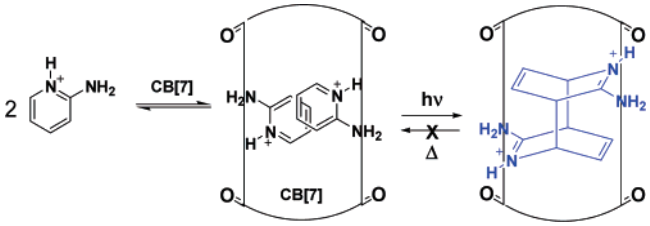
Cucurbit[7]uril Mediates the Stereoselective [4+4] Photodimerization of 2-Aminopyridine Hydrochloride in Aqueous Solution

Ruibing Wang, Lina Yuan, and Donal H. Macartney*

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

donal@chem.queensu.ca

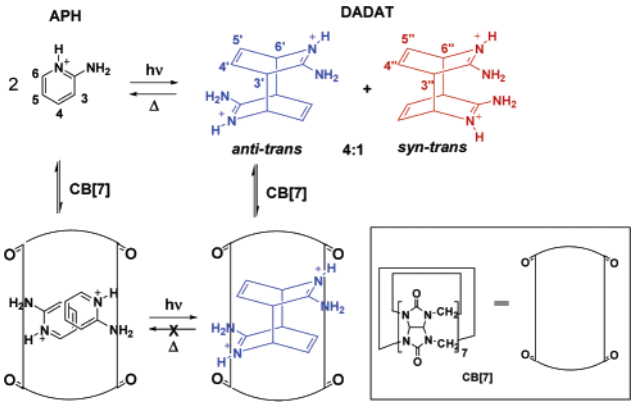
Received October 12, 2005



The 2:1 guest−host complex of 2-aminopyridine hydrochloride with cucurbit[7]uril (CB[7]) undergoes a stereoselective [4+4] photodimerization reaction in aqueous solution to yield exclusively the anti-trans isomer of 4,8-diamino-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-3,7,9,11-tetraene, and in the absence of CB[7], the photochemical reaction produces the anti-trans and syn-trans photodimers in a 4:1 ratio. In addition, encapsulation of the photodimer product in the CB-[7] cavity stabilizes it with respect to the otherwise observed rearomatization to the 2-aminopyridine monomer at room temperature.

In organic photochemistry, the stereoselective control of reactions such as photodimerization has been widely investigated.[1] This control can be achieved by using supramolecular chemistry to bring two reactants into close proximity with the desired orientations. Hydrogen bonding has been employed to induce the noncovalent self-assembly of reactants and templates into photoreactive supramolecular complexes to harvest stereoselective photodimer products in the solid state.[2] Cyclodextrins have been extensively applied to mediate stereoselective photodimerizations of aromatic guests, including anthracenes,[3] coumarins,[4] stilbenes,[5] and cinnamic acids, in either the solid state or an aqueous solution. The cucurbiturils have also been employed to a lesser extent to mediate photodimerization reactions. Mock and co-workers have reported that cucurbit[6]-uril catalyzes the 1,3-dipolar cycloadditon reactions of alkynes with alkyl azides to yield triazoles but preferentially binds the transition state compared with the reactants.[6] More recently, cucurbit[8]uril has been shown to control the stereoselectivity of the photodimerization of cinnamic acids in the solid state[7] and diaminostilbene[8] and *trans*-1,2-bis(4-pyridyl)ethylene[9] in aqueous solution. There have been no reports to date on the use of the smaller, but more water-soluble, cucurbit[7]uril (CB[7]) in the formation of 2:1 guest−host complexes with aromatic molecules for the control of photodimerization. In this Note, we report the results of an investigation of the inclusion of protonated 2-aminopyridine (APH^+) by CB[7] and the highly stereoselective product of the [4+4] photodimerization of APH^+. In addition, we have observed that the stability of otherwise unstable *anti-trans*-$DADAT^{2+}$ encapsulated in CB[7] is dramatically enhanced and the dimer does not rearomatize to the APH^+ monomer at room temperature (Scheme 1).

