Table I. Deprotonation of 3-Pentanone with LiTMP (1.0 mmol) in THF Solution at 0 °C in the Presence of Solvent Additives[a]

3-pentanone + LiTMP → (*E*)-**1** + (*Z*)-**1**

entry	3-pentanone, mmol	additive, mmol	(*E*)-**1**:(*Z*)-**1**	overall yield, %[b]
1	0.9		86:14	100
2	0.45		86:14	90
3	0.9	HMPT, 1.0	8:92	89
4	0.45	HMPT, 1.0	65:35	75
5	0.25	HMPT, 1.0	66:34	80
6	0.45	HMPT, 2.0	54:46	70
7	0.45	HMPT, 4.7	52:48	89
8	0.9	TMEDA, 1.0	17:83	70
9	0.45	TMEDA, 1.0	91:9	90
10	0.25	TMEDA, 1.0	95:5	70
11	0.45	TMEDA, 2.0	88:12	77
12	0.45	TMEDA, 4.7	86:14	90

[a] 3-Pentanone was added dropwise to a solution of LiTMP in 1.0 mL of THF containing the indicated amount of solvent additive. After 15 min, 1.2 mmol of trimethylchlorosilane was added, followed, after an additional 30 min, by 2.5 mL of saturated aqueous $NaHCO_3$. Aliquots were analyzed by GLC (⅛ in. × 40 ft stainless steel column packed with 20% Se-30 on Chromosorb W, 100 °C) for the silyl ethers, (*E*)-**2** and (*Z*)-**2**. Pure samples of (*E*)-**2** and (*Z*)-**2** were isolated by preparative GlC and exhibited spectral properties in agreement with published values.[9] [b] Overall yields obtained by internal GLC standard, based on 3-pentanone.

solutions at 0 °C containing LiTMP and either HMPT (entry 3) or TMEDA (entry 8) produces mainly enolate (*Z*)-**1**. However, addition of only 0.45 equiv of 3-pentanone to the same solutions produces mainly enolate (*E*)-**1** (entry 4, HMPT; entry 9, TMEDA). Furthermore, the absolute amount of (*E*)-**1** obtained from 0.45 equiv of 3-pentanone is greater than the absolute amount of (*E*)-**1** obtained from 0.9 equiv of 3-pentanone (compare entries 3 and 4 and entries 8 and 9). Clearly, isomerization of (*E*)-**1** to (*Z*)-**1** must occur in the reactions with 0.9 equiv of ketone. When even smaller amounts of 3-pentanone are added to the fixed amount of LiTMP, slightly greater *E* selectively is observed until a maximum value is reached where the (*E*)-**1**:(*Z*)-**1** ratio is 66:34 (HMPT, entry 5) or 95:5 (TMEDA, entry 10). We believe that these latter ratios are the results of a true kinetically controlled deprotonation and we note that under such conditions deprotonation actually occurs with slightly greater *E* selectivity in the presence of TMEDA (a well-known chelate for lithium) than in THF alone (entires 1 and 2). Kinetically controlled deprotonation of 3-pentanone in the presence of HMPT does give increased *Z* selectivity, but the major enolate formed under these conditions is still the *E* isomer (entries 5–7).

It is possible that the explanation presented here for the role of HMPT in controlling the stereochemistry of a ketone enolate may apply to the previously reported[1-4] deprotonation reactions of other carbon acids. If this is true, efficient anion equilibration mechanisms[10] must be available to such systems. We are actively exploring these possibilities.

Acknowledgment is made to the National Science Foundation and to the Alfred P. Sloan Foundation for partial support of this research.

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(8) Similar results were obtained with LDA in place of LiTMP except (*E*)-**1**:(*Z*)-**1** ratios were slightly greater with LiTMP under conditions of kinetic control, as reported by Kuwajima.[9]
(9) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079.
(10) Simple aldol-type equilibrations of the type shown in, e.g., **2** are probably too slow (or are irreversible) to account for the results with other carbon acids.

