Reactivity–Selectivity Relationships. Part 7.[1a] Solvent Effects on the Selectivity of Adamantyl Derivatives in Aqueous Ethanol

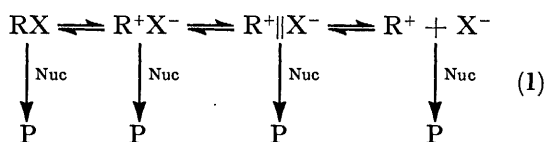By Yishai Karton and Addy Pross,* Department of Chemistry, Ben Gurion University, Beer Sheva, Israel

The influence of solvent composition on the selectivity (k_W/k_E) of adamantyl derivatives toward ethanol and water is investigated. Variations in the proportions of ethanol and water in binary mixtures were found to have little effect on substrate selectivity. Addition of acetone, however, to a 60% aqueous ethanol solution is found to increase substrate selectivity. These results are interpreted as evidence for a change in the relative nucleophilicity of ethanol and water in different solvent compositions. The implication of these results for octyl, benzyl, and diphenylmethyl systems is discussed.

IN previous papers of this series an attempt was made to understand the way in which changes in solvent ionizing power may influence the selectivity of solvolytic intermediates.[1,2]

In these studies the selectivity of octyl,[1] benzyl,[1] and diphenylmethyl[2] derivatives during solvolysis toward the competing nucleophiles, ethanol and water, was studied as a function of solvent ionizing power as measured by Winstein–Grunwald Y values. For all substrates, it was found that an increase in solvent ionizing power brought about a corresponding increase in selectivity.[1,2]

This general observation was attributed to one or more of three possible alternatives. (a) An increase in solvent ionizing power is expected to stabilize solvolytic intermediates in which substantial charge formation has occurred. This increase in stability is likely to induce a corresponding increase in selectivity; that is, the stabilized intermediate is expected to show greater discriminating ability in its reaction with a number of competing nucleophiles. This relationship between the reactivity and the selectivity of a chemical species is anticipated from the reactivity–selectivity principle (r.s.p.).[3]

(b) A change in solvent ionizing power is expected to vary the relative proportion of the solvolytic species undergoing product formation [equation (1)].[4] In more strongly ionizing media greater formation of more dissociated species is likely before nucleophilic attack takes place. Since each solvolytic species is expected to possess different intrinsic selectivity, the observed

$$\text{RX} \rightleftharpoons \text{R}^+\text{X}^- \rightleftharpoons \text{R}^+\|\text{X}^- \rightleftharpoons \text{R}^+ + \text{X}^-$$

$$\qquad\qquad\qquad\qquad\qquad\qquad (1)$$

selectivity, which represents an average value for all species undergoing product formation, is expected to change as the relative contribution of each species to the overall selectivity varies.[4]

(c) Changes in the reaction media influence not only the reactivity (and hence selectivity) of the solvolytic substrates but may influence the reactivity of the

medium itself at the molecular level. In other words, the relative reactivity of the components of the reaction medium may vary with changes in the medium composition. This means that changes in substrate selectivity may take place as a result of changes in relative nucleophilicity of the solvent components, this being in addition to any selectivity changes induced in the substrate itself.

The multiplicity of possible explanations to rationalize the effect of solvent composition on substrate selectivity is confusing and makes the use of this tool in analysing solvolytic mechanism somewhat uncertain. To a large extent this uncertainty stems from the fact that several solvolytic intermediates may be involved in the product-determining step. Our aim in this work is to clarify this uncertainty by studying solvolytic substrates which form products predominantly, if not exclusively, from one solvolytic intermediate only. In such a case the influence of solvent polarity on that species may be established more readily. Once such understanding is achieved, more complex systems in which more than one species are present during solvolysis, may be more clearly understood. In practice, however, substrates which solvolyse unequivocally through just one species are at present limited. However, one such class of compounds which does exist, consists of polycyclic alkyl derivatives which are hindered to back side attack. Examples of this class are 1- and 2-adamantyl derivatives. These compounds cannot form products via nucleophilic attack on neutral substrate or intimate ion pair since such a pathway requires attack from the rear, a process which has been shown to be highly unlikely for 2-adamantyl derivatives and is clearly impossible for 1-adamantyl substrates. Since the formation of the free carbocation is not energetically feasible for un-activated alkyl groups, the sole remaining pathway consists of nucleophilic attack on the solvent separated ion pair. These compounds, therefore, represent potentially excellent models for determining the influence of solvent polarity on the solvent separated ion pair and is the subject of the present study.

