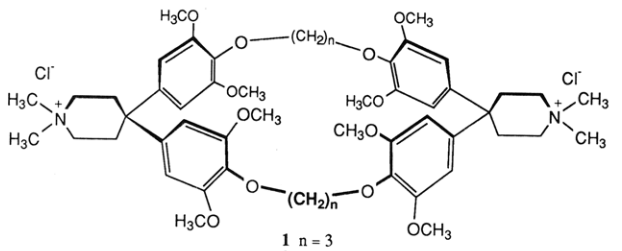
Strong Enthalpically Driven Complexation of Neutral Benzene Guests in Aqueous Solution

Summary: The extraordinarily strong complexation of neutral benzene derivatives in water by novel cyclophane hosts is completely enthalpically driven. A comparison of enthalpic and entropic contributions for complexation in water versus methanol provides evidence for a large enthalpic hydrophobic effect in aqueous solution.

Sir: Investigations involving cyclodextrins[1] and synthetic cyclophane hosts[2,3] have shown that stable complexes with apolar organic substrates can be formed in aqueous solution. Comparative binding studies[2,3e,i] show that the stability of these complexes is considerably reduced in organic solutions, thus demonstrating that water provides a special driving force for molecular complexation. The nature of the "hydrophobic effect",[4] which generates strong interactions between apolar surfaces in aqueous solution, has been the subject of extensive investigations. We report the results of temperature-dependent binding studies with novel hosts which show that molecular complexation of neutral substituted benzene guests in aqueous solution is driven by a strong *enthalpic hydrophobic effect*.

The new octamethoxy-substituted cyclophane hosts **1** and **2** were prepared by previously described methods[5a] and analyzed as dihydrates.[6] The addition of eight methoxy substituents dramatically enhances the complexation ability of **1** and **2** by increasing the cavity depth and by making the aromatic cavity walls more polarizable.



1 n = 3
2 n = 4

The X-ray structure of **1** as a diiodide[7] confirms the formation of a very deep and organized cavity due to the extension of the diphenylmethane cavity walls by the in-plane methoxy substituents (Figure 1). For the macrocycle analogous to **1** in which hydrogen atoms replace the eight methoxy groups,[5] the distance between two meta hydrogens is ≈4.3 Å, while in **1** the height of the cavity wall is almost doubled with a distance of ≈7 Å between the methyl carbon atoms of the two *m*-methoxy groups. The methoxy substituents are also responsible for the high critical aggregation concentrations (CAC's) of **1** and **2**. Macrocycles similar to **1** and **2** without methoxy substituents have CAC's of 2.5×10^{-3} and 1.6×10^{-4} mol L^{-1}, respectively,[5a] while **1** and **2** have CAC's greater than 1×10^{-2} mol L^{-1}.[8]

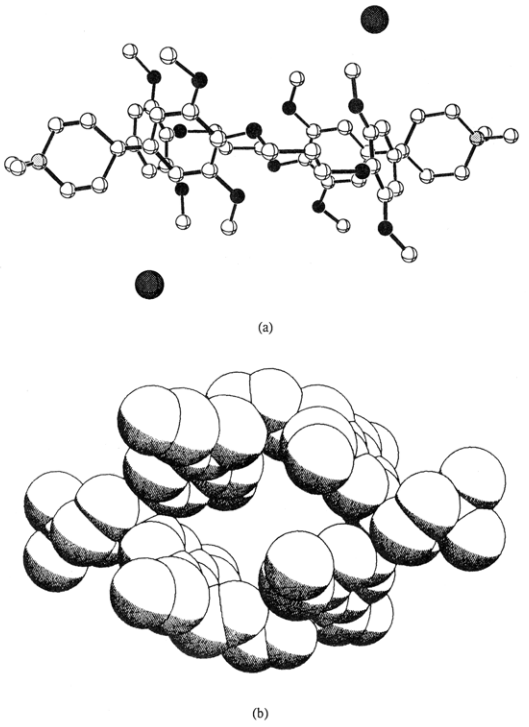


Figure 1. (a) Molecular structure of **1** (as a diiodide) viewed parallel to the mean molecular plane. (b) Space-filling representation of **1** viewed perpendicular to the mean molecular plane.