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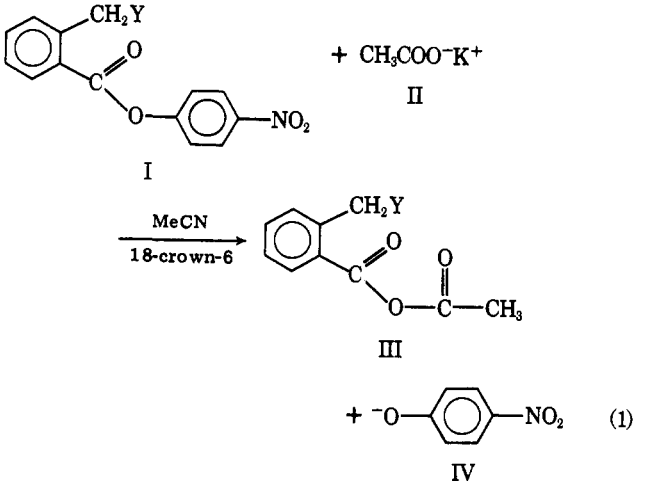
Catalytic Mechanisms of Acyl Transfer Reactions in Dipolar Aprotic Media. 1. Desolvated Carboxylate Ion as Acyl Acceptor[1]

Sir:

Elucidation of the mechanism of acyl transfer reactions in nonprotic media has become a timely and important problem since it was discovered that the active site of hydrolytic enzymes contains hydrophobic regions.[2] Nonenzymic model reactions are of potential value in this context as they can provide important insights and chemical precedents crucial for understanding the mechanism of enzyme catalyzed acyl transfer reactions.

In this communication we report that generating "naked" carboxylate ions in dipolar aprotic environment enhances the nucleophilic reactivity of the anion to the extent that it allows facile interconversion of *p*-nitrophenyl esters into highly reactive mixed anhydrides. Specifically, we have found that addition of potassium acetate to an anhydrous acetonitrile solution of the crown ether 18-crown-6 affords CH_3COO^- ions which readily cleave *p*-nitrophenyl *o*-toluates (eq 1) via direct



(1)

nucleophilic addition at the scissile carbonyl carbon. *o*-Toluyl acetate (**III**) is produced and 1 equiv of *p*-nitrophenolate is liberated. The reaction represents an example of *intermolecular* conversion of an ester to a highly reactive anhydride by a carboxylate nucleophile. By analogy the reaction also provides a physical organic model for the possible mechanism of enzyme-catalyzed acyl transfer reactions involving the catalytic participation of a "buried" carboxylate residue. Such glutamate and aspartate functions have been found at the active site of metalloproteases[3] as well as other hydrolytic enzymes which contain no catalytic serine residues.[4]

The reaction between desolvated acetate and *p*-nitrophenyl *o*-toluate proceeds at room temperature in quantitative yield

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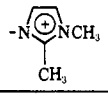
Table I. Second-Order Rate Constants for the Acyl Transfer Reaction between Acetate Ion and a Series of *p*-Nitrophenyl *o*-Toluates[a]

compd	substituent at the benzylic position, Y	$k_2^{25°}$, 1 mol^{-1} s^{-1}							
			MeOH[c]-MeCN, % (v/v)					H_2O[d]-MeCN, % (v/v)	
		MeCN[b]	0.15	0.3	1.0	1.5	3.0	0.8	1.5
Ia	-H	1.18×10^{-2}	7.9×10^{-3}	4.7×10^{-3}		1.1×10^{-3}	4.0×10^{-4}	1.2×10^{-3}	5×10^{-4}
Ib	$-N(C_2H_5)_3$	36.89			5×10^{-2}		6×10^{-3}		
Ic		19.90							

[a] All kinetic runs were carried out under pseudo-first-order conditions using $3–8 \times 10^{-5}$ M *p*-nitrophenyl *o*-toluate. For the cationic compounds the chloride and the bromide salts were used interchangeably, neither showing any effect on the rates. Potassium acetate concentrations were increased up to 1.2×10^{-1} M using equimolar 18-crown-6. Under these conditions all the semilogarithmic pseudo-first-order plots were strictly linear. The absolute values of the second-order rate constants are accurate within ±8% [b] MC & B Spectrograde, dried over Linde 4A molecular sieves. [c] MC & B Spectrograde. [d] Doubly distilled.

