immobilized enzyme stability. A review of the literature shows that enzymes have been immobilized for about 4 years, yet heretofore an immobilized enzyme could only be used continuously for 10–12 hr at or above room temperature without loss of activity.[9,10] Since the response of the urease electrode is not effected by cellophane coatings around the enzyme gel layer, it should be possible to trap a liquid enzyme layer in cellophane over the surface of an electrode sensor. Such enzymes containing membrane electrodes were first described by Clark and Lyons,[11] but no data were given with regard to response time and stability. Preliminary experiments have shown that a liquid layer of urease trapped in a double cellophane layer over a cation electrode may produce a useful enzyme electrode.

Finally, it is hoped that the primary disadvantage of the present electrode, namely the interference by Na^+ and K^+, can be overcome by the use of ion-exchange resins. Two approaches appear feasible: (1) the addition of 1 g of cation exchange to the solution, with stirring, before introduction of the electrode and (2) the placing of a cation-exchange resin membrane over the outside of the urease membrane in place of the cellophane. The latter would serve to both remove cations and help retain the enzyme urease.

Acknowledgment. The financial assistance of the National Science Foundation (Grant No. GM-12669) is gratefully acknowledged.

(9) G. P. Hicks and S. J. Updike, *Anal. Chem.*, **38**, 726 (1966).

(10) E. K. Bauman, L. H. Goodson, G. G. Guilbault, and D. N. Kramer, *ibid.*, **37**, 1378 (1965).

(11) L. C. Clark, Jr., and C. Lyons, *Ann. N. Y. Acad. Sci.*, **102**, 29 (1962).

Communications to the Editor

Solvent Assistance in the Solvolysis of Secondary Substrates. I. The 2-Adamantyl System, a Standard for Limiting Solvolysis in a Secondary Substrate

Sir:

The exact definition of the mechanistic details of the solvolysis of simple substrates has long presented difficulties, especially with regard to secondary systems.[1–7] Whereas primary substrates usually react by nucleophilic displacement (SN2,[2] N[3]) and tertiary substrates *via* carbonium ions (SN1,[2] **Lim**[3]), secondary systems often exhibit "borderline" behavior which has traditionally been described either by considering intermediate mechanisms or by assuming concurrent unimolecular and bimolecular pathways.[1–5]

More recently, several authors have presented data which were interpreted to show that intimate[8] and solvent-separated ion pairs intervene in the solvolysis of simple secondary substrates.[3,6,7,9] We feel that the degree to which solvent participates nucleophilically in the overall solvolytic process or in any of the component stages has not been clearly established for such substrates. Solvent must be closely involved at the backside, at least in the product-forming step, because the substitution product is now known to be virtually completely inverted.[5–7] In this initial set of communications, we are concerned solely with the degree to which the overall solvolysis rate (k_t) is affected by nucleophilic participation of the solvent.

We have recently provided experimental evidence[10] to support the thesis[11] that secondary β-arylalkyl systems can react by two discrete pathways: neighboring aryl assisted (k_Δ)[12] and solvent assisted (k_s).[12] This separation of pathways requires, if no crossover is to be observed, that *both* pathways, k_Δ and k_s, in competition

(1) Reviews: (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962; (b) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier, New York, N. Y., 1963; (c) E. R. Thornton, "Solvolysis Mechanisms," Ronald Press, New York, N. Y., 1964; (d) D. Bethell and V. Gold, "Carbonium Ions: An Introduction," Academic, New York, N. Y., 1967; (e) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 68–142.

(2) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter VII, p 418 ff; (b) M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 634 (1954).

(3) (a) S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, **73**, 2700 (1951); (b) A. F. Diaz, I. Lazdins, and S. Winstein, *ibid.*, **90**, 1904 (1968), and papers therein cited.

(4) V. Gold, *J. Chem. Soc.*, 4633 (1956).

(5) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966); N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc., B*, 355 (1968); M. Pánková, J. Sicher, M. Tichý, and M. C. Whiting, *ibid.*, 365 (1968).

