(3) Structural studies carried out at Columbia University employed as the pheromone source filter papers on which female cockroaches had been kept (a gift from Drs. R. H. Wharton and L. M. Roth, U.S. Army Natick Research Laboratories, Mass.). However, 4 years of isolation studies gave only 2 μg of periplanone-B and a smaller amount of a minor pheromone constituent, periplanone-A. These amounts were sufficient only for determining molecular weight and UV spectral data; cf. S. L. Chen, Ph.D. Dissertation, Columbia University, 1974.
(4) C. J. Persoons, P. E. J. Verwiel, F. J. Ritter, E. Talman, P. J. F. Nooijen, and W. J. Nooijen, *Tetrahedron Lett.*, 2055 (1976).
(5) E. Talman, P. E. J. Verwiel, F. J. Ritter, and C. J. Persoons, *Isr. J. Chem.*, **17**, 227 (1978).
(6) C. J. Persoons, P. E. J. Verwiel, E. Talman, and F. J. Ritter, *J. Chem. Ecol.*, **5**, 219 (1979).
(7) W. C. Still, *J. Am. Chem. Soc.*, preceding paper in this issue.
(8) All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block-diagonal least-squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge, ORNL-TM-305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL-3794; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast Fourier transform, G. Germain, P. Main and M. Woolfson, University of York.
(9) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(10) For use as a resolving agent for secondary alcohols, see S. L. Chen, K. Nakanishi, M. Morisaki, N. Ikehawa, and Y. Shimizu, *J. Am. Chem. Soc.*, **97**, 5297 (1975), and references cited therein.
(11) CD spectra were measured with a JASCO J-40 instrument equipped with a computerized data processor.
(12) Both the natural (isolated from the cockroach) and resolved synthetic periplanone-B had a negative CD Cotton effect. The $\Delta\epsilon$ value of -5 is approximate and estimated from weighed pheromone.
(13) C. J. Persoons, Thesis, Agricultural University, Wageningen, The Netherlands, 1977. See also ref 6.
(14) N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972); N. Harada, S. L. Chen, and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5345 (1975); N. Harada, Y. Takuma, and H. Uda, *ibid.*, **100**, 4029 (1978), and references cited therein.
(15) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).
(16) R. A. Grinter and S. F. Mason, *Trans. Faraday Soc.*, **60**, 274 (1964).
(17) A. W. Burgstahler, R. C. Barkhurst, and J. K. Gawronski in "Modern Methods of Steroid Analysis", E. Heftmann, Ed., Academic Press, New York, 1973, Chapter 16.
(18) A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *J. Am. Chem. Soc.*, **83**, 4661 (1961); U. Weiss, H. Ziffer, and E. Charney, *Tetrahedron*, **21**, 3105 (1965); E. Charney, H. Ziffer, and U. Weiss, *ibid.*, **21**, 3121 (1965).
(19) We are grateful to Professor A. W. Burgstahler for stimulating discussions.
(20) These studies were supported by National Institutes of Health Grant AI 10187 (to K.N.) and by the Hoffmann-La Roche Corp. (to J.C.).
(21) Fellow of the Damon Runyon–Walter Winchell Cancer Foundation (DRG-162F), 1977–1979.

Michael A. Adams,[21] Koji Nakanishi,* W. Clark Still
Department of Chemistry, Columbia University
New York, New York 10027

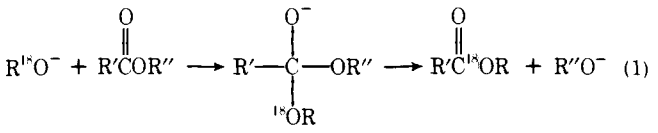
Edward V. Arnold, Jon Clardy*
Department of Chemistry, Cornell University
Ithaca, New York 14853

C. J. Persoons*
Centraal Laboratorium TNO, Delft, The Netherlands
Received January 15, 1979

Effect of Solvation upon Carbonyl Substitution Reactions

Sir:

