$$X^- + CH_3\overset{O}{\overset{\|}{C}}OC_6H_5 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}O^- + C_6H_5X \quad (3)$$

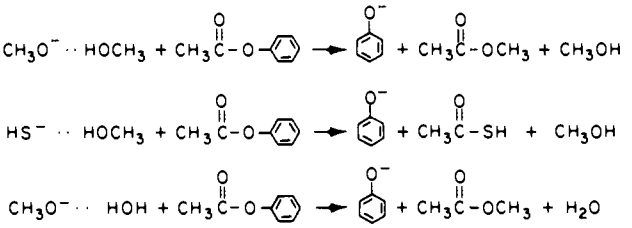
phenoxide at *m/e* 93$^-$, nor the M − 1 ion of phenyl acetate at *m/e* 135$^-$ was observed within the detection limits of the spectrometer. This means that the rate constants for channels 1 and 2 must be at least one hundred times smaller than for channel 3. These results demonstrate that nucleophilic aromatic substitution can be a facile process in the gas phase and that for some reason attack at the carbonyl is not observed in spite of its large exothermicity.

Because of this striking difference between solution and gas-phase reactivity, we decided to explore the effect of a solvent molecule on the reactivity of the nucleophile. Partially solvated nucleophiles were formed by reacting X^- with methyl formate (reaction 4), where $X^- = OH^-$ or CH_3O^-, as reported

$$X^- + HCOCH_3 \longrightarrow X^- \cdot \cdot HOCH_3 + CO \quad (4)$$

previously.[12] To make $HS^- \cdot \cdot HOCH_3$ cluster ion, H_2S was reacted with $CH_3O^- \cdot \cdot HOCH_3$ to displace methanol. Much to our surprise, phenoxide ion at *m/e* 93$^-$ was observed as a product for the reactions of the cluster ions shown in Scheme II. These reactions were confirmed by ICR double resonance

Scheme II



ejection of the cluster ions.[13,14] Thus, reaction at the carbonyl via the $B_{AC}2$ mechanism appears to be greatly enhanced by a single solvent molecule attached to the nucleophile. Solvated phenoxide ions are not observed. This is probably due to the large exothermicity of the reactions. It has not been possible to determine if the cluster ions also react via the S_N2 mechanism, since the phenoxide product reacts further with phenyl acetate to produce acetate.

These studies have demonstrated for the first time that a single solvent molecule clustered to a nucleophile can drastically change the reaction pathway.[15] It appears that, in the gas phase, charge-dispersed transition states such as in the S_N2 mechanism have lower kinetic barriers than charge-localized transition states such as in the tetrahedral intermediate of the $B_{AC}2$ mechanism. As a way of explaining out results, the solvent molecule in the cluster ion may be effective in dispersing the charge on the carbonyl oxygen of the tetrahedral intermediate to facilitate the $B_{AC}2$ channel. This is consistent with solution behavior where polar transition states are favored.

Acknowledgments. R. T. McIver, Jr., gratefully acknowledges grant support from the National Science Foundation (CHE 77-10024) and the National Institutes of Health (GM-23416-02).

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(15) Flowing afterglow studies have shown that clustering of molecules around a reactant ion can decrease its reactivity. For example, D. K. Bohme and L. B. Young (*J. Am. Chem. Soc.*, **92**, 7354 (1970)) found that $MeO^- \cdot HOCH_3$ reacts with CH_3Cl much slower than MeO^- to produce Cl^-. The reactions reported herein are the first example to our knowledge of clustering causing a change in reaction pathway.

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Micellar Stereoselectivity. Cleavage of Diastereomeric Substrates by Functional Surfactant Micelles

Sir:

In the cleavage of appropriate substrates, proteolytic enzymes exhibit high kinetic efficiency and stereospecificity. State of the art micellar biomimesis has made substantial progress in the development of kinetically potent, functional surfactant esterolytic reagents,[1-3] but considerably less success has attended the development of stereoselective reagents. Indeed, stereoselectivity in aqueous micelles is rare for any kind of reaction.

The stereochemical courses of the nitrous acid deamination of aminoalkanes[4] or of alkylsulfonate solvolyses[5] can be modestly modified in aqueous micelles, and various hydride transfers to certain ketones in (chiral) sodium cholate or quaternary ammonium ion micelles afford chiral alcohols (but in <2% optical yields).[6] *l*- and *d*-*p*-nitrophenyl α-methoxyphenylacetate were reported to differ by ~11% in esterolytic rate constants when solubilized in *l*-*N*-*n*-dodecyl-*N*-methylephedrinium bromide micelles;[7] similar experiments in *d*- or *l*-*N*-α-methylbenzyl-*N*,*N*-dimethylcetylammonium bromide micelles afforded little or no enantioselectivity.[8] Even kinetically more potent, head group functionalized micellar reagents bearing alanine,[9] histidine,[9] or cysteine[10] moieties were not enantioselective in the cleavage of D- or L-*N*-acetylphenylalanine *p*-nitrophenyl esters (*N*-Ac-Phe-PNP). Heretofore, the sole, significant enantioselectivity result in micellar esterolysis has been a 3:1 preference for the cleavage of L- over D-*N*-Ac-Phe-PNP, exhibited by a surfactant derived from coupling L-histidine methyl ester to 5-carboxyheptadecyltrimethylammonium chloride.[11]