SCHEME 1



Cucurbit[7]uril (CB[7]) is a member of a family of pumpkin-like macrocyclic host molecules[10] comprised of five, six, seven, eight, or ten methylene-bridged glycoluril units, which possess a hydrophobic cavity accessible through portals surrounded by polar carbonyl groups capable of including of a variety of hydrophobic or/and positively charged guest molecules. Recent modifications to the original synthesis of CB[6] have allowed for substantially higher yields of the otherwise minor CB[7] and CB[8] products.[11] The CB[8] host has the largest cavity

(1) For a recent review, see: Everitt, S. R. L.; Inoue, Y. In *Organic Photochemistry*: *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1999; Vol. 3, p 1.

(2) (a) Papaefstathiou, G. S.; Kipp, A. J.; MacGillivray, L. R. *Chem. Commun.* **2001**, 2462−2463. (b) Friscic, T.; Drab, D. M.; MacGillivray, L. R. *Org. Lett.* **2004**, *6*, 4647−4650.

(3) (a) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 966−972. (b) Ikeda, H.; Nihei, T.; Ueno, A. *J. Org. Chem.* **2005**, *70*, 1237−1242. (c) Yang, C.; Fukuhara, G.; Nakamura, A.; Origane, Y.; Fujita, K.; Yuan, D.-Q.; Mori, T.; Wada, T.; Inoue, Y. *J. Photochem. Photobiol., A: Chem.* **2005**, *173*, 375−383.

(4) Moorthy, J. N.; Venkatesan, K.; Weiss, R. G. *J. Org. Chem.* **1992**, *57*, 3292−3297.

(5) (a) Herrmann, W.; Wehrle, S.; Wenz, G. *Chem. Commun.* **1997**, 1709−1710. (b) Rao, K. S. S. P.; Hubig, S. M.; Moorthy, J. N.; Kochi, J. K. *J. Org. Chem.* **1999**, *64*, 8098−8104.

(6) (a) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Manimaran, T. L. *J. Org. Chem.* **1983**, *48*, 3619−3620. (b) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302−5308.

(7) Pattabiraman, M.; Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529−532.

(8) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938−1939.

(9) Pattabiraman, M.; Natarajan, A.; Kaliappan, R.; Mague, J. T.; Ramamurthy, V. *Chem. Commun.* **2005**, 4542−4544.

(10) (a) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368. (b) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24. (c) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630. (d) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870. (e) Liu, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 16798.

10.1021/jo052136r CCC: $33.50
Published on Web 12/30/2005

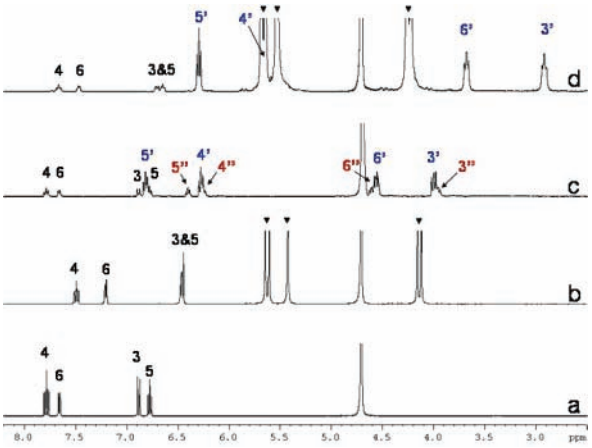


FIGURE 1. ^{1}H NMR spectra (D_2O) of APH^+ before (a) and after (c) 21 h of 365 nm irradiation and of $\{(APH)_2 \cdot CB[7]\}^{2+}$ before (b) and after (d) 21 h of 365 nm irradiation (proton labeling given in Scheme 1, CB[7] peaks (▼)).

size and has the capacity to bring two aromatic molecules together within the cavity, facilitating their [2+2] photodimerization in aqueous solution.[6,8,9] The relatively poor water solubility of CB[8], however, limits its efficiency for reaction control in aqueous solution. Although CB[7] exhibits superior solubility in aqueous solution, it is unable to simultaneously encapsulate two larger aromatic molecules, such as stilbenes. We have found, however, that a smaller cationic guest, protonated 2-aminopyridine, may rapidly (on mixing) form very stable 1:1 and 2:1 complexes with CB[7] in aqueous solution, as indicated by ^{1}H NMR (including a Job's plot of chemical-shift changes), UV−vis, and ES-MS spectra. The limiting upfield shifts of the APH^+ resonances (Figure 1b) in the presence of excess CB[7] are 0.7 ppm for protons 4 and 5 and 1.1 ppm for protons 3 and 6.

