Convergent Functional Groups Create a Microenvironment for Enolization Catalysis

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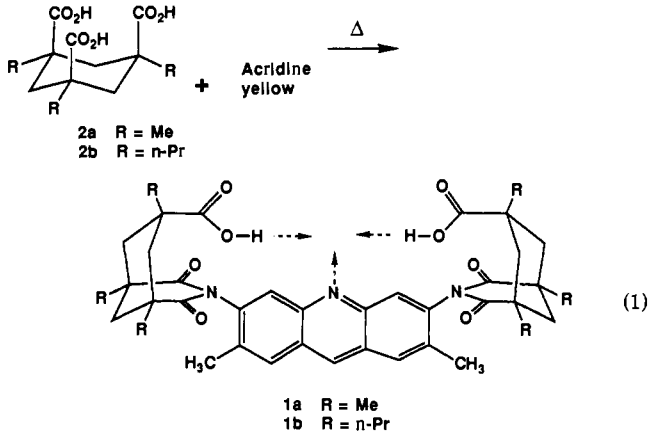
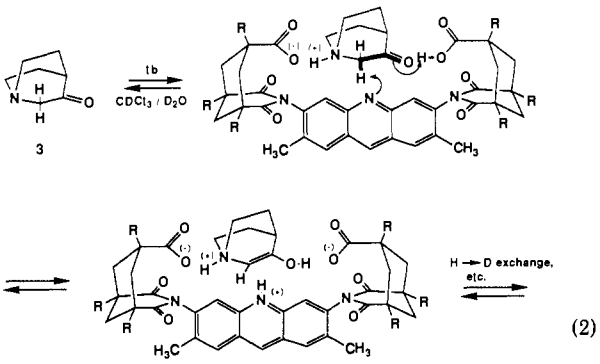
Concerted catalysis is a widely studied topic in bioorganic chemistry. Many enzymes feature arrays of electrophiles and nucleophiles or acids and bases at their active sites, poised for concerted catalysis,[1] but such arrays are difficult to achieve in model systems since rigid molecular frameworks are required to keep the catalytic from collapsing on each other. We describe here such a system, one arranged for concerted catalysis of enolization, and demonstrate its efficiency.

We have previously described the advantages of the acridine-derived diacid **1a** in dissociation of hemiacetal structures.[2] We have now prepared a version more soluble in organic solvents, **1b**, from **2b**,[3] the propyl analogue of Kemp's[4] triacid **2a**. Of particular relevance is the arrangement in which acidic and basic functionalities converge from perpendicular directions to focus on the center of the cleft (eq 1). This is the appropriate geometry[5] for the enolization of ketones, a process possessing a third-order kinetic term indicative of concerted acid-base catalysis.[6]



(1)

Titrations of **1b** with quinuclidinone **3** in dry $CDCl_3$ using NMR methods[7] showed a dissociation constant K_d of 10^{-3} M^{-1}. In $CDCl_3$ saturated with D_2O, exchange of the α-hydrogens of the substrate occurs at a remarkable rate (eq 2). This reaction, which has a half-life of 3 days in the absence of catalyst, proceeds with a half-life of just over 1 h in the presence of 0.1 equiv of **1b**. The reaction shows clean saturation kinetics. The data can be treated by a Lineweaver-Burk plot (Figure 1) giving the following kinetic parameters:[8] Thus the rate of the enolization is enhanced by



(2)

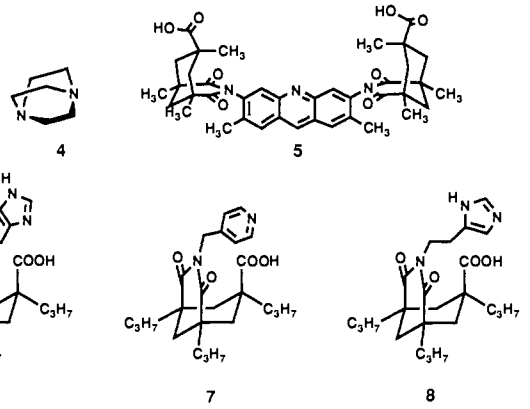
$V_{max} = 5.42 \times 10^{-6}$ M/s

$K_m = 0.006$ M

$k_{cat} = 0.0025$ s^{-1}

a factor of 10^3 in the presence of 2.5 mM **1b**.