(6) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 287, 292 (1965); R. A. Sneen and J. W. Larsen, *ibid.*, **88**, 2593 (1966); **91**, 362 (1969); **91**, 6031 (1969).

(7) A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, Jr., *ibid.*, **87**, 3682 (1965); A. Streitwieser, Jr., and T. D. Walsh, *ibid.*, **87**, 3686 (1965). Also see M. P. Balfe, W. H. F. Jackman, and J. Kenyon, *J. Chem. Soc.*, 965 (1954).

(8) Intimate carbonium ion pairs in such simple secondary systems should not be likened to free carbonium ions. In such ion pairs, significant bonding probably still exists between the charged fragments with the anion providing a great deal of specific or nucleophilic solvation. For this reason, it would probably be better not to represent such an ion pair in the conventional manner, R^+X^-, but as $R^{\delta+}\cdots X^{\delta-}$. R^+X^- suggests a similarity with R^+, but the two species can behave quite differently. The positive fragment of such ion pairs at best has only *some* "carbonium ion character"; it would perhaps be better to describe as "cationoid" the reactions of such species (H. C. Brown, private communication). That considerable bonding between partners in an ion pair exists is shown by the incomplete oxygen scrambling observed during ion-pair return (H. L. Goering and E. C. Linsay, *J. Amer. Chem. Soc.*, **91**, 7435 (1969), and references cited therein).

(9) V. J. Shiner, Jr., and W. Dowd, *ibid.*, **91**, 6528 (1969); V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969).

(10) C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291, 4296, (1969); C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *ibid.*, **91**, 4294 (1969); P. v. R. Schleyer and C. J. Lancelot, *ibid.*, **91**, 4297 (1969); *cf.* J. M. Harris, F. L. Schadt, P. v. R. Schleyer, and C. J. Lancelot, *ibid.*, **91**, 7508 (1969).

(11) (a) J. A. Thompson and D. J. Cram, *ibid.*, **91**, 1778 (1969); (b) A. F. Diaz and S. Winstein, *ibid.*, **91**, 4300 (1969), and references cited in both these papers. In general, the earlier workers *assumed* discreteness of pathways and used *product data* to partition the overall rate constants, *e.g.*, k_t, into Fk_Δ and k_s.[11b] We[10] provided independent methods to evaluate Fk_Δ and k_s kinetically and then showed that rate and product data were in agreement with one another.

(12) Definitions of these rate constants are found in paper III: P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, **92**, 2542 (1970).

Table I. Summary of Mechanistic Criteria for Solvolysis[a]

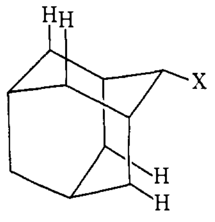
RX, R =	m (aqueous alcohol) X = Br	m (aqueous alcohol) X = OTs	$(k_{\text{aq alc}}/k_{\text{AcOH}})_Y$ X = Br	$(k_{\text{aq alc}}/k_{\text{AcOH}})_Y$ X = OTs	$k_{\text{OTs}}/k_{\text{Br}}$ 80% C_2H_5OH	$k_{\text{OTs}}/k_{\text{Br}}$ CH_3COOH
Methyl	0.22[b]	0.23 (75°)[c]		97 (75°)[c]	11 (50°)[d]	
Ethyl	0.34 (55°)[c,e]	0.25 (50°)[e]		70 (50°)[e]	10 (50°)[d]	
Isopropyl	0.43[f]	0.42	40 (50°)[e]	7.8	40 (50°)	470 (100°)[h]
Cyclohexyl		0.44		4.3		
2-Adamantyl	1.03	0.91	4.8	0.13	231	16,000
t-Butyl	0.94		3[e]		>4000[d]	
1-Bicyclo-[2.2.2]octyl	1.03		1.6		5000[g]	90,000
1-Adamantyl	1.08	0.99	4.2	0.16	9750	200,000

