Transition States in the Gas Phase and in Solution

Sir:

Our proposed analogy between rates of unimolecular dehydrohalogenation in the gas phase and those of the corresponding SN1 and E1 reactions in solution[1] has been questioned recently by Herndon, *et al.*[2] These authors point out that (i) 1-phenylethyl chloride and *t*-butyl chloride are solvolyzed at a similar rate in 80% aqueous ethanol, whereas in the gas phase, *t*-butyl chloride reacts appreciably faster; (ii) *exo*-norbornyl chloride eliminates more slowly in the gas phase than one would expect from its solvolytic behavior.

Table I. Rates of Dehalogenations in the Gas Phase and in Acetonitrile at 100° (k_1 in sec.$^{-1}$)

	sec-Bu	Cyclohexyl	Cyclopentyl	MeCHPh	*t*-Bu
$k_1 \times 10^{14}$ for RBr, gas phase	2.04[a]	3.24[b]	17.4[c]	...	2,510[d]
$k_1 \times 10^{16}$ for RCl, gas phase	2.00[e]	3.09[f]	15.1[g]	200[h]	1,290[i]
$k_1 \times 10^{7}$ for RBr, MeCN	1.57	1.62	10.1	1360[j]	31,600[j]

[a] M. N. Kale, Ph.D. Thesis, University of London, 1957. [b] J. H. S. Green and A. Maccoll, *J. Chem. Soc.*, 2449 (1955). [c] M. N. Kale and A. Maccoll, *ibid.*, 5020 (1957). [d] G. D. Harden and A. Maccoll, *ibid.*, 2454 (1955). [e] N. Capon, Ph.D. Thesis, University of London, 1964. [f] E. S. Swinbourne, *Australian J. Chem.*, **11**, 314 (1958). [g] E. S. Swinbourne *J. Chem. Soc.*, 4668 (1960). [h] M. R. Bridge, Ph.D. Thesis, University of London, 1964. [i] B. Roberts, Ph.D. Thesis, University of London,1961. [j] Reference 5.

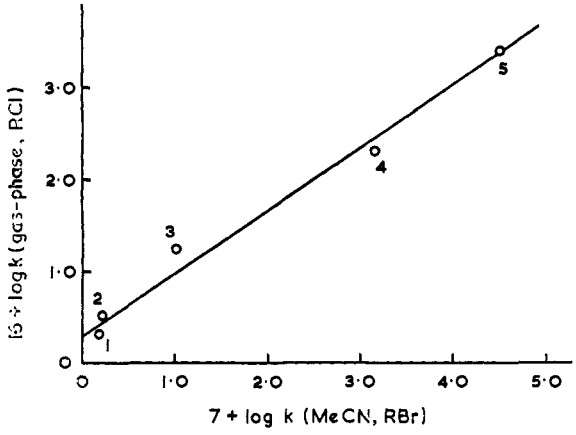


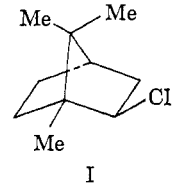
Figure 1. The logarithm of the rate of gas-phase elimination from chlorides as a function of the logarithm of the rate of unimolecular elimination of bromides in acetonitrile: 1, *sec*-butyl; 2, cyclohexyl; 3, cyclopentyl; 4, 1-phenylethyl; 5, *t*-butyl.

Concerning i, it has been known for a long time that, in general, solvolyses of 1-phenylethyl chloride do not proceed completely by way of mechanism SN1, but also have a bimolecular component; *e.g.*, in absolute methanol and ethanol, rates of substitution increase considerably on the addition of lyate ion,[3] whereas solvolyses of *t*-butyl halides are insensitive to this mechanistic test.[4] In accord with these findings we observe[5] that a less nucleophilic solvent such as acetonitrile does differentiate between these two alkyl systems (*cf.* Table I).