We now report (a) that the dipeptide diastereomeric substrates, LL- and DL-*N*-carbobenzyloxyalanylproline *p*-nitrophenyl ester (I), are stereoselectively cleaved by a variety of functional surfactants, affording examples of the largest micellar stereoselectivities yet encountered; (b) that both binding *and* functionalization are essential to the expression of substantial stereoselectivity; and (c) that the chirality of the substrates, rather than chirality of the surfactants, is the key feature.

LL- and DL-I were synthesized by the ethyl chloroformate mediated coupling of L- or D-Z-alanine to L-proline *p*-nitrophenyl ester in cold CH_2Cl_2. The dipeptides were obtained in

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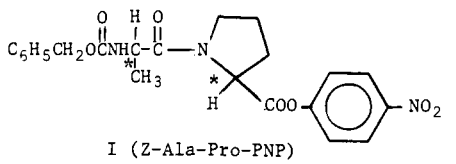
Table I. Micellar Cleavage of Z- (L- or D-) Ala-L-Pro-PNP[a,b]

surfactant	model	k_ψ^{LL}, s^{-1}	k_ψ^{DL}, s^{-1}	$k_\psi^{LL}/k_\psi^{D,L}$	$k_\psi^{LL}/k_\psi^{LL}{}_{S_a}$
buffer alone		0.000040 (4.5)	0.000065 (7.8)	0.62	
S_a		0.00134 (1.9)	0.00134 (0.7)	1.00	1.00
S_c		0.0150 (0.3)	0.00559 (0.5)	2.68	11.2
	M_c	*c*	*c*		
S_d		0.0146 (3.8)	0.00540 (4.3)	2.70	10.9
	M_d[c,d]	0.000413 (1.3)	0.000271 (4.8)	1.52	
S_e[e]		0.649 (3.1)	0.168 (2.8)	3.86	484
	M_e[d]	0.00056 (9.2)	0.00047 (4.7)	1.19	
S_b[f]		3.42 (1.4)	0.79 (3.2)	4.33	2550
	M_b	0.00172 (2.0)	0.00182 (3.0)	0.95	

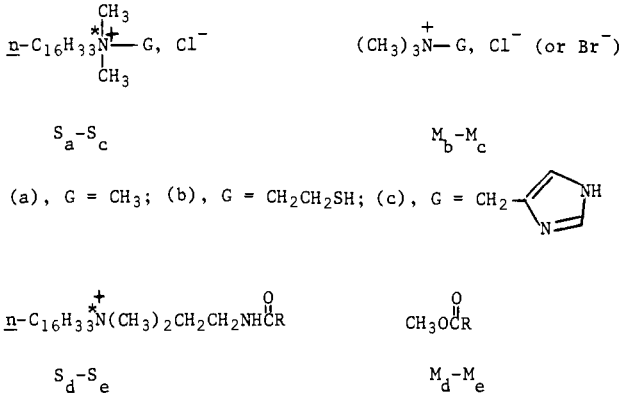
[a] See text for conditions. [b] Numbers in parentheses are percent average deviations of the rate constants from the mean constant of two or more reactions. [c] M_c is not catalytic toward Z-Ala-Pro-PNP, even at 0.04 M; for a relevant discussion see Moss, R. A.; et al. *Tetrahedron Lett.* **1975**, 3379. [M_d] = 0.02 M. [d] Rate constants are corrected for the buffer contribution. [e] 96% active S-H, pH 6.98. [f] 99% active S-H, pH 7.02.



I (Z-Ala-Pro-PNP)

~70% crude yields and were purified by column chromatography (under nitrogen) or Sephadex LH-20, using a 5:1 dioxane-methanol eluant. The hygroscopic LL- and DL-I melted at 42-45 °C and gave structurally consistent NMR spectra and satisfactory elemental analyses (C, H, N).

Surfactants S_a-S_e and analogously functionalized, nonmicellar model compounds M_b-M_e were available from previous studies.[2,9,10] Their structural formulae are shown. Pseudo-first-order rate constants for the cleavage of LL-I and DL-I were evaluated by monitoring the release of *p*-nitrophenoxide ion at 400 nm in 0.02 M phosphate buffer, pH 7.0, μ = 0.05 (KCl), at 25 °C. The concentrations of surfactants or models were fixed at 4.0×10^{-3} M[12] and substrate concentrations were held at 2.0×10^{-5} M. Least-squares rate constants ($r > 0.999$) appear in Table I.