Extraordinarily large association constants (K_a) for 10 complexes of **2** and six complexes of **1** with various para-substituted benzene guests were determined from ^{1}H NMR titrations[9] at 293.4 K in D_2O (Table I). While the participation of electron donor–acceptor (EDA) interactions has been observed in aqueous[2a,3j] and organic solutions,[10] the contribution of these interactions is surprisingly not obvious for complexes of **1** and **2** in aqueous solution.

(1) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978. (b) Saenger, W. *Angew. Chem.* **1980**, *92*, 343–361; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344–362.

(2) (a) For a recent review of molecular complexation of neutral organic guests, see: Diederich, F. *Angew. Chem.* **1988**, *100*, 372–396; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–386. (b) Diederich, F.; Dick, K.; Griebel, D. *J. Am. Chem. Soc.* **1986**, *108*, 2273–2286.

(3) (a) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504–2505. (b) Odashima, K.; Koga, K. In *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic: New York, 1983; Vol. 2, pp 629–678. (c) Winkler, J.; Coutouli-Argyropoulou, D.; Leppkes, R.; Breslow, R. *J. Am. Chem. Soc.* **1983**, *105*, 7198–7199. (d) Miller, S. P.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 1492–1494. (e) Schneider, H.-J.; Philippi, K.; Pöhlmann, J. *Angew. Chem.* **1984**, *96*, 907–909; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 908–910. (f) Merz, T.; Wirtz, F.; Vögtle, F. *Angew. Chem.* **1986**, *98*, 549–550; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 567–569. (g) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563–5566. (h) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440–4446. (i) Canceill, J.; Lacombe, L.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1987**, 219–221. (j) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983–1985.

(4) (a) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1985; Chapter 11, pp 293–310. (b) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, 2nd ed.; Wiley: New York, 1980. (c) Abraham, M. H. *J. Am. Chem. Soc.* **1982**, *104*, 2085–2094.

(5) (a) Diederich, F.; Dick, K.; Griebel, D. *Chem. Ber.* **1985**, *118*, 3588–3619. (b) Krieger, C.; Diederich, F. *Chem. Ber.* **1985**, *118*, 3620–3631.

(6) Elemental analysis and spectroscopic data (IR, 500-MHz ^{1}H NMR, and EI-MS or FAB-MS) corroborate structures **1** and **2** and all synthetic precursors.

(7) Crystal data of **1** as a diiodide: $C_{52}H_{72}N_2O_{12}I_2 \cdot 2H_2O$; M_r = 1206.98; orthorhombic; space group = *Pccn*; Z = 4; a (Å) = 16.5538 (4); b (Å) = 17.7556 (5); c (Å) = 18.8275 (5); V (Å^3) = 5520.80; D_c (g cm^{-3}) = 1.45; a total of 3195 reflections with $I > 3\sigma I$; final R = 0.048. Two water molecules are disordered inside the molecular cavity.

(8) The large CAC's provided optimal experimental conditions for this study. Many complexes that we analyzed have association constants greater than 2500 L mol^{-1}. At the endpoints of ^{1}H NMR titrations with [host] ≈ 1×10^{-2} mol L^{-1} and [guest] ≈ 5×10^{-4} mol L^{-1}, we observed ^{1}H NMR resonances that indicated greater than 98% complexation of the guest. The availability of binding titration data that represent ≈40–98% complexation of the guest provided extremely accurate association constants, which were needed to obtain significant values from the van't Hoff analysis.

(9) ^{1}H NMR spectra were acquired on a Bruker AM500 spectrometer. Temperatures given for the various temperature-dependent studies have an uncertainty of ±1.0 K, and all titrations were evaluated by a nonlinear least-squares curve-fitting procedure.