[a] All data at 25°, unless otherwise noted. [b] Reference 3a. [c] Reference 1a, p 64. [d] H. M. R. Hoffmann, *J. Chem. Soc.*, 6748, 6753, 6762 (1965). [e] S. Winstein, A. H. Fainberg, and E. Grunwald, *J. Amer. Chem. Soc.*, **79**, 4146 (1957). [f] E. D. Hughes, C. K. Ingold, and U. G. Shapiro, *J. Chem. Soc.*, 225 (1937), provide necessary data. [g] C. A. Grob, private communication. [h] For bromide rate, see W. C. Coburn, Jr., E. Grunwald, and M. P. Marshall, *J. Amer. Chem. Soc.*, **75**, 5735 (1953).

with one another be *strongly assisted.* If this interpretation is correct, it must follow that simple secondary substrates without neighboring groups, *e.g.*, isopropyl, should also solvolyze with *considerable nucleophilic solvent assistance* even in solvents such as acetic and formic acids. In view of conflicting opinion and lack of clear-cut definition of the nature of secondary solvolysis,[1,7,13] we have assembled new evidence pertaining to this question; this evidence supports our interpretation.[10]

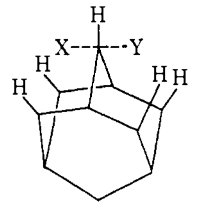
Tertiary compounds have traditionally been used to provide a model for "limiting"[3] (carbonium ion) behavior.[1–3] The correctness of this choice has been confirmed by the results of experiments on bridgehead systems for which neither nucleophilic nor electrostatic solvation is possible at the rear,[14] and participation seems highly unlikely. Despite this structural limitation, bridgehead systems and their acyclic counterparts behave analogously, as, for example, in their sensitivity to changes in solvent, as measured by the Grunwald–Winstein m values[1,3a,15] (Table I).

A secondary substrate disposed toward "limiting" (carbonium ion) behavior is needed as a model. This substrate should react by a k_c (anchimerically and nucleophilically unassisted)[12] pathway, *i.e.*, anchimeric as well as nucleophilic solvent participation should be absent. Suitable compounds are difficult to find. We have chosen the 2-adamantyl system[16] (I) for this purpose. Solvent participation should be absent because pentacovalent transition states or intermediates are strongly hindered by the axial hydrogens shown in II, since both nucleophile and leaving group suffer from severe nonbonded interactions. In contrast, such nonbonded interactions are absent in the corresponding trigonal carbonium ion intermediate, which should be reasonably open toward general, electrostatic solvation. At most, the transition states and ion pairs preceding this open cation could experience nonbonded interactions only on the leaving group side, but not on the backside. Anchimeric assistance also appears unlikely; neither rearrangement nor nonclassical ion formation can occur without appreciable increase in strain. Careful study has shown that less than 0.5% of rearranged products are formed in an acetolysis of 2-adamantyl tosylate under buffered conditions.[17] Elimination from I is ruled out because of the enormous strain which must be present in adamantene.[18]



I

X = OTs or Br



II

We have used three standard criteria to assess the sensitivity of the 2-adamantyl system to nucleophilic displacement by solvent: the "m" value,[1a,3a,14] the $(k_{\text{aq alc}}/k_{\text{AcOH}})$ ratio at constant Y,[1a,3a] and the tosylate/bromide leaving group rate ratio.[19] Table I summarizes the data and provides comparisons with primary, secondary, and tertiary (bridgehead and nonbridgehead) substrates. The marked contrast between the behavior of isopropyl derivatives and the corresponding 2-adamantyl compounds is immediately apparent. By every criterion, isopropyl behaves in a manner intermediate between primary and tertiary systems. We interpret this to indicate that much of the nucleophilic character of primary solvolysis is retained in the reaction of simple secondary systems, as exemplified by isopropyl.