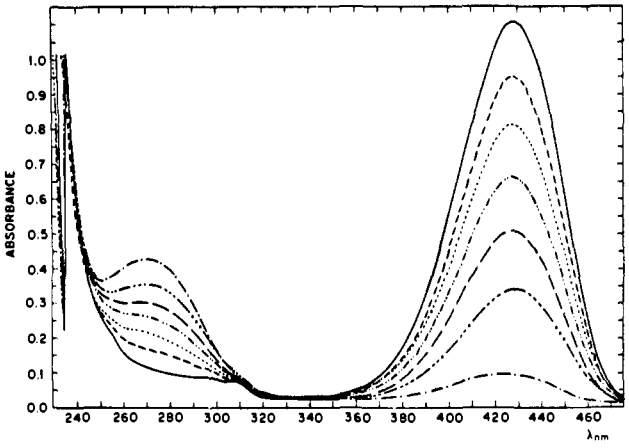


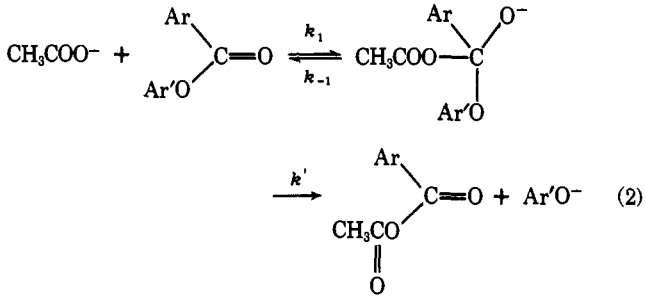
Figure 1. The time course of the acyl transfer reaction between 5.6×10^{-2} M potassium acetate and 5.3×10^{-5} M *p*-nitrophenyl *o*-toluate in acetonitrile containing 5.8×10^{-2} M 18-crown-6. The absorption of the solution was recorded beginning at — · — (14 s), — · · · — (342 s), — — — 652 s) - · · - (1000 s), --- (1450 s), and - - - (2180 s) after mixing the reactants. The final curve —— indicates the spectrum of the products.

(Figure 1). In acetonitrile the reverse reaction has not been observed. The rate of acyl transfer can be determined either by following the disappearance of the *p*-nitrophenyl ester at 271 nm[5] or by monitoring the formation of the *p*-nitrophenolate ion at 418 nm. The reaction is first order in each of the reactants. Kinetically no saturation behavior is observed; the linear dependence of the rate on the concentration of crown ether solvated potassium acetate is consistently maintained up to the 0.1 M range (i.e., the solubility limit of the salt). The second-order rate constant obtained is $k_2^{25°} = 0.0118$ l mol^{-1} s^{-1}.

Cleavage of *p*-nitrophenyl esters by acetate shows an absolute dependence on nonprotic media. Addition of small amounts of hydroxylic solvents dramatically reduces the magnitude of the rate constants. In presence of 1.5% methanol or 0.8% water, a tenfold decrease in the rates is observed (Table I). Since the inhibition becomes apparent when the molar concentration of the hydroxylic component significantly exceeds that of the carboxylate, the inhibitory effect is likely to operate via solvation of the ionic nucleophile. Based on product analyses we have found no evidence for competing carboxylate-assisted nucleophilic addition by the hydroxylic solvent.

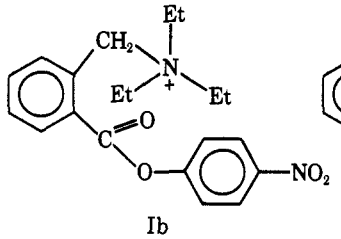
The acyl transfer reaction can readily be reversed by adding excess protic solvent to the reaction mixture. Thus addition of excess aniline to the product mixture (III and IV) results in rapid regeneration of the starting ester (I) with only a small amount of acetanilide produced[6] (no *o*-toluylanilide is formed under these conditions). Considering the well-known high reactivities of nucleophilic alkoxides and hydroxides in dipolar aprotic media,[7] we have exercised great care in ascertaining that no such species were present in the reaction mixtures. This can readily be accomplished, since in highly purified anhydrous acetonitrile no detectable KOH or $KOCH_3$ can be dissolved, even in presence of 0.14 M crown ether.[8] In agreement, we found no hydrolytic products corresponding to hydroxide or alkoxide attack at the scissile carbonyl in the reaction mixture.