The presence of a reactive catalyst-substrate, or Michaelis, complex was supported by competitive inhibition experiments. For example, the bicyclic diamine DABCO (**4**) forms a complex with diacid **1a** in $CDCl_3$ with dissociation constants in the micromolar range.[9] Indeed, when **4** is added to solutions of quinuclidinone and **1b**, NMR spectra indicate the presence of a complex. Formation of this complex completely surpresses catalysis of exchange.



The effects of prior complexation were examined by using other acid-base pairs as shown,[10] including the divergent derivative of the acridine diacid **5**. These compounds mimic **1b** in terms of their acidic and basic functionalities but cannot form complexes with quinuclidinone. The results are given in Table I. The best noncomplexing catalyst was about 1 order of magnitude less efficient than **1b**.

Molecular modeling using MacroModel 2.5[11] indicates that the quinuclidinone fits just inside the cleft as suggested in eq 2. In this complex the acridine nitrogen is poised for general base catalysis of enolization. In addition, one carboxyl can act as a general acid, creating a situation with the potential for concerted catalysis.[12]

In summary, this system exhibits behavior characteristic of enzymes such as saturation, turnover, and competitive inhibition.

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(7) Association constants were determined by nonlinear least-squares fit of NMR titration data to the 1:1 binding isotherm; see: Tjivikua, T.; Deslongchamps, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8408-8414.

(8) The apparent dissociation constant K_m for the complex in $CDCl_3/D_2O$ is consistent with that determined titrimetrically in dry $CDCl_3$. Wilcox has observed that addition of water to a $CDCl_3$ solution can weaken the binding by a factor of 2-6. See: Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.*, in press.

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(10) All new compounds were characterized by a full complement of spectroscopic data. For **1b**, mp = 254 °C dec; **6**, mp = 317 °C dec; **7**, mp = 115 °C; **8**, mp = 134 °C.

(11) MacroModel 2.5, W. Clark Still, Columbia University, 1989.

(12) Stepwise catalysis cannot be excluded in this system. For a discussion of this issue in model systems, see: Anslyn, E.; Breslow, R. *J. Am. Chem. Soc.* **1989**, *111*, 8931.

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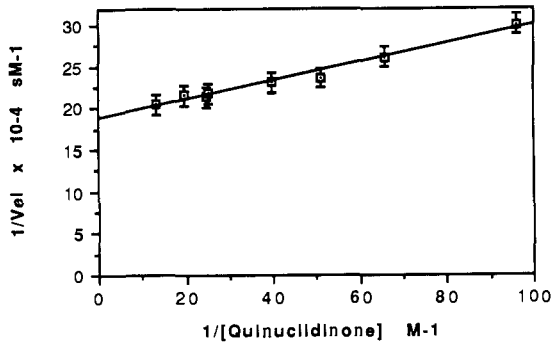

Figure 1. Lineweaver-Burk plot of the enolization of quinuclidinone 3 catalyzed by 0.0025 M **1b** at 20 °C.

Table I. Deuteration of Quinuclidinone 3 in $CDCl_3/D_2O$ at 20 °C[a]

catalyst	$k_{obsd} \times 10^5$, s^{-1}	approx half-life
none	0.3	64 h
6	0.4	49 h
7	0.5	36 h
8	2.4	8 h
5	2.0	10 h
1b	17.0	66 min

[a] In all cases, initial quinuclidinone concentration is 0.025 M and catalyst concentration is 0.0025 M.

It underscores the importance of effective complexation in bringing recognition and catalytic functionality together to create a microenvironment for catalysis.