(10) Ferguson, S. B.; Diederich, F. *Angew. Chem.* **1986**, *96*, 1127–1129; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1127–1129.

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Table I. Association Constants K_a and Enthalpic ($\Delta H°$) and Entropic ($-T\Delta S°$) Contributions to the Free Energies of Complexation ($\Delta G°$) at 293.4 K for Complexes of Hosts 1 and 2 with 1,4-Disubstituted Benzene Guests in D_2O and Methanol-d_4

	K_a,[a] L mol^{-1}	$\Delta G°$,[b] kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$-T\Delta S°$, kcal mol^{-1}
	Complexes of **2** in D_2O			
dimethyl *p*-benzenedicarboxylate[c]	1.17×10^5	−6.81	−10.7 ± 1.0	4.0 ± 1.0
p-nitrotoluene[c]	3.00×10^4	−6.01	−9.6 ± 3.0	3.6 ± 3.0
p-tolunitrile[c]	2.99×10^4	−6.01	−9.8 ± 2.5	3.8 ± 2.5
p-nitrophenol[c]	2.31×10^4	−5.86	−11.7 ± 1.5	5.8 ± 1.5
p-dimethoxybenzene[c]	1.02×10^4	−5.38	−10.2 ± 2.5	4.8 ± 2.5
p-xylene[c]	9.33×10^3	−5.33	−7.4 ± 1.0	2.1 ± 1.0
p-dicyanobenzene[d]	7.83×10^3	−5.23	−9.5 ± 1.0	4.3 ± 1.0
p-dinitrobenzene[c]	7.76×10^3	−5.22	−9.5 ± 1.0	4.3 ± 1.0
p-cresol[c]	3.21×10^3	−4.71	−9.1 ± 1.5	4.4 ± 1.5
p-diaminobenzene[e]	3.58×10^2	−3.43	−7.1 ± 1.5	3.7 ± 1.5
	Complexes of **1** in D_2O			
p-nitrophenol[c]	2.17×10^3	−4.48	−10.1 ± 1.5	5.6 ± 1.5
p-nitrotoluene[c]	2.13×10^3	−4.47	−8.5 ± 2.5	4.0 ± 2.5
dimethyl *p*-benzenedicarboxylate[c]	2.07×10^3	−4.45	−8.0 ± 1.0	3.5 ± 1.0
p-xylene[c]	1.30×10^3	−4.18	−6.4 ± 1.0	2.2 ± 1.0
p-dicyanobenzene[e]	1.02×10^3	−4.04	−7.3 ± 1.0	3.3 ± 1.0
p-dimethoxybenzene[e]	3.71×10^2	−3.45	−5.7 ± 1.5	2.2 ± 1.5
	Complexes of **2** in Methanol-d_4			
p-dicyanobenzene[e]	2.4×10^1	−1.86	−4.2 ± 1.5	2.4 ± 1.5
p-dimethoxybenzene[e]	8×10^0	−1.20	−4.4 ± 1.5	3.2 ± 1.5

[a] Association constants of complexes in D_2O have an uncertainty of 10% and those of complexes in methanol-d_4 have uncertainties of 25%. [b] Free energies of complexation have an uncertainty of 0.07 kcal mol^{-1} for complexes in aqueous solutions and 0.17 kcal mol^{-1} for complexes in methanolic solutions. [c-e] Temperature range for *c* 293.4–315.8 K, *d* 275.8–315.8 K, and *e* 269.9–293.4 K.