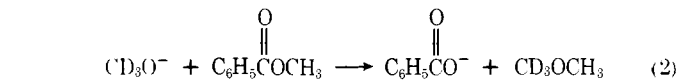
Extensive mechanistic studies have established that alkaline hydrolysis of esters and transesterification proceed by attack of the nucleophile at the carbonyl carbon to form a tetrahedral intermediate followed by cleavage of the acyl-oxygen bond ($B_{AC}2$) (eq 1).[1] In addition to the direct evidence[2] which has



(1)

been obtained by studies with ^{18}O, ester hydrolysis occurs at a rate which is unreasonably fast for an alternate mechanism, such as an S_N2 reaction at the alkyl carbon atom to produce alkyl-oxygen cleavage. These results are usually interpreted to mean that the carbonyl carbon atom is much more susceptible to nucleophilic attack than the alkyl carbon atom.

Recently, reactions of this type have been studied in the gas phase to elucidate how solvation effects nucleophilic reactivity. A surprising result of this work is that other reaction channels become competitive or dominant over the $B_{AC}2$ mechanism.[3] For example, in the absence of solvation, the reaction of deuteriomethoxide with methyl benzoate produces only benzoate (by the S_N2 mechanism) (eq 2).[4] Even attachment of elec-

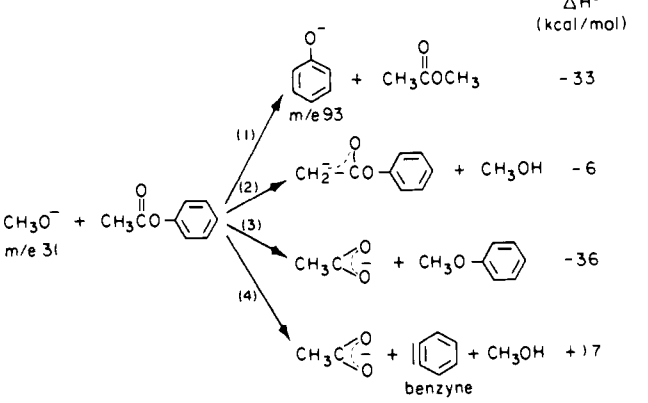


(2)

tron-withdrawing groups to the carbonyl carbon fails to activate the carbonyl sufficiently to compete with the S_N2 channel.

These discrepancies between the mechanisms in the gas phase and in solution prompted us to examine reactions of phenyl acetate with various nucleophiles. Phenyl acetate was chosen because it appeared to be a likely substrate for observing the $B_{AC}2$ mechanism in the gas phase. Presumably the S_N2 channel would be shut off because this would require nucleophilic aromatic substitution upon an unactivated benzene ring, and phenoxide would be expected to enhance the probability of the $B_{AC}2$ mechanism because it is a good leaving group. Using methoxide ion as an example, there are four possible reactions with phenyl acetate (Scheme I). Our estimates of the

Scheme I



exothermicity for each channel are shown at the far right side.[5] On the basis of the thermochemistry, channel 1 ($B_{AC}2$), channel 2 (α-proton abstraction), and channel 3 (S_N2) are allowed. The large endothermicity for channel 4 (β elimination) removes it as a possibility because the reaction would be far too slow to be observed. Channel 2 is unusual from the point of view of solution chemistry; however, it is allowed in the gas phase because hydrogens α to a carbonyl group are more acidic than aliphatic alcohols.[9] Furthermore, since the only previous report of gas-phase nucleophilic aromatic substitution showed the rate to be very slow,[10] we expected carbonyl attack (channel 1) or proton abstraction (channel 2) to be the most likely reactions.