The [4+4] photochemical dimerization of protonated 2-aminopyridine (APH^+) to 4,8-diamino-3,7-diazatricyclo[4.2.2.2^{2,5}]-dodeca-3,7,9,11-tetraene ($DADAT^{2+}$), in acidic aqueous solution, was first reported nearly a half century ago.[12] The templating effect of CB[7] represents its first employment in a stereoselective photodimerization of aromatic molecules. The crystallized photodimer in the original study was assigned to be the *anti-trans*-$DATAT^{2+}$ isomer of the four potential stereoisomers. UV irradiation of an aqueous solution of the $\{(APH)_2 \cdot CB[7]\}^{2+}$ complex at 365 nm for 21 h gives exclusively *anti-trans*-$DADAT^{2+}$ with a yield of up to 90% conversion without any side products (Figure 1d), which is significantly higher than the previously reported yield.[12] For comparison purposes, we investigated the APH^+ photodimerization in the absence of CB[7] and observed (by ^{1}H NMR (Figure 1c)) after 21 h of irradiation a 4:1 ratio of the anti-trans and syn-trans isomers (Scheme 1). In the previous study,[11] the solid crystallized from the reaction solution containing only the anti-trans isomer. The anti-cis and syn-cis isomers do not appear to be formed in solution, likely because of the Coulombic repulsions

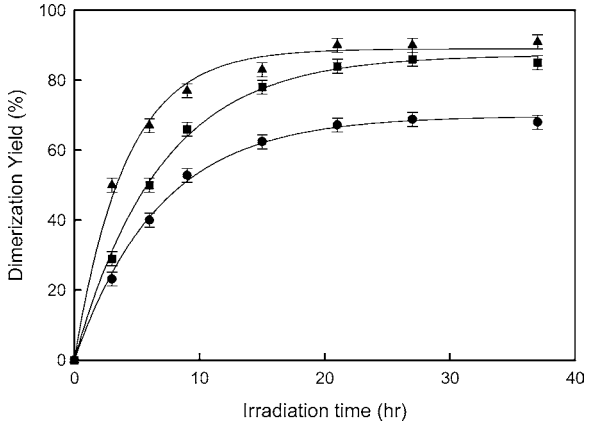


FIGURE 2. Dimer yield (based on one experiment) as a function of irradiation time for APH^+ photodimerization in the presence of CB[7] (triangles, anti-trans dimer) and in the absence of CB[7] (squares, both anti-trans and syn-trans dimers; and circles, anti-trans dimer only).

between the positively charged pyridinium nitrogens. The yields of the photodimer isomers as a function of irradiation time (Figure 2) were evaluated from integration of their respective ^{1}H NMR resonances (Figure 1).

The high stereoselectivity may be related to the anti-trans alignment of the two APH^+ molecules in the CB[7] cavity, stabilized by cation−dipole and hydrogen-bonding interactions.[13] The results (Figure 2) also indicate that the photodimerization is somewhat faster in the presence of CB[7] (3 vs 6 h in the absence of CB[7] for 50% conversion to a dimer). With CB[7] present, the unidentifiable side products seen in the ^{1}H NMR spectra after prolonged irradiation of APH^+ without CB[7] were not observed.

The dimer undergoes spontaneous rearomatization back to the APH^+ monomer very slowly at room temperature or quickly by adding base.[12] In this study, the *anti-trans*-$DADAT^{2+}$ encapsulated in CB[7] does not undergo rearomatization at room temperature but does do so upon addition of base to the solution, which presumably deprotonates the guest, releasing it from its stabilizing environment. Although the mechanism of the thermal rearomatization of $DADAT^{2+}$ to APH^+ is not clear yet, stabilization of otherwise unstable photochemical products by means of supramolecular encapsulation in host containers has precedence.[14] Specifically and more recently, CB[7] has also been employed to stabilize *cis*-stilbene derivatives[15] and fluorescent rhodamines.[16] The observed behavior in the APH^+/$DADAT^{2+}$ system may be useful in the design of pH/photochemically controlled on/off switchable (reversible)

(11) (a) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541. (b) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100.