Acyl transfer to acetate involves nucleophilic addition of a fairly good leaving group to the carbonyl carbon. Therefore, reaction is likely to proceed through an unfavorable preequilibrium (eq 2) leading to the tetrahedral intermediate, which

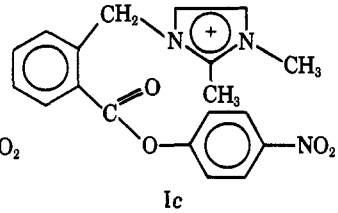


(2)

might readily revert to starting materials. It seemed therefore important to ascertain if electrophilic activation of the carbonyl function could facilitate the formation of the tetrahedral intermediate by stabilization of the developing negative charge of the adduct.[9] We have chosen two model compounds (Ib and Ic), utilizing quaternary ammonium and imidazolium neighboring groups as alkyl analogues of protonated lysine and histidine side chains, widely occurring in the catalytic sites of hydrolytic enzymes.[4,10] We have found that both functionalities are effective in catalyzing the reaction, the corresponding rates being accelerated by a factor of 10^3 compared with that of uncatalyzed reaction (Table I). Considering the conformational flexibility of the compounds examined, the neighboring-group effects exhibited most probably represent only a fraction of what might be achieved using more constrained systems.



Ib



Ic

In line with the observed electrophilic catalysis by the quaternary ammonium and imidazolium groups, we have found that the inhibitory effect of hydroxylic solvents (methanol and water) on the catalytic rates is greater than the one observed for the uncatalyzed reaction. These results are readily expli-

cable in terms of solvation of the cationic electrophile as well as the carboxylate by the protic reaction component.

Additional studies of our system and related systems will be necessary before the mechanisms of acyl transfer to carboxylate ions in dipolar aprotic solvent becomes fully understood. Obviously, problems such as determination of the rate-limiting step in the reaction as well as the catalytic importance of leaving-group stabilization (i.e., by neighboring-group participation) will have to be addressed. Nevertheless, the present studies clearly demonstrate that, under appropriate conditions, carboxylate ions can effectively function as nucleophilic catalysts in hydrolytic reactions.

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(5) The absorption of the crown ether in the 220–240-nm region prevented us from monitoring the changes in the absorption of the carboxylic functions.
(6) (a) Hydrolysis of the mixed anhydride by "traces of water" under the reaction conditions could readily be ruled out by complete absence of *o*-toluate ion in the product solution, as determined by thin layer chromatographic comparison with an authentic sample of sodium *o*-toluate. For this purpose the acyl transfer reaction was carried out by stepwise addition (in small portions) of 1 equiv of *p*-nitrotoluate to 10 mL of 0.1 M crown ether solvated potassium acetate. The resulting solution was then added to 2 mL of freshly distilled aniline. The product solution was spotted on thin layer chromatographic plates and run against independently prepared acetanilide, *o*-toluylanilide, and sodium *o*-toluate. Absolutely no *o*-toluate was observed, and only small amounts of acetanilide were obtained. Significantly we found no traces of *o*-toluylanilide and the major component was the ester *p*-nitrophenyl *o*-toluate. (b) Direct observation of the mixed anhydride intermediate was possible by taking the IR spectrum of a sample of the acyl transfer product solution in acetonitrile. The long-wavelength carbonyl peak observed at 1765 cm^{-} (absent in the spectra of the individual starting materials) strongly suggests the presence of *o*-toluylacetate (iii).
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(8) Finely powdered potassium and sodium hydroxide as well as the corresponding methoxides were suspended in dry acetonitrile solution of 0.14 M 18-crown-6 and 15-crown-5, respectively. The mixtures were stirred at room temperature for several days. Using *p*-nitrophenol as indicator we found no ^{-}OH or $^{-}OCH_3$ ions in solution. Under similar conditions tetramethylammonium hydroxide readily deprotonated the indicator.
(9) It is now well recognized that the rate-determining step of hydrolytic acyl transfer reactions may vary depending on the system; changes in the solvent and the nucleophile may be involved. While in aqueous solution hydrolysis of aromatic esters by hydroxide ion the formation of the tetrahedral intermediate is rate limiting (ref 2, p 21), in case of aminolysis of esters in nonprotic media the collapse of the tetrahedral intermediate is the slow step; cf. F. M. Menger and A. C. Vitale, *J. Am. Chem. Soc.*, **95**, 4931 (1973), and F. Rivetti and U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 1176 (1977).
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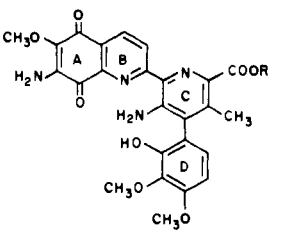
Total Synthesis of Streptonigrin