These contributions may be masked by other effects such as differences in the solvation and hydrophobicity of the various benzene substrates.[11] The K_a values presented in Table I demonstrate that macrocycle **2** has a greater affinity for para-substituted benzenes than **1** has for these guests. ^{1}H NMR complexation shifts provide evidence for the formation of highly organized complexes. Complexes of both **1** and **2** have similar geometries with the axially oriented guest presumably adopting a position in the cavity which favors both π–π and T-shaped aryl–H_{guest}···π-$aryl_{host}$ interactions between the two binding partners.[2a,5b]

Association constants for complexes of **2** with both *p*-dimethoxybenzene and *p*-dicyanobenzene were also determined in methanol-d_4 (Table I). These complexes are 3–4 kcal mol^{-1} (at 293.4 K) less stable than the corresponding complexes formed in aqueous solution. This data is representative of studies involving various benzene guests and demonstrates a special driving force for complexation, which exists only in aqueous solution. Temperature-dependent studies over an approximately 25 °C range determined the thermodynamic quantities by a van't Hoff analysis (Table I). This rather narrow temperature range was chosen to avoid nonlinearity of van't Hoff plots resulting from possible heat capacity changes.[12,13] Although large uncertainties are associated with the values of $\Delta H°$ and $-T\Delta S°$, all complexes studied in aqueous solution demonstrate a favorable enthalpic contribution and a large unfavorable entropic contribution to the free energy of complexation. The complexation of benzene derivatives with our hosts in aqueous solution is completely enthalpically driven. Enthalpically controlled complexation was previously observed in protein binding of aromatic substrates[14] and cyclodextrin binding of substituted benzenes.[15,16] A comparison of enthalpic and entropic contributions for complexation in water versus methanol demonstrates a very large favorable enthalpic driving force that is present only in aqueous solution (Table I). Since the geometry of the complexes in water and methanol is approximately the same,[17] the difference in the enthalpic driving force cannot be explained by differences in attractive interactions between host and guest. Therefore, a large part of the favorable enthalpic component in water results from specific contributions of the solvent. We explain the strong enthalpic hydrophobic effect on complexation by reduced cohesive interactions between water molecules, which solvate the interior of the free binding site and the surface of the free guest.[18] Since water molecules are much less polarizable than organic substrates, the dispersion interactions between water molecules and the organic surfaces of both the binding site and the guest are also less favorable than the interactions between the organic surfaces in the complex.[4a,c] Hence, complexation in water is also driven by increasing attractive London dispersion interactions.

These temperature-dependent complexation studies will be continued with biological substrates and expanded to include larger aromatic guests (e.g. naphthalene, pyrene, perylene). The latter investigations will determine whether entropic contributions to the free energy of complexation become more favorable when guests have much larger hydrophobic surfaces.[4a,19]

(11) The Hansch partition coefficients of the benzene guests differ substantially, e.g. log $P_{octanol}$ = −0.26 for *p*-diaminobenzene and +3.20 for *p*-dimethoxybenzene, two electron-donating guests. For definitions and values of log *P*, see: Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–616.

(12) Sturtevant, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2236–2240.

(13) When the **2**-*p*-dicyanobenzene complex was analyzed over a larger temperature range, 275.8–315.8 K, the van't Hoff plot remained linear.

(14) Biltonen, R. L.; Langerman, N. *Methods Enzymol.* **1979**, *61*, 287–318.

(15) Eftink, M. R.; Harrison, J. C. *Bioorg. Chem.* **1981**, *10*, 388–398.

(16) Harata, K.; Tsuda, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *J. Incl. Phenom.* **1988**, *6*, 135–142.

(17) Complexation-induced ^{1}H NMR shifts at saturation binding of both host and guest resonances are similar for specific complexes formed in both aqueous and methanolic solutions indicating similar geometries; see ref 2a.

(18) This enthalpic hydrophobic effect is contrary to the classical hydrophobic effect, which is defined by a large favorable $T\Delta S°$ term; see ref 4.

(19) (a) Hermann, R. B. *J. Phys. Chem.* **1972**, *76*, 2754–2759. (b) Chothia, C. *Nature (London)* **1974**, *248*, 338–339.