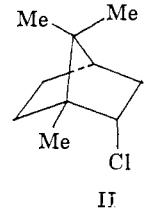
A logarithmic plot of the gas-phase data (for the chlorides) against the data for the bromides in acetonitrile (see Figure 1) gives a satisfactory straight line in accord with our proposal.[1]

At present, an accurate estimate of charge development in the transition state of a gas-phase heterolysis is still difficult. It has been shown, however,[5] that for SN1 and E1 reactions, which go from a nonpolar initial state to a dipolar transition state, a less polar solvent will also favor a less polar transition state. Since the gas phase is by far the least polar medium, *the transition state of a heterolysis in the gas phase will be considerably less ionic than in solution.* Clearly, for a reaction in solution, the solvent stabilizes the developing charges and facilitates the formation of a more ionic transition state, lowering the activation energy (*e.g.*, for *t*-butyl bromide from 42 kcal./mole in the gas phase to 23 kcal./mole in acetonitrile). A comparatively weakly ionic transition state in the gas phase is consistent with other observations[6]; *e.g.*, the rates of elimination for the alkyl bromides are less sensitive to a change in alkyl structure in the gas phase than in solution (*cf.* Table I). Similarly, for gas-phase heterolysis, a vinyl group attached to the α-carbon atom of an alkyl halide is equivalent to only about one methyl group.[1] In no case, however, can the heterolytic nature of these dehydrohalogenations be in doubt. The experimental technique, which is described elsewhere[1b] and includes the use of seasoned reaction vessels, free radical traps, and the variation of pressure over a wide range, does effectively rule out the competitive homolytic bond fission for most reactions.

We can now turn to the question of synartetic acceleration in the gas phase; previously, a study of the trimethylnorbornyl halides I and II has shown[7] that



I



II

at 400° isobornyl chloride (I) pyrolyzes about 20 times faster than bornyl chloride (II), or only about 2.3 times faster than *sec*-butyl chloride; at 100° the difference in reactivity is slightly more pronounced, with I reacting some 20 times faster than *sec*-butyl chloride,

(1) (a) A. Maccoll in "Theoretical Organic Chemistry," Butterworths, London, 1953, p. 230; (b) "Technique of Organic Chemistry," Vol. VIII, Part I, Interscience Publishers, Inc., New York, N. Y., 1961, Chapter X.

(2) W. C. Herndon, J. M. Sullivan, M. B. Henley, and J. M. Manion, *J. Am. Chem. Soc.*, **86**, 5691 (1964).

(3) E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1201 (1937).

(4) E. D. Hughes, *Trans. Faraday Soc.*, 37, 603 (1941).

(5) H. M. R. Hoffmann, submitted for publication.

(6) For the pyrolysis of alkyl iodides, a semiionic transition state has been suggested by S. W. Benson and A. N. Bose, *J. Chem. Phys.*, 39, 3463 (1963).

(7) R. C. L. Bicknell, Ph.D. Thesis, University of London, 1962; R. C. L. Bicknell and A. Maccoll, *Chem. Ind.* (London), 1912 (1961).

but the *exo/endo* ratio is still only about 30. This low ratio stands in striking contrast to the one observed for solvolyses,[8] which is $\sim 10^5$ at 25°, and it is concluded *that neighboring group assistance is energetically less favored in the gas phase than in solution.* Two reasons probably do account for this: firstly, neighboring group migration is usually associated with some loss of rotational entropy for the reactant on ring closure to the transition state.[9] This entropy loss, which impedes reactivity, will inevitably be more pronounced in the gas phase than in solution. Secondly, since neighboring group assistance depends, among other factors, critically upon the charge development at the migrating center, the driving force for migration in the gas phase is reduced.

For the solvolysis of the 2-norbornyl chlorides, the *exo/endo* ratio is about 10^2–10^3,[8a,10] *i.e.*, smaller than for I and II, and it is therefore not surprising that *exo*-norbornyl chloride eliminates at a rate even closer to *sec*-butyl chloride in the gas phase.

Finally, it should be noted that the small *exo/endo* ratios of these norbornyl derivatives in the gas phase and the high ratios in solution provide more evidence for a "nonclassical" transition state in the solvolysis of the *exo* isomers, as has been suggested some time ago,[8b-d,11] and, in the light of some recent doubts, reaffirmed.[8a,10]

(8) (a) P. Beltramé, C. A. Bunton, A. Dunlop, and D. Whittaker, *J. Chem. Soc.*, 658 (1964); (b) F. Brown, E. D. Hughes, C. K. Ingold, and J. F. Smith, *Nature*, **168**, 65 (1951); (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell & Sons, Ltd., London, 1953, Chapter IX; (d) S. Winstein, E. Grunwald, *et al.*, *J. Am. Chem. Soc.*, **74**, 1127 (1952).