We have recently studied the gas-phase reactions of phenyl acetate with various nucleophiles using a pulsed ion cyclotron resonance (ICR) spectrometer,[11] and, surprisingly, the only reaction observed is channel 3, where $X^- = OH^-, CH_3O^-, CN^-, SH^-, CH_3S^-$, or $C_6H_5O^-$. The rate constants determined for the various nucleophiles are all close to the diffusion-controlled limit and range from 3 to 8×10^{-10} cm^3 molecule^{-1} s^{-1}. Neither the expected product of the $B_{AC}2$ channel,

0002-7863/79/1501-2498$01.00/0

$$X^- + CH_3COC_6H_5 \longrightarrow CH_3CO^- + C_6H_5X \quad (3)$$

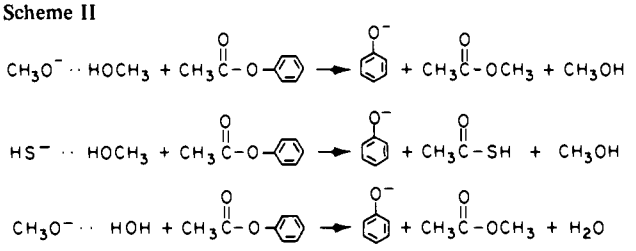
phenoxide at *m/e* 93$^-$, nor the M − 1 ion of phenyl acetate at *m/e* 135$^-$ was observed within the detection limits of the spectrometer. This means that the rate constants for channels 1 and 2 must be at least one hundred times smaller than for channel 3. These results demonstrate that nucleophilic 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).

References and Notes

(1) See, for example, J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, 1962, pp 275–282.
(2) See, for example, M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).
(3) K. Takashima and J. M. Riveros, *J. Am. Chem. Soc.*, **100**, 6128 (1978).
(4) M. Comisarow, *Can. J. Chem.*, **55**, 171 (1977).
(5) The following heats of formation (kilocalories/mole) were taken from ref 6: $\Delta H_f^\circ(CH_3OH) = -47.96$; $\Delta H_f^\circ(CH_3CO_2CH_3) = -97.9$; $\Delta H_f^\circ(CH_3OC_6H_5) = -17.27$. The heat of formation of phenyl acetate is estimated to be −67.9 using the method of Franklin,[7] and the heat of formation of benzyne is estimated in ref 8 to be +83. For the ions, heats of formation were derived from measurements of gas-phase acidities:[9] $\Delta H_f^\circ(CH_3O^-) = -36.0$; $\Delta H_f^\circ(C_6H_5O^-) = -38.8$; $\Delta H_f^\circ(CH_3CO_2^-) = -122.5$; $\Delta H_f^\circ(^-CH_2CO_2C_6H_5) = -62.1$.
(6) H. M. Rosenstock, K. Draxl, B. W. Steiner, and J. T. Herron, *J. Phy. Chem. Ref. Data*, **6**, Suppl. 1, 774–783 (1977).
(7) J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949).
(8) S. Pollack and W. J. Hehre, private communication.
(9) J. Bartmess and R. T. McIver, Jr., from "The Gas Phase Acidity Scale", a chapter in "Gas Phase Ion Chemistry", M. T. Bowers, Ed., Academic Press, New York, 1979.
(10) S. M. J. Briscese and J. M. Riveros, *J. Am. Chem. Soc.*, **97**, 230 (1975).
(11) R. T. McIver, Jr., *Rev. Sci. Instrum.*, **49**, 111 (1978).
(12) P. C. Isolani and J. M. Riveros, *Chem. Phys. Lett.*, **33**, 362 (1975).
(13) R. T. McIver, Jr., and R. C. Dunbar, *Int. J. Mass Spectrom. Ion Phys.*, **7**, 471 (1971).
(14) D. J. DeFrees, W. J. Hehre, R. T. McIver, Jr., and D. H. McDaniel, *J. Phys. Chem.*, in press.
(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 $MeO^- \cdot \cdot HOCH_3$ 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.

Elaine K. Fukuda, Robert T. McIver, Jr.*
Department of Chemistry, University of California
Irvine, California 92717
Received January 15, 1979

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

0002-7863/79/1501-2499$01.00/0