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Electrostatic Contributions to Solvation Energies: Comparison of Free Energy Perturbation and Continuum Calculations

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Recently, considerable progress has been made in the application of free energy perturbation techniques to the calculation of solvation energies and solvation energy differences.[1-3] These methods can be used to artificially create a solute molecule in the solvent by varying one or more perturbation parameters such as atomic radius and charge. Cavity and van der Waals terms can be separated from electrostatic terms by first "growing in" the cavity and then "growing in" the charge.[3] The electrostatic term can then be compared directly to the predictions of continuum calculations in which the solute is treated in atomic detail but the solute is treated as a dielectric continuum.[4] In this communication we compare electrostatic contributions to the solvation free energies of polar solutes in water using both methods.[5] Our results suggest

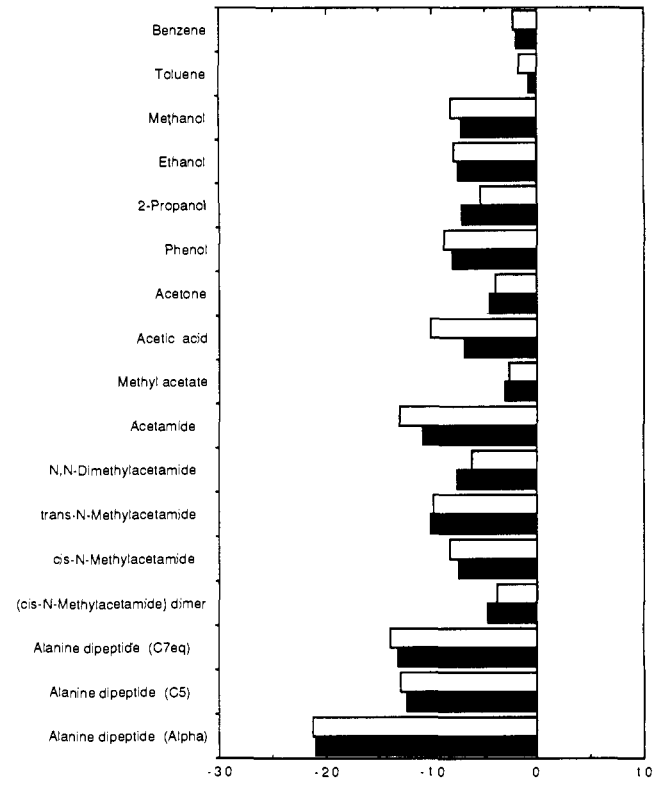

Figure 1. Comparison of electrostatic solvation free energies obtained from free energy perturbation (unfilled bars) and the continuum electrostatic method with no solute polarizability ($\epsilon = 1$, solid bars).

that the continuum and microscopic treatments of water provide very similar descriptions of solute-solvent interaction free energies.

The continuum calculations are based on the finite difference Poisson-Boltzmann (FDPB) method and were carried out with the Delphi program.[6] The solute/solvent system is mapped onto a three-dimensional lattice by assigning a value of the charge, dielectric constant, and ionic strength to each lattice point. The solute molecule is treated as a region of space defined by its solvent-accessible surface. Charges are placed at atomic nuclei as in any conventional force field. The volume enclosed by the solute is assigned a uniform dielectric constant (ϵ). The molecular dielectric constant is normally taken as 2 to account for electronic polarizability.[7] However, in order to be consistent with the free energy calculation which ignores electronic polarizability in the solute, calculationss were carried out with the molecular dielectric constant set to 1. The solvent is assigned a dielectric constant of 80. The atomic radii used to define the solute cavity are set equal to van der Waals radii given by $(2)^{-5/6}\ \sigma$ where σ is the Lennard Jones diameter defined in the OPLS force field.[8] Atomic charges are also taken from the OPLS force field.

The free energy perturbation (FEP) calculations were carried out by using the BOSS Version 2.0 program[9] kindly provided by Professor William Jorgenson. The solute molecules are placed in a 20-Å box containing ~512 TIP4P[10] water molecules. The perturbation consisted of electrically charging and discharging

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