(9) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964).

(10) S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *J. Am. Chem. Soc.*, **87**, 337 (1965).

(11) C. K. Ingold, private communication to H. B. Watson, in *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **36**, 197 (1939).

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The Synthesis of D-Oxytocin, the Enantiomer of the Posterior Pituitary Hormone, Oxytocin[1]

Sir:

The synthesis of the optical antipode of the posterior pituitary hormone oxytocin (Figure 1) has now been completed as part of a general study of the relationship of the stereochemistry of the hormone to its biological activity.

The desired protected nonapeptide amide, N-carbobenzoxy-S-benzyl-D-cysteinyl-D-tyrosyl-D-isoleucyl-D-glutaminyl-D-asparaginyl-S-benzyl-D-cysteinyl-D-prolyl-D-leucylglycinamide, was prepared by the stepwise nitrophenyl ester method,[2] as employed for the synthesis of oxytocin,[3] starting from the protected tripeptide amide, N-carbobenzoxy-D-prolyl-D-leucylglycinamide. Preparation of the latter compound was accomplished

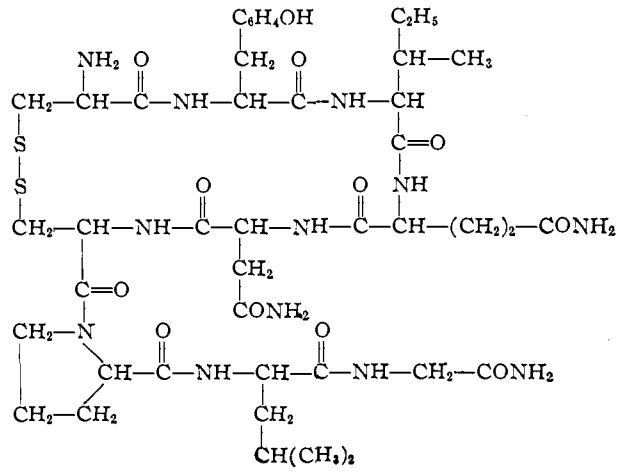

Figure 1. Structure of oxytocin.

by ammonolysis of ethyl N-carbobenzoxy-D-prolyl-D-leucylglycinate, made by the method used by Cash[4] for the synthesis of the L- isomer.[5]

The protected nonapeptide amide possessed m.p. 250–252° and $[\alpha]^{19}D$ +51.2° (*c* 1, dimethylformamide) (*Anal.* Calcd. for $C_{65}H_{86}N_{12}O_{14}S_2$: C, 59.0; H, 6.55; N, 12.7. Found: C, 59.0; H, 6.61; N, 12.6); lit.[3] (L- isomer) m.p. 245–248°, $[\alpha]^{20}D$ −50.5° (*c* 1, dimethylformamide).

The protected nonapeptide amide was treated with sodium in liquid ammonia, as employed in the original synthesis of oxytocin,[6] and the resulting disulfhydryl compound was oxidized in dilute aqueous solution with potassium ferricyanide.[7] After removal of ferrocyanide and ferricyanide ions with the ion-exchange resin AG3X4, in the chloride form, the solution gave a negative reaction to nitroprusside and to Ellman's reagent.[8] This solution of the crude material, on bioassay, did not appear to possess any avian-vasodepressor[9] or oxytocic[10] activity. The solution was concentrated to a small volume and subjected to countercurrent distribution in the system 1-butanol–1-propanol–0.5% aqueous acetic acid containing 0.1% pyridine (6:1:8).[11] The distribution pattern, as detected by determination of the Folin–Lowry color values,[12] was identical with that obtained for oxytocin in the same system. The material obtained from the main peak (K = 0.48) by lyophilization was a white fluffy powder, $[\alpha]^{20}D$ +22.2° (*c* 0.5, 1 *N* acetic acid) *Anal.* Calcd. for $C_{43}H_{66}N_{12}O_{12}S_2 \cdot C_2H_4O_2$: C, 50.6; H, 6.61; N, 15.8. Found: C, 50.2; H, 6.52; N,

(1) This work was supported in part by Grant HE-01675 from the National Heart Institute, U. S. Public Health Service.

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(12) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *ibid.*, **193**, 265 (1951).