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.

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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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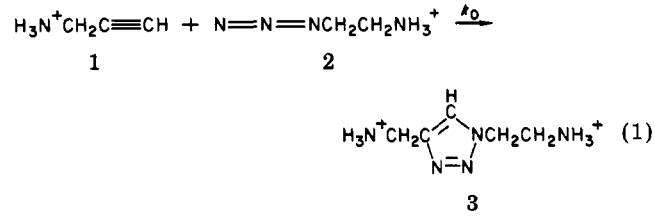
Cycloaddition Induced by Cucurbituril. A Case of Pauling Principle Catalysis

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

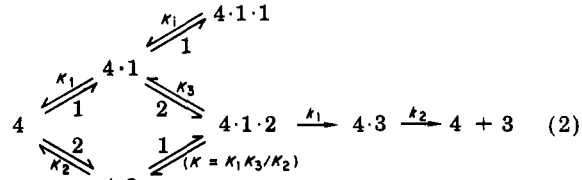
Sir: Alkynes undergo 1,3-dipolar cycloadditions with alkyl azides, yielding substituted triazoles (eq 1). In the particular case shown, the reaction proceeds slowly ($k_0 = 1.16 \times 10^{-6}$ M^{-1} s^{-1} in aqueous formic acid at 40 °C), yielding 3 and a regioisomeric adduct (having vicinal triazole 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.

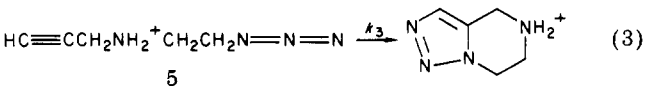
(5) Cleland, W. W. *Acc. Chem. Res.* **1975**, *8*, 145.

0022-3263/83/1948-3619$01.50/0

of dissociation constants for the individual substrates by methods previously described: $K_1 = 6.5 \times 10^{-4}$ M, $K_2 = 2.5 \times 10^{-3}$ M (eq 2).

Our kinetic data has been processed so as to provide an estimate of k_1, the limiting first-order rate constant for conversion of the termolecular reactant complex **4·1·2** to product complex **4·3** as well as an apparent dissociation constant for **4·1·2**, namely, K_3 (eq 2). The analysis is complicated by *substrate inhibition* (another "enzyme-like" feature). Very high concentrations of **1** actually retard the cycloaddition, and this seriously hampers determination of a value for the maximum rate (k_1). However, we have been able to fit our data so as to obtain K_i, an inhibition constant for formation of the unreactive ternary complex **4·1·1**. Our evidence indicates that K_3 and K_i have nearly the same numerical value, which is a chemically plausible observation. In order to limit the number of adjustable parameters, we specify that $K_i = K_3$ in our present analysis.

The values obtained by least-squares treatment of our reaction velocity data are as follows: $k_1 = 0.019$ (± 0.002) s^{-1} and $K_3 = K_i = 0.30$ (± 0.04) M. Assessment of "catalytic acceleration" is a sometimes controversial matter. Because k_1 is a *first-order* rate constant (spontaneous conversion of **4·1·2**), it is obviously inappropriate to compare its value with the rate constant (k_0) for the bimolecular reaction of **1** plus **2** in the absence of **4**. However, since K_3 is actually a Michaelis constant, the ratio k_1/K_3 constitutes a second-order rate constant for reaction between **2** and the saturated complex **4·1**. Hence, the kinetic acceleration by comparison of bimolecular reactions is a factor of 5.5×10^4. This constitutes the proper index of effectiveness for **4**.[6] As an independent check, we have prepared the model substance **5**, which undergoes uncatalyzed intramolecular cycloaddition (eq 3) with a rate constant of $k_3 = 2.0 \times 10^{-5}$



(3)

5

s^{-1} under the standard conditions. Comparison of this number with k_1 indicates an acceleration of 9.4×10^2 for the cycloaddition within **4**. The model **5** has free rotations about several bonds, which must be frozen in the transition state for cycloaddition. Consequently, its relative unreactivity may be explained.

However, we believe that **4** accomplishes more in our reaction than just elimination of entropic constraints, as may be shown by a comparison of dissociation constants. Of particular significance is the fact that K_3, which formally corresponds to binding of **2** to the preexisting complex of **4** and **1**, *exceeds* the corresponding binary dissociation constant K_2 by a factor of 120. This suggests that the cavity of **4** is not sufficiently large to accommodate both **1** and **2** without some *strain*[7] (equivalent to a $\Delta G \simeq$ 3 kcal/mol). When both substrates are bound simultaneously, they must be *compressed* together, and this results in additional kinetic acceleration beyond that expected solely by proper orientation of the substrates at their van der Waals distance. Stated differently, the substrates together exceed the binding capacity of **4** but the *transition state* for the cycloaddition more closely corresponds to the dimensions of the ideal guest for **4**.[3,8] This is the Pauling principle for catalysis, which states that an enzyme should be complementary to the activated complex of a reaction rather than to the substrates (or products).[9] The latter concept is an important refinement of the classical Fischer lock-and-key theory, and it is here demonstrated in a nonbiochemical host–guest system for the first time.

Further analysis of the kinetics and mechanism of this reaction suggests that the contribution to catalysis specifically from bound-substrate destabilization may in fact be greater than the minimum of 11-fold rate enhancement which is indicated by our evidence.[10] Because of a strong possibility of nonproductive substrate binding modes, the actual velocity for properly oriented (and compressed) substrates may be very much greater than the apparent reaction rate.[11] These considerations must await a fuller exposition of this reaction.

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Registry No. **1**, 87156-39-6; **2**, 87156-41-0; **3**, 87156-43-2; **4**, 80262-44-8.

(6) Because $k_1 > k_2$ (product release), the overall catalysis is only a factor of 4.9×10^2 by this criterion.

(7) Strictly speaking, **4** induces a *stress* in **1·2**; the reflexive term strain is used by chemical convention; Fersht, A. "Enzyme Structure and Mechanism"; Freeman: San Francisco, 1977; p 269.

(8) Swieton, G.; von Jouanne, J.; Kelm, H.; Huisgen, R. *J. Org. Chem.* **1983**, *48*, 1035.

(9) Pauling, L. *Am. Sci.* **1948**, *36*, 51. For a discussion, see: Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219.

(10) Although $K_3/K_2 = 120$, the corresponding strain energy should be regarded as *equally* partitioned between host and guests, with only that associated with guests contributing to a reduction of the activation energy for cycloaddition.

(11) For example, the rate constant observed (k_1) may correspond to conversion of a nonproductive to a productive complex and not to the cycloaddition itself. In this case the actual dissociation constant for the *productive* ternary complex would be undetermined and the Pauling principle unquantified with respect to the foregoing interpretation.

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