phosphines, and the cyclopropanation of TME by 1 and triphenylphosphine can best be explained by formation and dissociation of the difluoromethylene ylide. Whether the driving force for this facile dissociation is the stability of difluorocarbene or whether this behavior is general for ylides cannot be ascertained without additional work. However, caution should be excercised when one writes these types of ylide reactions as irreversible processes without any experimental justification.

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Registry No. 1, 58201-66-4; **2a**, 1608-26-0; **2b**, 1038-95-5; **2c**, 122-52-1; **5a**, 58310-30-8; **5a** (phosphorane), 58310-29-5; **5b**, 87137-21-1; **6**, 87145-05-9; **6** (phosphorane), 87137-22-2; **7**, 58310-28-4; **8**, 823-25-6; **9**, 65094-22-6; TME, 563-79-1.

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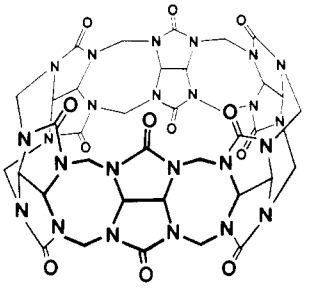
Host–Guest Binding Capacity of Cucurbituril

Summary: The novel cage substance cucurbituril encapsulates and tightly binds substituted ammonium ions having dimensions smaller than a para-disubstituted benzene ring.

Sir: Cucurbituril (1, $C_{36}H_{36}N_{24}O_{12}$) is a recently rediscovered nonadecacyclic cage structure of hexagonal symmetry, which is readily assembled from urea, glyoxal, and formaldehyde.[1,2] It has a relatively rigid structure, with



1

a hollow core of several angstroms diameter, which is accessible from the exterior. The substance dissolves readily in acidic aqueous solutions. According to the following evidence, it forms a novel series of host–guest complexes with alkylammonium ions. For example, gradual addition of 1 to a dilute formic acid solution of isobutylamine [$(CH_3)_2CHCH_2NH_2$] results in diminution of the proton NMR methyl signal for the isobutyl group and concurrent emergence of a new doublet approximately 1 ppm to higher field. This is attributed to encapsulation of the aliphatic residue within the cavity of 1. The complexation is stoichiometric (1:1, by NMR integration), and quite evidently exchange between external and internal environments is slow, since there is no averaging of NMR signals at 40 °C when excess isobutylammonium ion is present.

Table I. Dissociation Constants for Representative Alkylammonium and Alkyldiammonium Ions in 1:1 Aqueous Formic Acid (v/v)[a]

guest (RNH_3^+)	K_d, M
$CH_3CH_2CH_2NH_3^+$	8.2×10^{-5}
$CH_3CH_2CH_2CH_2NH_3^+$	1.0×10^{-5}
$CH_3CH_2CH_2CH_2CH_2NH_3^+$	4.2×10^{-5}
$(CH_3)_2CHCH_2CH_2NH_3^+$	2.8×10^{-5}
$(CH_3)_3CCH_2CH_2NH_3^+$	5.7×10^{-2}
$(CH_2)_2CHCH_2NH_3^+$ (cyclopropanemethyl)	6.8×10^{-5}
$(CH_2)_3CHCH_2NH_3^+$ (cyclobutanemethyl)	2.7×10^{-6}
$(CH_2)_4CHCH_2NH_3^+$ (cyclopentanemethyl)	3.0×10^{-6}
$(CH_2)_5CHCH_2NH_3^+$ (cyclohexanemethyl)	not bound[a]
$C_6H_5CH_2NH_3^+$	3.7×10^{-3}
p-$CH_3C_6H_4CH_2NH_3^+$	3.1×10^{-3}
m-$CH_3C_6H_4CH_2NH_3^+$	not bound[b]
o-$CH_3C_6H_4CH_2NH_3^+$	not bound[b]
2-$C_4H_3SCH_2NH_3^+$ (thiophenemethyl)	4.3×10^{-6}
$NH_3^+(CH_2)_4NH_3^+$	6.5×10^{-6}
$NH_3^+(CH_2)_5NH_3^+$	4.1×10^{-7}
$NH_3^+(CH_2)_6NH_3^+$	3.6×10^{-7}
$NH_3^+(CH_2)_7NH_3^+$	2.3×10^{-5}
$NH_3^+(CH_2)_8NH_3^+$	1.1×10^{-4}

[a] $K_d = (RNH_3^+)(1)/(RNH_3^+ \cdot 1)$. [b] Unmeasurable by present technique, estimate $K_d > 5 \times 10^{-2}$.

