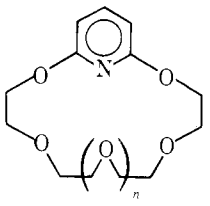
Catalysis of Ester Aminolysis by Macrocyclic Ionophores[1]

Sir:

The proposed[2] mechanism for ester aminolysis in an aprotic solvent has features in common with the mechanism proposed[3] for the same reaction in protic solvents. These mechanisms suggest the initial formation of a zwitterionic intermediate, $T^{\pm}$, followed by C–O bond breaking and proton transfer (not necessarily in that sequence and perhaps even in a coupled process) (eq 1). In aprotic solvents the breakdown of $T^{\pm}$ is rate

$$\mathrm{ArOCCH_3} + \underset{\text{BA}}{\mathrm{BuNH_2}} \longrightarrow \mathrm{ArOCCH_3}\ (\mathrm{^+NH_2Bu})\ (T^{\pm}) \xrightarrow{[\text{base}]} \mathrm{ArOH} + \mathrm{CH_3CNHBu} \quad (1)$$

limiting. This rate-limiting step has been shown[4] to involve some type of proton transfer to a base, either another molecule of amine or some other molecule that can serve as a base. The overall process can be described as proceeding from neutral reactants to neutral products via polar intermediates and transition states. Therefore, a polar cavity with proton acceptor sites might be a good catalytic environment for this reaction. On this basis, multiheteromacrocycles possessing 2,6-pyridino subunits connected by carbon–oxygen linkages, **1** and **2**, synthesized by Newkome et al.,[5] could serve as catalysts for ester aminolysis in an aprotic solvent.



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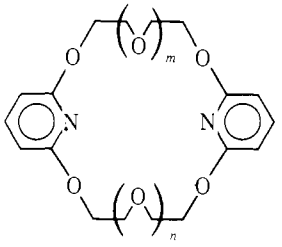

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We wish to report the results of kinetic studies on butylaminolysis of *p*-nitrophenyl acetate in chlorobenzene at 25 °C in the presence of **1** (n = 1–3) and **2** (n = 2, m = 3; n = m = 3, 4, 5). Previous kinetic studies[2,4] on this reaction are consistent with the mechanism shown in eq 1. At 25 °C, the rate equation

$$k_{\text{obsd}} = k[\text{BA}]^2 + k'[\text{BA}][\text{base}] \quad (2)$$

contains only two terms,[4] one which is second order in butylamine and the other which is first order in butylamine and first order in base. Values for k', the catalytic rate constant for a given base, have been determined from plots of k_{obsd} vs. [base]. In all the cases studied thus far, we have found good linear plots over the concentration range employed.[6]

Our results are summarized in Table I and Figure 1. Table I lists the values of k' determined in this study for the macrocycles, **1**, and **2**, and dibenzo-18-crown-6. Included for comparison are k' values for tetrahydrofuran and 2,6-dimethylpyridine[4] and our k value for butylamine. 2,6-Dimethoxypyridine, an acyclic analogue of **1** and **2**, does not catalyze the reaction. Also included in Table I is the rate constant for "water-catalyzed" propylaminolysis of *p*-nitrophenyl acetate[7] in water at 25 °C. To gain further insight into the reasons for the rate enhancements and to facilitate comparison with other

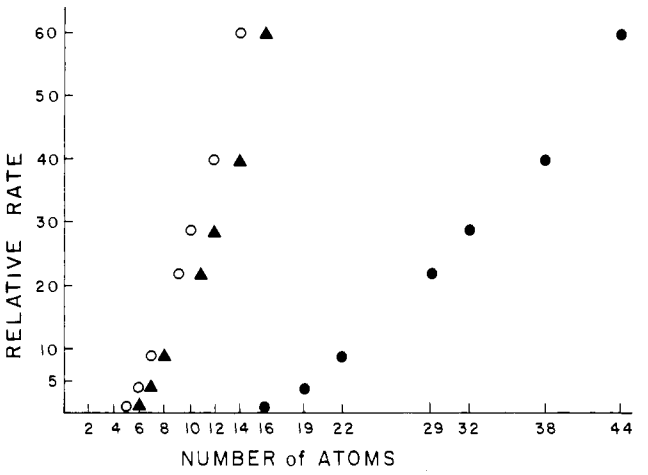

Figure 1. Plot of relative rate of catalysis vs. ring size of catalyst (●), number of oxygen atoms (○), and number of heteroatoms (▲).