The behavior of the 2-adamantyl derivatives (Table I) is unique for secondary systems. The m values are in the range found for tertiary compounds, the $(k_{\text{ROH}}/k_{\text{AcOH}})_Y$ ratios are among the lowest ever reported for the particular leaving groups used,[1a,3a] and the tosylate/bromide rate ratios tend toward the very high tertiary values.[20a] Furthermore, the 2-adamantyl system solvolyzes with excess retention over inversion,[20b] in

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(13) "The cases of the ethyl, isopropyl, and benzyl compounds belong to the N category in the aqueous alcohols, but some of these such as isopropyl p-bromobenzenesulfonate or bromide may approach the Lim. category in acetic acid and more closely in formic acid." [3a] "Formic acid is outstanding as an ionizing solvent and will promote dominating unimolecular reactions even of primary alkyl halides." [2a]

(14) P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 2700 (1961); R. C. Fort, Jr., and P. v. R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 283 (1966); D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, in press.

(15) E. Grunwald and S. Winstein, *ibid.*, 70, 846 (1948), and subsequent papers in the same series.

(16) P. v. R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 182 (1961).

(17) M. L. Sinnott, H. J. Storesund, and M. C. Whiting, *Chem. Commun.*, 1000 (1969); R. E. Hall, unpublished observations.

(18) R. C. Fort, Jr., and P. v. R. Schleyer, *Chem. Rev.*, **64**, 277 (1964); J. E. Nordlander, S. P. Jindal, and D. K. Kitko, *Chem. Commun.*, 1136 (1969).

(19) (a) C. H. DePuy and C. A. Bishop, *J. Amer. Chem. Soc.*, **82**, 2532 (1960); (b) Table I, footnote *d*.

(20) (a) NOTE ADDED IN PROOF. We are now of the opinion that tosylate/bromide ratios have limited mechanistic significance but are

striking contrast to the nearly complete inversion found with typical secondary systems.[5,7] In contrast to all other secondary systems for which data are available, 2-adamantyl exhibits more limiting character and provides a new standard against which the behavior of other secondary systems can be calibrated and reevaluated.[21] The following papers present further evidence and methods for estimating the magnitude of solvent participation.[12,23]

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dominated by steric effects involving the tosylate but not the bromide leaving group. We attribute the very high tertiary values to relief of ground-state tosylate nonbonded strain. (b) J. A. Bone and M. C. Whiting, *Chem. Commun.*, 115 (1970), work with *syn-* and *anti* 5-methyl-2-adamantyl tosylates. We thank Professor Whiting for communicating results prior to publication.

(21) It now seems necessary to reexamine the basis for the success of the Foote–Schleyer relationship.[22]

(22) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964); P. v. R. Schleyer, *ibid.*, **86**, 1854, 1856 (1964).

(23) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *ibid.*, **92**, 2540 (1970).

(24) National Institutes of Health Postdoctoral Fellows: (a) 1967–1969; (b) 1969–1970; (c) 1968–1970.

(25) National Institutes of Health Predoctoral Fellows: (a) 1967–1968; (b) 1968–1970.

(26) American Can Company Fellow, 1966–1967; Ph.D. Thesis, Princeton University, 1970.

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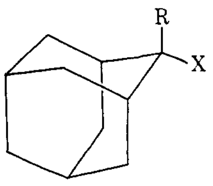
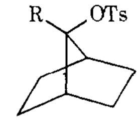
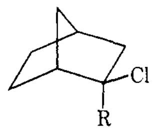
Solvent Assistance in the Solvolysis of Secondary Substrates. II. The α-Methyl/Hydrogen Rate Ratio for the 2-Adamantyl System

Sir:

According to the results of three standard tests to delineate the nature of solvolysis, secondary 2-adamantyl derivatives (I) behave like tertiary systems and quite unlike typical secondary substrates (isopropyl, cyclohexyl, etc).[1] This behavior has been attributed to a basic difference with respect to the magnitude of nucleophilic solvent participation: large in ordinary, unhindered secondary (and primary) systems and small or absent in crowded substrates such as 2-adamantyl and tertiary derivatives.[1] We report here the results of a fourth diagnostic test, the effect of α-methyl substitution.