The latter feature permits measurement of relative binding constants by the simple expedient of allowing two different alkylammonium ions to compete for a limited amount of 1. NMR integration of the pertinent signals gives an affinity ratio directly (in favorable cases). By application of this technique we have accumulated extensive data on the host–guest specificity of 1. By spectral perturbations (UV) of the reference guest species, (4-methylbenzyl)ammonium ion, these measurements have been put on an absolute scale. Table I contains a sampling of our data (expressed as dissociation constants).

Among the straight-chain aliphatic monoamines, the *n*-butylammonium ion seems to be bound most tightly, with the measured K_d values increasing (weaker binding) for its higher or lower *n*-alkyl homologues. The isopentylammonium ion is bound about as well as the *n*-butyl ammonium ion, but the neohexylammonium ion is held relatively weakly and does not show the characteristic NMR shift, suggesting that the *tert*-butyl group is too large to be encapsulated by 1. The capacity of 1 is further defined by the cycloaliphatic series, in which (cyclopentanemethyl)ammonium ion seems to have the maximum size accommodated. For the (methylbenzyl)ammonium ions, affinity toward 1 is low, with only the *p*-methyl derivative able to adapt to the cavity. Evidently aromatic substituents must be oriented to the carbonyl-fringed portals of 1, and the ortho and meta substitution pattern cannot fit.[3] The comparatively stronger binding of (thiophenemethyl)ammonium ion further suggests that the larger, six-membered aromatics may not be ensconced within 1 without some distortion, resulting in higher K_d values.[4] Therefore, a para-disubstituted benzene ring

(1) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.
(2) Compounds such as 1 have been given the class name cavitand: Moran J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
(3) This specificity stands in contrast to the cyclodextrin complexes, in which arene substituent pattern has only a minor effect upon strength of binding: VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.

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represents an upper limit to the binding capacity of cucurbituril. Binding is notably stronger for the α,ω-alkanediammonium ions, with the K_d minimum at six carbons. The interatomic distance between nitrogens in the extended conformation of 1,6-hexanediamine exactly matches the distance between carbonyl oxygens axially spanning the cavity of 1, suggesting a specific interaction (NH^+···O=C). The range of K_d values in Table I corresponds to sizable differences in binding energies ($\Delta\Delta G_{max}$ = 7.4 kcal/mol); the increments are large enough that quantitative interpretations may be applied with some confidence.

From these and additional data, we have evolved a model of the host–guest complexes of 1. The primary interaction is a charge-dipole attraction between the ammonium cation and the electronegative oxygens of the urea carbonyls that surround the portals of 1. Multiple hydrogen bonding from the ammonium ion to the carbonyl oxygens seems certain. If an alkyl (aryl) substituent on the ammonium ion is sufficiently small, it enters the cavity of 1, displacing and freeing solvent molecules. The normal hydrophobic effect then provides additional stabilization.[5] In favorable cases these factors appear to be of nearly equal importance; e.g., a small ring may be almost as efficacious as a second ammonium ion. It may be noted that binding energies in this system are of the same magnitude or greater than those of common enzyme–substrate interactions, and the observed specificities also mimic biochemical behavior. Our ability to quantitatively assess the influence of structure upon K_d values in our system should yield insight into factors governing this important kind of noncovalent chemical affinity.

Acknowledgment. This work was supported by the Dow Chemical Company Foundation and the University of Illinois Research Board.

Registry No. 1, 80262-44-8; $CH_3CH_2CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-90-0; $CH_3CH_2CH_2CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-91-1; $CH_3CH_2CH_2CH_2CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-92-2; $(CH_3)_2CHCH_2CH_2NH_3^+\cdot1\cdot HCO_2$, 87115-93-3; $(CH_3)_3CCH_2CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-94-4; $(CH_2)_2CHCH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-95-5; $(CH_2)_3CHCH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-96-6; $(CH_2)_4CHCH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-97-7; $C_6H_5CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-98-8; p-$CH_3C_6H_4CH_2NH_3^+\cdot1\cdot HCO_2^-$, 87115-99-9; 2-$C_4H_3SCH_2NH_3^+\cdot1\cdot HCO_2^-$, 87116-00-5; $NH_3^+(CH_2)_4NH_3^+\cdot1\cdot2HCO_2^-$, 87116-01-6; $NH_3^+(CH_2)_5NH_3^+\cdot1\cdot2HCO_2^-$, 87116-02-7; $NH_3^+(CH_2)_6NH_3^+\cdot1\cdot2HCO_2^-$, 87116-03-8; $NH_3^+(CH_2)_7NH_3^+\cdot1\cdot2HCO_2^-$, 87116-04-9; $NH_3^+(CH_2)_8NH_3^+\cdot1\cdot2HCO_2^-$, 87116-05-0.