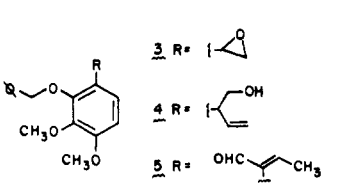
Sir:

Streptonigrin (**1**), a metabolite of a few species of *Streptomyces* and *Actinomyces*,[1,2] has been found quite effective in treatment of a variety of human tumors, although its high toxicity has precluded general clinical use.[3] Considerable work on elucidation of the biosynthesis[4] and the mechanism of action[5] of streptonigrin has recently been described. Many reports have also appeared[6,7] concerning synthesis of analogues of **1** and on model studies directed toward the synthesis of streptonigrin itself. We now describe the first total synthesis of this unique heterocyclic natural product.

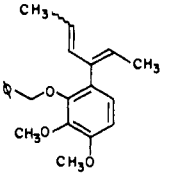


1 R = H **2** R = CH_3

2-Benzyloxy-3,4-dimethoxybenzaldehyde[8] was converted into epoxide **3** [$(CH_3)_3SI$, Me_2SO, NaH, −10 °C; 99%][9] which without purification was added to vinylmagnesium bromide (THF, 0 °C, 1 h) to give alcohol **4** in 97% yield. Oxidation of **4** with CrO_3–pyridine in methylene chloride, followed by brief treatment of the crude reaction product with dilute HCl, gave the conjugated unsaturated aldehyde **5**: 79%; IR (film) 2720, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (3 H, d, J = 7 Hz), 6.85 (1 H, d, J = 7 Hz), 9.5 (1 H, s).

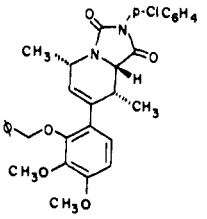


3 R =
4 R =
5 R =

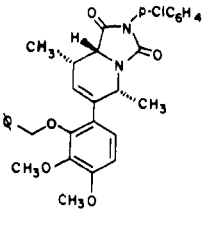


6

Treatment of aldehyde **5** with 1 equivalent of triphenylphosphonium ethylide (THF, −78 °C), followed by addition of 1 equivalent each of *n*-butyllithium and *t*-BuOK in *t*-BuOH (Schlosser procedure[10]), afforded diene **6** (75%) as an inseparable mixture of trans and cis isomers (~2.5:1, respectively, as estimated by NMR). This diene mixture was heated with 1-(*p*-chlorophenyl)-4-methoxyhydantoin (**7**)[11] (xylene, reflux, 72 h) to give an inseparable mixture of the desired Diels–Alder adduct **8** along with regioisomer **9**, in a ratio of ~3:1, respectively. We have never been able to get this cycloaddition reaction to go to completion, and thus routinely recycled unreacted diene **6**. The total yield of adducts **8** and **9** after one recycle was 56% and could be somewhat improved by further recycling.[12]



8



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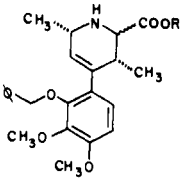

10 R = H
11 R = CH_3

The mixture of adducts **8** and **9** was hydrolyzed with $Ba(OH)_2$ (dioxane–H_2O, reflux, 24 h) to give a mixture of

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