reactions with **1a** and **1b** can be attributed to lowered electron density in the C=C bond (making easier the approach of the nucleophile) and to delocalization by the sulfonyl group of the negative charge developed at the β position in the SN2′ transition state (or intermediate).

For most abnormal displacement reactions in allylic systems it is extremely difficult to chose between the SN2′ and SNi′–SN2 mechanistic labels. SNi′ rearrangements can be very rapid,[2] and the rate of formation of the ion pair (or intermediate) is no doubt even faster.[3] The demonstration of the absence of rearranged chloride in an incomplete reaction does not conclusively rule out the SNi′–SN2 pathway since the rearranged chloride usually undergoes SN2 displacement much faster than does the unrearranged halide and may, therefore, be removed selectively. Furthermore, attack of the nucleophile may occur on the SNi′ ion pair (or intermediate); if this occurs, rearrangement to the isomeric halide is by-passed. The SNi′–SN2 route for chlorides **1a** and **1b** is excluded by their extreme reluctance to undergo ionization.[4] These halides are, therefore, good models for assessing the ability of nucleophiles to effect SN2′ reactions.

Halides **1a** and **1b** proved to be inert to the action of thiourea in alcohol or N-methylpiperidine in benzene. Sodium bromide in acetone gave the SN2 product with **1a**. No reaction could be detected with **1b** and lithium bromide in acetone in 31 days at room temperature; no reaction occurred with N-methylpiperidine in 23 days at 50° plus 35 days at room temperature. The rate for the reaction of N-methylpiperidine with **1b** must be *at least* 10^3 times slower than that with piperidine, whereas with allyl bromide the rates differ by only one order of magnitude. It would appear that the hydrogen atom on nitrogen in piperidine is playing an important role in the reaction, probably through hydrogen bonding, as originally suggested.[5] This conclusion is strengthened by the observation that the rate for **1b** is ninefold *faster* in benzene than in methanol (Table I); the solvent effect in SN2 reactions is equally large but in the reverse direction.[6]

Our conclusion is that SN2′ reactions can be realized only with a select group of allylic systems and nucleophiles. The assignment of the SN2′ mechanistic label in many earlier studies wherein thiourea, bromide ion, a tertiary amine, or an alkoxide ion was used as the nucleophile needs to be reexamined, and the label needs to be used with increased caution in the future.

Acknowledgment. This investigation was supported by Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

(2) W. G. Young, S. Winstein, and H. L. Goering, *J. Am. Chem. Soc.*, 73, 1958 (1951).
(3) S. Winstein, J. S. Gall, M. Hojo, and S. Smith, *ibid.*, 82, 1010 (1960).
(4) No chloride ion could be detected from tertiary allylic chloride **1b** even after heating a methanolic solution at 50° for 21 days; a further period of 35 days at room temperature still gave no chloride ion.
(5) R. E. Kepner, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, 71, 115 (1949). See also W. G. Young, R. A. Clement, and C. H. Shih, *ibid.*, 77, 3061 (1955), and ref 1b.
(6) N. Menschutkin, *Z. Physik. Chem.*, 6, 43 (1890).

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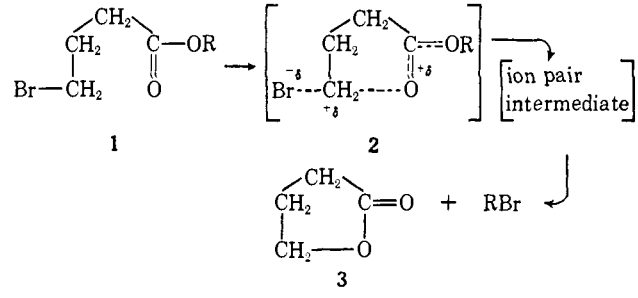
Regarding the Mechanism of Gas-Phase Dehydrohalogenation

Sir:

Gas-phase dehydrohalogenation, a reaction which has been extensively studied and discussed in numerous reviews,[1] has been characterized by a mechanism involving the intermediate formation of a tight carbonium halide ion pair. We are concerned here with the question of just how closely joined the counterions may be in gas-phase heterolysis, as compared to the corresponding reaction in solution to which it is frequently referred as a model for interpretation.[2]

A case in point may now be submitted which appears to afford increased understanding of the differences in heterolytic nature that distinguish the gas- and solution-phase reactions. We have been able to demonstrate that a reaction which involves neighboring group participation and ionic intermediates in solutions of widely varying dielectric properties does not take place in the gas phase at all accessible temperatures. The reaction of interest is the lactonization of γ-bromo esters.[3]



1 2 3

The rate data we have gathered and presented in Table I confirm the ionic nature of this process.