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Supplementary Material Available: Elemental analyses and spectroscopic data of hosts 1 and **2**, experimental details of the temperature-dependent binding studies and of the crystal structure determination, and crystal data tables of atomic coordinates, equivalent isotropic thermal parameters, anisotropic thermal parameters, hydrogen positional parameters, and details of the molecular geometry for 1 as a diiodide (8 pages). Ordering information is given on any current masthead page.

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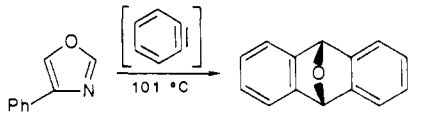
Isolation of a 1:1 Oxazole–Benzyne Cycloadduct: An Improved Method for Generating Benzyne and a New Approach to Isobenzofuran[1]

Summary: A dual syringe pump addition procedure for benzyne generation from 1-aminobenzotriazole with $Pb(OAc)_4$ is applied to 4-phenyloxazole at 0 °C, to give the *isolable* 1:1 benzyne/oxazole Diels–Alder adduct in essentially quantitative yield; mild solution thermolysis of this adduct gives isobenzofuran.

Sir: Reactions of acetylenic dienophiles with oxazoles form the basis of a useful synthesis of substituted furans.[2] With one curious exception,[3] all such reactions involve facile loss of nitrile from the initially formed Diels–Alder adduct, precluding isolation of this species.

Benzyne is among the most reactive "acetylenic" dienophiles known, and we hoped that its use at low temperature might allow the isolation of such cycloadducts. The single report[4] of reactions of benzyne with (trisubstituted) oxazoles is not informative on this point, since the reaction was carried out in refluxing dioxane (101 °C). At this temperature rapid retro-Diels–Alder loss of nitrile occurs, followed by addition of a second benzyne to the intermediate (isobenzo)furan, to form the 2:1 adduct. This overall process appears to be relatively insensitive to substituents (H, alkyl, aryl) on the oxazole. For example, when subjected to the Reddy–Bhatt[4] conditions (anthranilic acid + RONO, 101 °C), we find that 4-phenyloxazole[5] (**1**) gives the 2:1 adduct **2**[6] in good yield (53% recrystallized).



1 2 (1)

Various limitations surface when low temperature formation of benzyne is addressed. The anthranilic acid method, because of thermal stability (in solution) of the intermediate diazonium carboxylate, requires a temperature well above ambient. Strong base induced methods are not suitable for 2-unsubstituted oxazoles.[7] The 1-aminobenzotriazole (ABT)–$Pb(OAc)_4$ method developed by Campbell and Rees[8] was especially attractive since it had been shown to produce benzyne rapidly even at −78 °C and, alone of the benzyne procedures considered, it gives high yields of biphenylene when carried out in the absence of other reactants.[8] Biphenylene formation, even if diffusion controlled,[9,10] requires that the (steady state) concentration of benzyne reach a level[9] not attained, because of the intervention of various side reactions, in alternative procedures.

The Rees procedure[8] calls for dropwise addition of ABT to a mixture of substrate and $Pb(OAc)_4$, and good yields of cycloadduct have been obtained by using this approach with very reactive dienes. The method is also satisfactory with less reactive dienes such as furan when these substrates can be employed in large excess (e.g. as solvent).[11]

Slow (syringe pump) addition of a CH_2Cl_2 solution of ABT (ca. 1 molar equiv) to an equimolar mixture of **1** and $Pb(OAc)_4$ in the same solvent at 0 °C gave a crude product that contained (by NMR) substantial amounts of starting material and biphenylene. This disappointing result could be construed merely as signifying an unfavorable activation energy for the cycloaddition of benzyne with **1**, but this would be an oversimplification. In fact **1** is highly competitive for reaction with benzyne when the process is given equal opportunity; problems arise instead because an alternative pathway for consumption of benzyne (dimeri-

(1) Part of this work was presented at the Third Chemical Congress of North America, Toronto, Canada, June 1988 (ORGN: 466).