Table I. Catalytic Rate Constants for Butylaminolysis of *p*-Nitrophenyl Acetate in Chlorobenzene at 25 °C

Base	Ring size	$10^3k'$, $M^{-2}\ s^{-1}$	Rel rate	$10^3k'$/ oxygen atoms
1, n = 1	16	7.2	1	1.4
1, n = 2	19	27	3.8	4.5
1, n = 3	22	62	8.6	8.9
2, n = 2, m = 3	29	160	22	17.7
2, n = m = 3	32	210	29	21.0
2, n = m = 4	38	290	40	24.2
2, n = m = 5	44	430	60	30.7
Dibenzo-18-crown-6	18	34		5.6
2,6-Dimethoxypyridine		No catalysis		
Butylamine		60[a]		
2,6-Dimethylpyridine[b]		9		
Tetrahydrofuran[b]		4		4
H_2O[c]		290[d]		290

[a] k in eq 2, mean value (±5%) from our experiments, excellent agreement with value of Su and Watson.[4] [b] Reference 4. [c] In water, propylaminolysis; ref 7. [d] Derived by dividing the spontaneous rate constant by [H_2O] = 55.5 M.

oxygen bases, k' values for **1**, **2**, and dibenzo-18-crown-6 are divided by the number of oxygens in each compound and these values are listed in Table I. Figure 1 illustrates three plots of the relative rate data for **1** and **2**. Plots vs. the number of oxygen atoms, vs. the number of heteroatoms, and vs. macrocycle size produce smooth correlations of all data.

Comparisons of the catalytic rate constants for **1** and **2** with those for other bases reveal that the macrocycles are very efficient catalysts. Analogues of **1** and **2** are better catalysts than 2,6-dimethylpyridine, a nonnucleophilic nitrogen base, and tetrahydrofuran, a one-oxygen cyclic ether. Analogues of **2** are better catalysts than butylamine. The best macrocyclic catalyst, **2** (n = m = 5), is a better catalyst on a molar basis than water. However, a fairer comparison of the relative catalytic abilities is on a per oxygen basis. On this basis, water is 9.5-fold more effective as a catalyst.

The results seem to imply that the pyridine nitrogen is not a necessary feature for catalysis. This conclusion is based on our observations that dibenzo-18-crown-6 is just as efficient as **1** (n = 2) and that 2,6-dimethoxypyridine does not catalyze the reaction, whereas 2,6-dimethylpyridine does.[8] Since ethers such as tetrahydrofuran and dibenzo-18-crown-6 can catalyze this reaction in aprotic solvents, there is no shortage of proton acceptor sites on the macrocycles.

The catalytic efficiency within the series of macrocycles increases as the molecules increase in size. This increase is likely due to two factors: the number of oxygen atoms and the

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ring size. That the increase is not entirely due to the former factor is readily seen in Table I. Dividing k' by the number of oxygen atoms in the macrocycle yields the catalytic efficiency of **1** and **2** on a per mole of oxygen scale. Since this value increases as macrocyclic size increases, it is apparent that ring size is a contributing factor to catalysis. From the trend, an even greater catalytic effect may be expected from larger macrocycles.

Precise answers to the question of how and why these macrocycles are such effective catalysts remain to be resolved by further studies. The increasing catalytic ability of the macrocycle with increasing ring size, indicates that the polyether chains might be attracting the entire transition-state structure not just the cationic part. A CPK model of **2** ($n = m = 5$) indicates an ellipsoidal cavity (having a major axis of ~12 Å and a minor axis of ~8 Å) which can easily accommodate most of a CPK model of $T^{\pm}$ (it is likely that the transition-state structure resembles $T^{\pm}$). It may not be necessary that the transition-state structure be inside the cavity, a host–guest[12] relationship. An alternative idea is that the flexible polyether chains are folding around the transition-state structure. Both ideas are similar in that they describe a local "solvation" effect on the polar transition-state structure, viz., stabilization of the charged species in the apolar solvent by interaction with the oxygens of the polyether chains.