(12) (a) Taylor, E. C.; Kan, R. O.; Paudler, W. W. *J. Am. Chem. Soc.* **1961**, *83*, 4484−4485. (b) Taylor, E. C.; Kan, R. O. *J. Am. Chem. Soc.* **1963**, *85*, 776−784.

(13) One reviewer suggested that an alternative mechanism could involve dimerization of APH^+ outside of the CB[7] cavity, with the CB[7] then preferentially binding the *anti-trans*-$DADAT^{2+}$ product, producing the observed stereospecificity. This could be a minor parallel process; however, the addition of CB[7] to the mixture of anti-trans and syn-trans products, obtained from dimerization in the absence of CB[7], did not result (in the time scale of the experiment in Figure 2) in a subsequent conversion from syn to anti products. This process, involving initial rearomatization to the monomer is very slow under the conditions employed in the dimerization reaction.

(14) (a) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024−1027. (b) Warmuth, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1347−1350. (c) Warmuth, R. *Chem. Commun.* **1998**, 59−60. (d) Kusukawa, T.; Fujita, M. *J. Am. Chem. Soc.* **1999**, *121*, 1397−1398.

(15) Choi, S.; Park, S. H.; Ziganshina, A. Y.; Ko, Y. H.; Lee, J. W.; Kim, K. *Chem. Commun.* **2003**, 2176−2177.

(16) Mohanty, J.; Nau, W. M. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 3754.

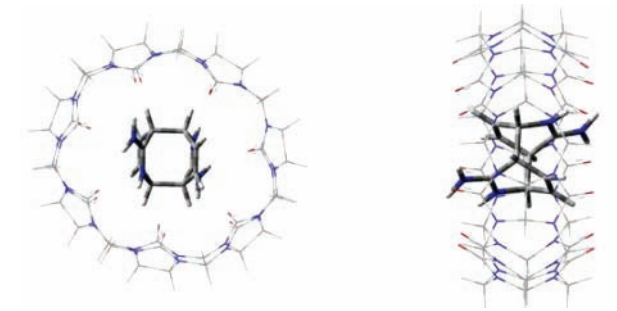


FIGURE 3. Energy-minimized structures of {*anti-trans*-DADAT·CB-[7]}$^{2+}$ in the gas phase (HF/3-21G** basis set). DADAT^{2+} is indicated by the tube-type structure, and CB[7] is indicated by the wireframe-type structure.

photodimerization because in switch design both states need to be stable. This aspect is currently under study.

The stabilization of the anti-trans photodimer in the CB[7] ($K_{CB} = (8 \pm 2) \times 10^5$ M^{-1} by ^{1}H NMR dilution experiments) relies on multiple noncovalent hydrophobic cation−dipole and hydrogen-bonding interactions. An energy-minimized structure of the {*anti-trans*-DADAT·CB[7]}$^{2+}$ complex by ab initio (HF/3-21G** basis set) calculations is shown in Figure 3.[17] The photodimer is held tightly in the cavity of CB[7], with several hydrogen-bonding interactions between the amine hydrogens and the portal oxygens at each end of the cavity. The orientation of the dimer in the CB[7] cavity is consistent with the magnitudes of the upfield shifts in the ^{1}H NMR resonances of the alkene and bridgehead protons (Figure 1d).

In conclusion, we have demonstrated that the [4+4] photodimerization of protonated 2-aminopyridine within a 2:1 guest−host complex with CB[7] is highly stereoselective, producing exclusively the *anti-trans*-DADAT^{2+} isomer and protecting the dimer from thermal rearomatization. This result demonstrates the potential application of CB[7] in mediating stereoselective photodimerizations of small aromatic molecules in aqueous solution.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian* 03, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

Experimental Section

^{1}H NMR spectra (400 MHz) were obtained in D_2O, with proton assignments determined from 2D COSY experiments. Electrospray mass spectra were recorded on samples in aqueous solution.