I, R = H
II, R = CH_3
IIa, R = other


III, R = H or CH_3


IV, R = H or CH_3

The variation of behavior along the series methyl, ethyl, isopropyl, *t*-butyl has always played an important role in mechanistic studies of the solvolysis reaction: for SN2 processes the rates fall along the series, whereas for SN1 reactions they rise sharply.[2] In a similar manner, the effect on reaction rate produced by substitution of a methyl group for a hydrogen atom at the reaction site has become an important mechanistic tool to probe for charge delocalization in the transition state of a solvolysis reaction.[2,3] The theory is direct and reasonable. A tertiary cation is considerably more stable than a secondary ion; hence the latter should benefit more than the former from stabilization by resonance or by neighboring group participation in the solvolysis transition state. Thus, once a "normal" α-CH_3/H rate ratio has been established, downward deviations from this "normal" value have been taken to indicate that charge delocalization is less in the methyl-substituted compound than in the parent.[2,3]

This diagnostic tool is only valid, however, when k_c*-type*[1] *(carbonium ion) behavior is involved.* If there is significant nucleophilic solvent assistance in the solvolysis of secondary derivatives, then α-CH_3/H rate ratios will not be reliable criteria for intramolecular charge delocalization. The extent of such solvent assistance will vary not only with the conditions, but also from substrate to substrate. For this reason it is important to establish what the *limiting* value of the α-CH_3/H rate ratio should be.

Following Winstein and Marshall,[2b] Streitwieser[2c] estimated 10^6 to be "the minimum stabilization of a tertiary carbonium ion relative to a secondary in a limiting solvolysis."[4] This value, widely quoted,[2,3] seems generally to have been accepted because (until recently) it had never been exceeded experimentally for any system.[2,3] For example, the highest α-CH_3/H rate ratio ever reported for an unstrained system is the value $10^{5.6}$ for formolysis of isopropyl- *vs.* ethylmercuronium perchlorates.[2d]

Theoretically, an even higher value than 10^6 (8.3 kcal/mol at 25°) may be expected. From gas-phase values,[2e,6a] energy differences in the range 12–16 kcal/mol (equivalent to α-CH_3/H rate ratios of 10^9–10^{12}) are found for corresponding tertiary and secondary

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(1) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970), preceding paper.

(2) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter VII, p 418 ff; (b) S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952); (c) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962; (d) F. R. Jensen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **85**, 363 (1963); (e) D. Bethell and V. Gold, "Carbonium Ions: An Introduction," Academic, New York, N. Y., 1967; (f) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 68–142.

(3) (a) S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.*, 70, 828 (1948). For recent, leading references, see: (b) E. F. Fox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961); (c) H. C. Brown and M. H. Rei, *ibid.*, **86**, 5008 (1964); H. C. Brown, *Chem. Brit.*, **2**, 199 (1966); (d) T. Tsuji, I. Moritani, S. Nishida, and G. Tadokoro, *Bull. Chem. Soc., Jap.*, **40**, 2344 (1967); (e) H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *J. Amer. Chem. Soc.*, **89**, 2928 (1967); (f) K. L. Servis, S. Borčić, and D. E. Sunko, *Tetrahedron*, **24**, 1247 (1968).

(4) This estimate, based on the formolysis rates of *t*-butyl *vs.* isopropyl bromide, was very crude, due to the unavailability of the necessary data at that time. Using better but still incomplete data,[5] a ratio of $10^{5.34}$ can be estimated at 25°.

(5) (a) S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, **73**, 2700 (1951); (b) A. H. Fainberg and S. Winstein, *ibid.*, **79**, 1602 (1957); (c) E. D. Hughes, C. K. Ingold, and U. G. Shapiro, *J. Chem. Soc.*, 225 (1936).

(6) G. A. Olah and P. v. R. Schleyer, Ed., "Carbonium Ions," Vol. I, Interscience, New York, N. Y., 1968: (a) J. L. Franklin, Chapter 2, p 85; (b) E. M. Arnett and J. W. Larsen, Chapter 12, p 441.