The following observations derive from Table I. (a) The reactivity ordering toward LL-I of the micellar catalysts ($S_b > S_e > S_d \sim S_c > S_a$) is similar to that observed with *p*-nitrophenyl acetate (PNPA[9,10]). (b) More importantly, the innate reactivity of DL-I exceeds that of LL-I with water or hydroxide ion (by a factor of 1.6 in pH 7 buffer), but binding of these diastereomeric substrates to functional surfactant micelles S_b-S_e leads to strongly expressed stereoselectivity for the cleavage of LL-I. (c) Note that the extent of stereoselectivity increases with increasing kinetic potency of the surfactants,[13] leading to k_ψ^{LL}/k_ψ^{DL} values of 3.9 and 4.3 with thiol surfactants S_e and S_b. (d) *Both* binding *and* functionalization are required for substantial stereoselectivity in cleavage of the diastereomeric substrates. Table I reveals that, although binding to nonfunctional S_a or cleavage by such nonmicellar models as cysteine methyl ester or thiocholine (M_e or M_b) can afford rate enhancements, appreciable stereoselectivity is not observed. Only with the functional surfactants is this phenomenon encountered.[14] (e) A chiral surfactant is not required for diastereomeric selectivity. Indeed, the most stereoselective reagent is the achiral, long-chain thiocholine, S_b.

We offer a speculative rationale for the observed stereoselectivity. Polar molecules such as substrates I should be solubilized within the Stern layer of cationic micelles.[1a] An examination of models suggests that LL-I, more readily than DL-I, can assume an *extended* conformation (optimal for binding to the micelle[1a]), in which the scissile carbonyl group is exposed and the aryl moieties, the hydrophobic "side" of the proline ring, *and* the alanyl methyl group simultaneously project downward (i.e., onto the hydrocarbon core of the micelle). This could lead to more-defined binding of the LL isomer to a functional surfactant micelle, and hence to a more rapid micelle-mediated cleavage. There is here a tantalizing resemblance to the proteolytic enzymes, in which high binding energies and defined binding sites for hydrophobic substrate residues are important.[15] We are currently preparing various substrates analogous to I to test these ideas.

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(12) The surfactant concentrations are substantially above the critical micelle concentrations.[2,9,10] For models M_c and M_d, higher concentrations had to be used in order to differentiate the model-driven reactions from buffer hydrolysis; see Table I.
(13) This parallelism probably originates in greater bonding between surfactant functionality and substrate carbonyl at the cleavage reaction transition states with the more reactive surfactants: greater bond formation results in more accelerated cleavage *and* more stereochemical information transfer (i.e., greater stereoselectivity).
(14) Interestingly, cleavages mediated by the models also favor LL-I over DL-I. However, substantial stereoselectivity ($k_\psi^{LL}/k_\psi^{DL} > 2$) is encountered only with S_b–S_e. Note that the 1.5-fold stereoselectivity exhibited by M_d is expressed at 0.02 M, a concentration five times greater than that employed with S_d. At 4×10^{-3} M, enhancement by M_d is only ~50%, relative to buffer rates.
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Stereoselective Synthesis of *threo*-3-Hydroxy-2-methylcarboxylic Acids Using Alkoxyalkyl Propionates

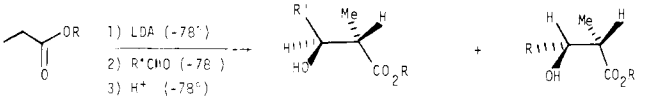
Sir:

Among the most fundamental and significant synthetic reactions is carbon-carbon bond formation via aldol or related processes (Scheme I).[1] In recent years, a considerable amount of activity has ensued with the emphasis focusing on stereoselectivity accompanying the C–C bond-forming step. In this regard, studies have been reported[2] involving the effects of steric bulk, solvent, nature of the metal, kinetic vs. thermodynamic control, and the geometry of the enolate species. Closely related to this problem is the stereoselective formation of β-hydroxy acids, readily prepared from lithio enolates of simple carboxylic esters (Scheme I, R = *O*-alkyl) and carbonyl compounds.[3] Heathcock[4] has recently reported routes to *erythro*- and *threo*-β-hydroxy acids by use of bulky α-silyloxy enolates (Scheme I, R = $-C(Me)_2OSiMe_3$) or chromium(II)-mediated addition of allylic halides to aldehydes. Mulzer,[5] using ester enolates, was able under equilibrating conditions to form, in certain instances, high ratios of *threo*-β-hydroxy-α-alkylcarboxylic acids.