Table I. Rates of Lactonization of Ethyl-γ-bromobutyrate at 200° in Various Media

Solvent	Dielectric constant	$K \times 10^6$ sec^{-1}	Relative rate
Acetonitrile	37.5	850[a]	320
Dimethyl phthalate	20	320	139
Chlorobenzene	5.7	35	16
Pure hydrocarbon[b]	1.9	2.7	1
Gas phase	1+		0

[a] Extrapolated from data at 150, 160, 170, and 186°. [b] 1,3-Dimethyl-5-ethyladamantane was kindly provided by Dr. A. Schneider, Sun Oil Co.

The solvent dielectric clearly is an important factor controlling rate such that a less than 20-fold change in ϵ is correlated with a rate factor of >300. Among the solvents chosen ionizing power also appears to parallel dielectric strength.[4] Furthermore, the presence of small amounts of added neutral salts in the medium accelerates reaction. It is also to be noted that, even in solvents of extremely low dielectric strength such as the pure hydrocarbon solvent, the rate of formation of

(1) The most recent review has been presented in A. Maccoll, *Advan. Phys. Org. Chem.*, 3, 91 (1965).
(2) A. Maccoll and E. S. Swinbourne, *Proc. Chem. Soc.*, 409 (1960); *J. Chem. Soc.*, 149 (1964).
(3) For a discussion of the course and mechanism of this reaction see D. B. Denney and J. Giacin, *Tetrahedron*, 20, 1377 (1964), and J. Weinstock, *J. Am. Chem. Soc.*, 78, 4967 (1956).
(4) C. Reichardt, *Angew. Chem. Intern. Ed. Engl.*, 4, 29 (1965).

3 is quite measureable. Yet in the gas phase, having nearly the same ϵ as cyclohexene, no reaction leading to lactone takes place at temperatures up to 450° (and under conditions which leave the lactone unchanged). These data, taken in conjunction with earlier stereochemical and tracer studies,[3] have therefore established that reaction occurs in solution *via* participation by the neighboring carbalkoxyl group with development of a mesomeric ion pair resembling **1**.

Clearly the ion pair formed in the gas phase does not possess the same structure (as its solution analog) in that the counterion, Br^-, is stringently localized to the region of the carbon atom with which it was covalently associated in the substrate. Therefore the only reaction possible is that in which Br^- abstracts the β-hydrogen in an elimination product-forming step (rather than the lactone-forming step in which it customarily engages when free in solution). However, in light of our observation that purely thermal elimination of HBr from **1** does *not* occur with a notable rate increase as compared to *n*-butyl bromide, it can also be said that ionization of the C–Br bond in **1** in the gas phase does not realize any benefit from neighboring group participation.

It may be noted, as well, that an ionization process, taking place in solution through a cyclic transition state such as **2**, should develop more readily in the gas phase, *if solvation were not a requirement for such ionization.* A polar, cyclic transition state is not resisted by a large negative entropy of activation if it is formed in the absence of solvent. That is to say, $\Delta F_{el} = \Delta H_{el}$ and $\Delta S_{el} = 0$ in the gas phase, where the subscript el designates the electrical parameters.[5] We must therefore conclude that the quasiheterolytic transition state for gas-phase dehydrohalogenation described by Maccoll[1] does not result in an ion-pair intermediate resembling the array of somewhat loosely bound counterions characteristic of the solution-phase heterolysis. Rather it should now be assumed that a considerably smaller degree of ionization may occur upon extension of the carbon–halogen bond in the absence of solvation which cannot be adequately calibrated by reference to the corresponding event in the solution-phase reaction.

Acknowledgment. We are greatly obliged to Professor P. D. Bartlett for very valuable suggestions in connection with the preparation of this manuscript.

(5) For a discussion of the evidence supporting this conclusion see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961, and E. A. Moelwyn-Hughes, *Proc. Roy. Soc.* (London), **A155**, 308 (1936).