In summary, catalysis of ester aminolysis in an aprotic solvent by macrocyclic polyether compounds shows a striking dependence on ring size. It may be that the optimum ring size for maximal catalysis has not yet been achieved in the compounds studied. These macrocycles may serve as models of a polar solvent shell. It is suggested that catalysis may arise from electrostatic stabilization of a polar transition-state structure. Work is in progress in this laboratory to uncover the nature of this catalysis.

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References and Notes

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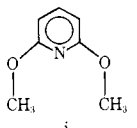
(4) C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974).
(5) G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khosboo, and J. Broussard-Simpson, *J. Org. Chem.*, **42**, 1500 (1977).
(6) A typical kinetic experiment would employ a concentration of 0.1 M of butylamine and a concentration range of 0.007–0.03 M of macrocycle. For *1* ($n = 1$), the value of k' was found to be independent of butylamine concentration.
(7) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).
(8) The failure of 2,6-dimethoxypyridine to catalyze this reaction may stem from two factors: (a) basicity of nitrogen and (b) inaccessibility to the nitrogen. In aqueous solution, 2,6-dimethylpyridine is 5 pK units stronger in basicity than 2,6-dimethoxypyridine,[9] but this may not be representative of their basicities in chlorobenzene. In fact the methoxy group increases the proton affinity of pyridine in the gas phase,[10] and MINDO/3 calculations[11] suggest that 2,6-dimethoxypyridine has a greater proton affinity than pyridine. MINDO/3 calculations[11] also suggest that conformation i



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is the most stable conformation of 2,6-dimethoxypyridine. If this is correct when the molecule is in chlorobenzene, then the steric factor would appear to be the better explanation for the lack of catalysis by 2,6-dimethoxypyridine.
(9) A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc. B*, 562 (1966).
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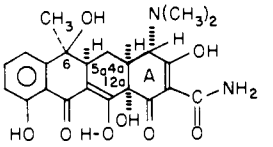
3-Benzyloxyisoxazole System in Construction of Tetracyclines

Sir:

The complex and sensitive functionality present in the important antibiotics related to tetracycline (**1**) has generated synthetic approaches of considerable sophistication.[1] A number



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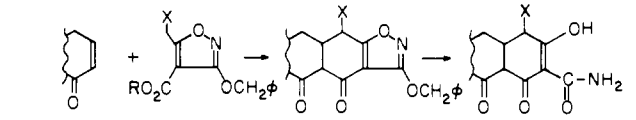
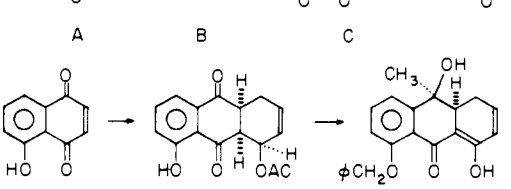
of these use a Claisen cyclization to form the C_1–C_{12a} bond.[2,3,4] This attractive approach is complicated, however, by the density of functional groups in ring A. We show in this communication that derivatives of 3-hydroxyisoxazoles admirably serve the purpose of storing the β-keto amide system of the A ring of tetracyclines and illustrate the principles involved with the synthesis of dedimethylamino-12a-deoxyanhydrotetracycline (**14**) and of 12a-deoxyanhydrotetracycline (**16**).

The fundamental process of this scheme (A → B → C → D) seemed especially promising because the tricyclic dienolone **3** which we shall call "Shemyakin ketone" is available in six steps,[5] beginning with the Diels–Alder reaction of 5-hydroxy-1,4-naphthoquinone (juglone) and 1-acetoxybutadiene.[6]



A B C D



2 3

The attractiveness of this route to **3** was greatly enhanced by the finding that the difficultly separable mixtures of regioisomers (3:1 in favor of **2**) obtained under the reported conditions could be avoided under carefully defined Lewis acid catalysis (0.04 mol equiv of boron trifluoride etherate, benzene, or chloroform, 55 ± 5 °C). The desired regio isomer **2** was then obtained (94%) to the exclusion (<0.5%) of the unwanted one.[7] The rest of the synthesis of **3** followed the Shemyakin procedure.

We eventually settled on a 3-benzyloxyisoxazole so that the C → D transformation could be effected in a single hydrogenolytic step. The feasibility of the scheme was tested with the ethoxyethyl ester **7b**. The required isoxazole was prepared

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