(4) The postulated distortion can actually be seen in a crystallographic structural determination of cucurbituril·$H_2NCH_2C_6H_4CH_2NH_2$·2HCl; W. A. Freeman, unpublished results.

(5) Cyclopentane itself also binds according to the NMR criterion.

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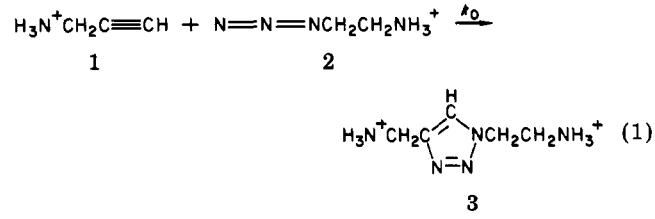
Cycloaddition Induced by Cucurbituril. A Case of Pauling Principle Catalysis

Summary: A 1,3-dipolar cycloaddition is accelerated by a factor of 5.5×10^4 under the catalytic influence of cucurbituril.

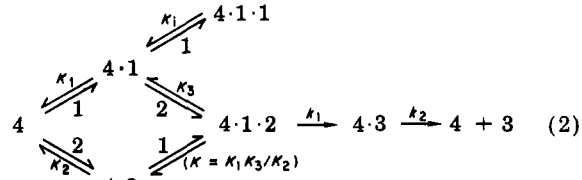
Sir: Alkynes undergo 1,3-dipolar cycloadditions with alkyl azides, yielding substituted triazoles (eq 1). In the particular case shown, the reaction proceeds slowly ($k_0 = 1.16 \times 10^{-6}$ M^{-1} s^{-1} in aqueous formic acid at 40 °C), yielding 3 and a regioisomeric adduct (having vicinal triazole substituents). The cycloaddition appears to be a typical concerted pericyclic reaction; previous investigations have not provided evidence for any intermediate in such transformations.[1]



(1)

Cucurbituril (4) is a novel nonadecacyclic cage compound[2] with an exceptional capacity to encapsulate substituted ammonium ions within its hollow core (see accompany communication[3]). We find that a catalytic amount of 4 markedly accelerates formation of triazole 3, rendering the reaction regiospecific. This result is explained by a transient ternary complex between 4, 1, and 2. According to NMR evidence and specificity studies,[3] alkylammonium ions (RNH_3^+) bind to 4 with the charged moiety (NH_3^+) hydrogen bonded to the urea carbonyls and with the substituent (R) extending into the interior of 4. Simultaneous binding of both 1 and 2 (with one NH_3^+ coordinated to each set of carbonyls of 4) aligns the reactive groups within the core of 4 so as to facilitate production of 3.[4]

Quantitative kinetic studies of this catalysis have been undertaken, revealing a number of enzymelike features. The reaction brought about by 4 exhibits saturation behavior; with sufficient amounts of 1 and 2, the cycloaddition becomes independent of substrate concentration. Data for the velocity of reaction as a function of reactant concentration may be fitted to the kinetic scheme of eq 2.



(2)

Under steady-state conditions the slow step is release of product from its complex with 4 ($k_2 = 1.7 \times 10^{-4}$ s^{-1}). This may be proven by preparing the stoichiometric complex and independently measuring its rate of dissociation (by a displacement technique—shown to be a unimolecular process). Product release as the rate-limiting step in enzymic reactions is a common phenomenon.[5]

By use of catalyst 4 in relatively high concentrations, it is feasible to examine the pre-steady-state kinetics of the cycloaddition, i.e., to measure k_1. Our technique is to monitor the decay of azide absorption (UV) with time. This has provided initial rate data for various concentrations of 1 and 2 in combination (at 40 °C, 5.0×10^{-3} M in 4). Analysis is simplified by independent measurement

(1) Huisgen, R.; Szeimies, G.; Moebius, L. *Chem. Ber.* **1967**, *100*, 2494. Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

(2) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.

(3) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.*, previous communication in this issue.

(4) Certain Diels–Alder reactions are accelerated by β-cyclodextrin: Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(5) Cleland, W. W. *Acc. Chem. Res.* **1975**, *8*, 145.

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