2-Aminopyridine Hydrochloride (APH$^+$). A portion of 2 mg of 2-aminopyridine was added to a mixture of 1.6 mL of D_2O and 20 μL of concentrated DCl (35 wt % solution in D_2O), and half of the solution (∼0.8 mL) was transferred into one NMR tube: ^{1}H NMR (D_2O, 400 Mz) δ 7.78 (ddd, $J_{3,4} = 9.1$ Hz, $J_{4,5} = 7.0$ Hz, $J_{4,6} = 0.8$ Hz, H4, 1H), 7.66 (dd, $J_{5,6} = 6.5$ Hz, H6, 1H), 6.88 (dd, $J_{3,5} = 0.8$ Hz, H3, 1H), 6.77 (dt, H5, 1H) ppm.

{(APH)$_2$·CB[7]}$^{2+}$. A portion of 7 mg of CB[7] was added into the previously made APH solution (∼0.8 mL). The solution (APH and CB[7] in a 2:1 molar ratio) was sonicated to dissolve the CB-[7] and was transferred to a second NMR tube: ^{1}H NMR (D_2O, 400 MHz) δ 7.49 (H4, 2H), 7.20 (H6, 2H), 6.46 (H3 and H5, 4H), 5.69 (d, CH_2 of CB[7], 14H), 5.47 (s, CH of CB[7], 14H), 4.19 (d, CH of CB[7], 14H) ppm; ESI-MS *m*/*z* 676.6 [M]$^{2+}$.

Photodimerization Experiments. The NMR tubes with APH$^+$ and {(APH)$_2$·CB[7]}$^{2+}$ were irradiated with UV light (365 nm) directly, and the photoproducts were monitored by ^{1}H NMR spectroscopy every 3 h.

***anti-trans*-DADAT$^+$ (4,8-Diamino-3,7-diazatricyclo[4.2.2.2^{2,5}]-dodeca-3,7,9,11-tetraene):** ^{1}H NMR (D_2O/DCl, 400 Mz) δ 6.82 (t, $J = 7$ Hz, H5′, 2H), 6.28 (t, $J = 7$ Hz, H4′, 2H), 4.56 (dd, $J = 9.7$ Hz, 7 Hz, H6′, 2H), 3.98 (t, $J = 7$ Hz, H3′, 2H) ppm (literature[12] (D_2O, 60 MHz) δ 6.90 (H5′, 2H, $J_{4',5'} = 7.5$ Hz, $J_{5',6'} = 6.5$ Hz, $J_{3',5'} = 1.5$ Hz), 6.35 (H4′, 2H, $J_{3',4'} = 6.5$ Hz, $J_{4',6'} = 1.5$ Hz), 4.68 (H6′, 2H, $J_{3',6'} = 9.5$ Hz), 4.11 (H3′, 2H) ppm); ESI-MS *m*/*z* 189.2 [M]$^+$.

{*anti-trans*-DADAT·CB[7]}$^{2+}$: ^{1}H NMR (D_2O, 400 Mz) δ 6.29 (t, $J = 7.2$ Hz, H5′, 2H), 5.66 (t, H4″, 2H), 3.68 (t, $J = 8$ Hz, H6″, 2H), 2.92 (t, $J = 8.1$ Hz, H3″, 2H), 5.68 (d, CH_2 of CB[7], 14H), 5.55 (s, CH of CB[7], 14H), 4.26 (d, CH of CB[7], 14H) ppm; ESI-MS *m*/*z* 676.4 [M]$^{2+}$.

(*syn-trans*-DADAT}$^+$: ^{1}H NMR (D_2O, 400 Mz) δ 6.40 (t, H5″, 2H), 6.26 (t, H4″, 2H), 4.61 (t, H6″, 2H), 3.95 (t, H3″, 2H) ppm; ESI-MS *m*/*z* 189.2 [M]$^+$.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support of this research and Shihao Wang and Dr. Natalie Cann for assistance with the energy-minimized structure calculations.

Supporting Information Available: ^{1}H NMR and ES-MS spectra of the photochemical reactions, Job's plot, calculations of the guest−host stability constant, and details of energy-minimized structure calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052136R