We now report some preliminary results of a study in which various alkoxyalkyl propionates, **1**, via their lithio enolates give rise to high threo:erythro ratios of 2-methyl-3-hydroxycarboxylic acids **2**. It appears that no serious effort has been reported which considers the effect of internal lithium chelation in the enolate *prior to addition* to the carbonyl component. Table I describes the result of this effect with the simple methyl ester of propionic acid as a control. It can be seen that generating the *Z* lithio enolate (THF, −78 °C)[2a] of methyl propionate and addition (−78 °C) of isobutyraldehyde gives a 1.2:1 threo:erythro ratio of **2**. However, this ratio climbs to 8.5–10:1 when various alkoxyalkyl esters are metalated and alkylated under identical conditions. In the case of the MEM ester (footnote *e*, Table I), which led to a 10:1 ratio of diastereomeric esters, produced exclusively the threo ester when isobutyraldehyde was introduced into the enolate solution at −98 °C. This implies that even greater stereochemical control is attainable at lower alkylation temperatures. This was not to be the case, however, with acetaldehyde addition which gave essentially 2:1 threo:erythro products at −98 °C. The lithium enolates of the alkoxyalkyl esters were trapped with trimethylsilyl chloride and shown (^{1}H NMR, VPC) to be a single (>98%) geometric isomer which we assigned as *E* in accordance with previous results obtained by others.[2,6] With regard to the kinetic and thermodynamic nature of the preponderant threo product, we can only say at this time that there was no change in product ratio after 20 h at −78 °C. Unfortunately, side reactions occur in the adduct above −50 °C which precluded examination of the product ratios at higher temperature. For optimum yield of product, the reactions should be quenched, after 5–10 min at −78 °C, with acetic acid (1.05 equiv) in THF.

The major point of interest in these results appears to be the generality with which coordinating groups increase the selectivity of the 3-hydroxy-2-methyl acids, regardless of the nature of the alkyoxyalkyl group. It can be assumed at this time that the in situ generation of a bulky group in the enolate provides the steric control necessary for enhanced stereo-

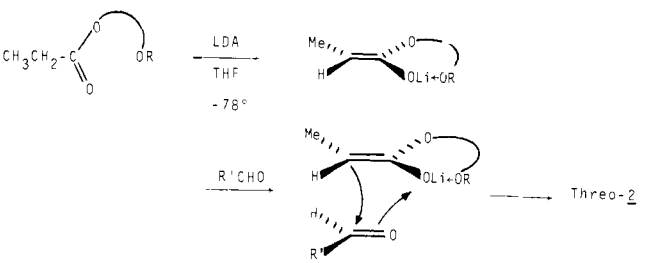
Table I. Stereoselectivity Using Alkoxyalkyl Ester Enolates



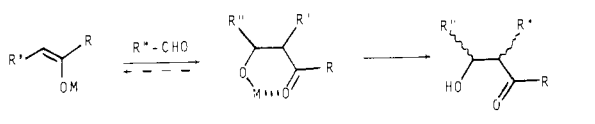
1 threo-2 erythro-2

R	R′CHO	ratio[a]	% threo[b,c]	% erythro
Me	*i*-PrCHO	1.2:1	55	45
CH_2OMe[d]	*i*-PrCHO	8.5:1	90	10
$CH_2O(CH_2)_2OMe$[e]	*i*-PrCHO	10:1	91	9
$C(CH_3)OEt$[f]	*i*-PrCHO	10:1[g]	91	9
Me	CH_3CHO	1.3:1	57	43
CH_2OMe	CH_3CHO	2:1	67	33
Me	PhCHO	1.2:1	55	45
$CH_2O(CH_2)_2OMe$	PhCHO	3:1[g]	75	25

[a] Determined by high pressure liquid chromatography (Waters 244 system) using 1-ft micro-Porasil column and eluted with $CHCl_3$–CH_3CN, 99:1, at a flow rate of 3 mL/min. [b] Assigned by ^{1}H NMR spectrum of C-2, C-3 protons and couplings (J = 7 Hz for *threo*-**2** and 4 Hz for *erythro*-**2**). [c] Chemical yields ranged from 84 to 98% for total product. [d] Prepared from propionic acid, potassium *tert*-butoxide, and chloromethylmethyl ether in anhydrous ether, bp 125–126 °C (atm), 80%. [e] Prepared as in *d* using 1.0 equiv of methoxyethoxy chloromethyl ether (MEM-Cl, Aldrich), distilled by Kugelrohr apparatus (0.05 Torr, trap distillate at −78 °C), 82%. [f] Prepared from propionic acid, excess methylvinyl ether, and a trace of toluenesulfonic acid (1 h, 25 °C), bp 37–38 °C (20 mm, 85%). [g] Product ratio determined after hydrolysis of ester.



Scheme I



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