(2) (a) Grigg, R.; Hayes, R.; Jackson, J. L. *Chem. Commun.* **1969**, 1167. (b) Grigg, R.; Jackson, J. L. *J. Chem. Soc.* **1970**, 552. (c) Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* **1970**, *92*, 4340. (d) Kondrat'eva, G. Y.; Medvedskaya, L. B.; Ivanova, Z. N.; Shmelev, L. V. *Dokl. Akad. Nauk SSSR* **1971**, *200*, 1358 (Engl. transl. p 862). (e) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (f) Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* **1979**, *9*, 789. (g) Gorgues, A.; Le Coq, A. *Tetrahedron Lett.* **1979**, 4829. (h) Ansell, M. F.; Caton, M. P. L.; North, P. C. *Tetrahedron Lett.* **1981**, *22*, 1727. (i) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (j) Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473.

(3) Crank, G.; Khan, J. R. *J. Heterocycl. Chem.* **1985**, *22*, 1281. This paper describes the *exothermic* reaction of various 2-aminooxazoles with DMAD to give 1:1 cycloadducts. NMR data that support the *2-aza-7-oxabicyclo[2.2.1]hepta-2,5-diene* structures are reported. The isolation of these products is especially interesting given possible alternative reactions such as the (very rapid) Michael-type addition of amines to DMAD (see: George, M. V.; Khetan, S. K.; Gupta, R. K. *Adv. Heterocycl. Chem.* **1976**, *19*, 279) and recent evidence (see: Chung, Y. S.; Duerr, B. F.; Nanjappan, P.; Czarnik, A. W. *J. Org. Chem.* **1988**, *53*, 1336) that shows that bridgehead amino anthracene cycloadducts undergo retro-Diels–Alder reaction even more rapidly than their alkoxy analogues. The analogous 2- and 5-alkoxyoxazole 1:1 cycloadducts of acetylenic dienophiles have not been isolated and must expel nitriles rapidly at or below room temperature.[1a,b,g] The only other mention of the 1:1 adduct ring system found in a CAS ONLINE partial structure search involves the claim of an intramolecular cycloaddition of a furan diene and nitrile dienophile (Tagmazyan, K. T.; Mkrtchyan, R. S.; Babayan, A. T. *Russ. J. Org. Chem.* **1974**, *10*, 1657); only IR, mp, and (marginal) N, H analytical data are given, and alternative structural possibilities were not ruled out.

(4) Reddy, G. S.; Bhatt, M. V. *Tetrahedron Lett.* **1980**, *21*, 3627; simultaneous addition of anthranilic acid and amyl nitrite was used to generate benzyne.

(5) 4-Phenyloxazole was prepared in 41% overall yield from phenacyl bromide and sodium formate, followed by heating with ammonium acetate in HOAc. The general procedure is that of Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 328.

(6) Compound **2** has been made previously, by treatment of preformed isobenzofuran with benzyne: Crump, S. L.; Netka, J.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 2746.

(7) Oxazoles that bear an H in the 2-position are very rapidly lithiated by RLi. To illustrate, treatment of a mixture **1** and *o*-dibromobenzene with *n*-BuLi followed by D_2O quench gave 2-deuterio-4-phenyloxazole; thus deprotonation occurs more rapidly than Br/Li exchange (compare the reactions of isobenzofuran[6]).

(8) Campbell, C. D.; Rees, C. W. *Proc. Chem. Soc.* **1964**, 296; *J. Chem. Soc. C* **1969**, 742.

(9) The (gas phase) dimerization of benzyne occurs at or near the diffusion-controlled limit;[10] if a rate constant of $\leq 10^{10}$ mol^{-1} s^{-1} for reaction in solution is assumed, the steady state benzyne concentration must be $\geq 10^{-7}$ M to account for the rate (amount per L/time) of biphenylene formed in a typical reaction.

(10) Shafer, M. E.; Berry, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 4497.

(11) For a novel application of furan and a bis-aminotriazole, see: Hart, H.; Ok, D. *J. Org. Chem.* **1986**, *51*, 979.

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