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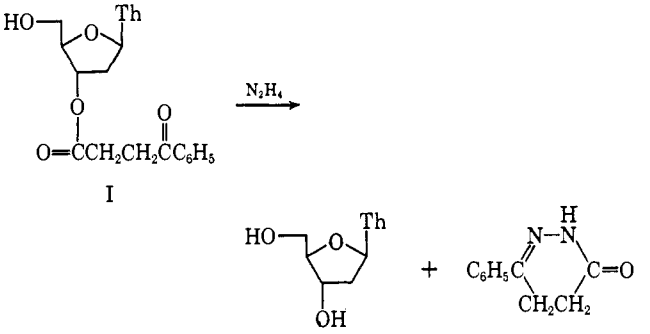
Oligonucleotide Syntheses Utilizing β-Benzoylpropionyl, a Blocking Group with a Trigger for Selective Cleavage[1,2]

Sir:

For synthetic work with nucleosides a blocking agent for hydroxyl groups was needed which was stable in pyridine solutions of arenesulfonyl chlorides and in aqueous pyridine yet could be removed efficiently at will under essentially neutral conditions. We have found that the benzoylpropionyl group satisfies these stipulations and is a very promising agent for protecting hydroxyl groups in polyfunctional compounds in general that are sensitive to acidic and basic reagents. Unblocking is accomplished by treatment at room temperature with hydrazine hydrate in pyridine buffered with acetic acid.[3] The keto function serves as a trigger for the cleavage, reacting selectively with the added reagent, hydrazine, to form an intermediate in which the nucleophilic NH_2 is favorably positioned to attack the neighboring ester. Under the reaction conditions hydrazine does not attack the heterocyclic rings of thymidine, deoxycytidine, deoxyadenosine, and deoxyguanosine,

The properties of the group are illustrated by the chemistry of compounds I and II. 3′-O-Benzoylpropionylthymidine (I), mp 158–160°, was obtained in 78% yield by esterification of 5′-O-di-(*p*-methoxytrityl)-thymidine with β-benzoylpropionic acid and dicyclohexylcarbodiimide in pyridine[4] and subsequent hydrolysis of the dimethoxytrityl ether with 80% aqueous acetic acid. On treatment with 0.5 *M* hydrazine in pyridine–acetic acid (80:20 v/v) for 3 hr this ester was converted quantitatively to thymidine and 4,5-dihydro-6-phenylpyridazone. Under these conditions O-acetyl groups



I

are not affected. Compound II was obtained in 63% yield from 1.0 mmole of 5′-O-monomethoxytritylthymidine and 1.5 mmoles of I by the method used for preparation of β-cyanoethyl derivatives of dinucleoside phosphates[5] (I used in place of thymidine). Both I and II gave satisfactory C, H, and N analyses. Each of the blocking groups in II could be removed independently, leaving the other two intact. Thus 80% aqueous acetic acid (10 min at steam-bath temperature) selectively cleaved the methoxytrityl ether, ammonium hydroxide (1 min at room temperature) selectively eliminated the cyanoethyl group, and hydrazine in pyridine–acetic acid (3 hr at room temperature) selectively removed the benzoylpropionyl group. The product of the hydrazine reaction serves as a useful intermediate in the stepwise

(1) Part X in a series on Nucleotide Chemistry. Part IX: T. Shimidzu and R. L. Letsinger, *J. Org. Chem.*, in press.

(2) This research was supported by the Division of General Medical Sciences, National Institutes of Health, GM-10265, and by Public Health Service Predoctoral Fellowships from the Division of General Medical Science awarded to M. H. C. (1-F1-GM23,558) and P. S. M. (5F1-GM34,033).

(3) T. Curtius reported in 1895 (*J. Prakt. Chem.*, [2] 50, 529 (1895)) that equimolar amounts of ethyl β-benzoylpropionate and hydrazine hydrate react exothermically when mixed to yield 4,5-dihydro-6-phenylpyridazone. The potential of the β-benzoylpropionyl group as a blocking agent for alcohols, however, has apparently hitherto been overlooked.

(4) Attempts to prepare the acid chloride of benzoylpropionic acid for use in the esterification were unsuccessful as a consequence of the facile conversion of the acid to the unsaturated lactone.

(5) R. L. Letsinger and K. K. Ogilvie, *J. Am. Chem. Soc.*, **89**, 4801 (1967).