RESULTS AND DISCUSSION

Adamantyl Derivatives.—The selectivity of a series of typical 1- and 2-adamantyl halides and arenesulphonates

[1] (a) Part 6, A. Pross, H. Aronovitch, and R. Koren, *J.C.S. Perkin II*, 1978, 197; (b) A. Pross and H. Aronovitch, *J.C.S. Chem. Comm.*, 1976, 817.
[2] Y. Karton, and A. Pross, *J.C.S. Perkin II*, 1977, 1860.
[3] A. Pross, *Adv. Phys. Org. Chem.*, 1977, 14, 69.
[4] J. M. Harris, D. C. Clark, A. Becker, and F. A. Walden, *J. Amer. Chem. Soc.*, 1974, 96, 4478.

were examined as a function of variable solvent composition and temperature. Substrates were solvolysed in aqueous ethanol solutions (50—95% v/v) as well as ternary aqueous ethanol–acetone mixtures and the selectivity, S, of the ion pair intermediate toward competitive nucleophilic attack by ethanol and water determined by examination of the product ratio, adamantanol : adamantyl ether, using g.l.c. The selectivity values were obtained using equation (2),[4] where

$$S = k_W/k_E = \frac{[\text{adamantanol}][\text{ethanol}]}{[\text{adamantyl ether}][\text{water}]} \quad (2)$$

k_W and k_E are the specific rate constants for reaction of the ion pair species with water and ethanol respectively. The data for aqueous ethanol–acetone mixtures are

TABLE 1

Selectivity [a] of adamantyl derivatives in 60% aqueous ethanol–acetone solutions at 75°

	% Acetone (v/v) [b]				
Substrate	0	20	40	60	80
1-Adamantyl bromide	1.76	1.90	2.06	2.23	
2-Adamantyl tosylate	1.74	1.95	2.21	2.50	3.08
2-Adamantyl p-nitrobenzene-sulphonate	1.79	1.98	2.18	2.61	3.11

[a] Selectivity defined as k_W/k_E and evaluated using equation (2). Error is estimated as $\pm 5\%$. [b] Solutions made up using $x\%$ acetone and $(100 - x)\%$ 60% aqueous ethanol.

TABLE 2

Selectivity [a] of adamantyl derivative in aqueous ethanol solutions at 100°

	% Ethanol (v/v)					
Substrate	50	60	70	80	90	95
1-Adamantyl bromide	1.65 [b]	1.76 [b]	1.89	1.89	1.82	1.72
2-Adamantyl tosylate		1.75, 1.74 [b]	1.89	2.05	2.05	2.00
2-Adamantyl p-nitrobenzene-sulphonate			1.79	1.90	2.17	2.17	1.95
2-Adamantyl bromide	1.62	1.69	1.77	1.77	1.64	1.56
1-Adamantyl chloride	1.82	1.95	2.02	1.98	1.90 [c]	1.77 [c]

[a] Selectivity defined as k_W/k_E and evaluated using equation (2). Error is estimated as $\pm 5\%$. [b] Data obtained at 75°. [c] Data obtained at 100°.

listed in Table 1 and for aqueous ethanol in Table 2. The effect of temperature on 1-adamantyl bromide selectivity is listed in Table 3.

For all solutions studied k_W/k_E values were found to be >1, $i.e.$, in all cases water exhibits greater nucleophilicity than ethanol. This inversion in the relative nucleophilicity of ethanol and water from that generally observed has been previously reported for the solvolysis of 2-adamantyl arenesulphonates in 70% aqueous ethanol[5] and is considered to be indicative of product formation through front side attack in the solvent separated ion pair. Since back side attack on neutral substrate and intimate ion pair is either highly unlikely (for the 2-adamantyl derivative) or impossible (for the

[5] J. M. Harris, A. Becker, J. F. Fagan, and F. A. Walden, *J. Amer. Chem. Soc.*, 1974, **96**, 4484.

1-adamantyl derivative), and since the formation of free carbocations is energetically unfavourable, product formation is considered to be almost exclusively from

TABLE 3

Selectivity [a] of 1-adamantyl bromide in aqueous ethanol at 50, 75, and 100°

	Temperature (°C)		
	50	75	100
50% Ethanol	1.69	1.65	
60% Ethanol	1.77	1.76	
70% Ethanol	1.82	1.82	1.89
80% Ethanol	1.89	1.89	1.89
90% Ethanol		1.77	1.82
95% Ethanol		1.71	1.72

[a] Selectivity defined as k_W/k_E and evaluated using equation (2). Error is estimated at $\pm 5\%$.

collapse of solvent separated ion pairs. Stereochemical studies by Bone and Whiting [6] on substituted adamantyl derivatives support this conclusion.
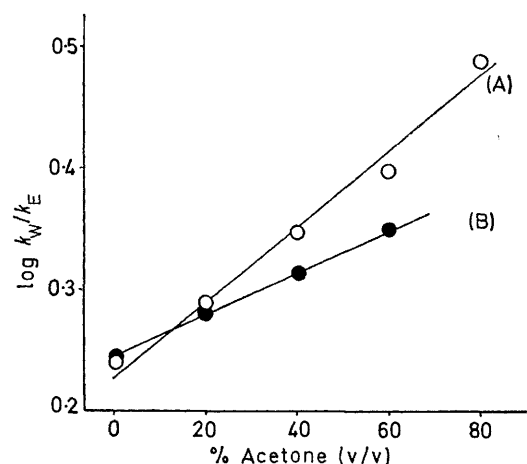

FIGURE 1 Effect of added acetone to the selectivities of (A) 2-adamantyl tosylate and (B) 1-adamantyl bromide in 60% aqueous ethanol at 75°

The selectivity data at various temperatures for 1-adamantyl bromide listed in Table 3 indicate the absence of a significant temperature effect. This means that $\Delta\Delta H^{\ddagger}$, the enthalpy of activation difference for ethanol and water attack in the product-determining step, must be close to zero. The implication is therefore that activation enthalpies for both ethanol and water attack in the product-determining step must be small such that their difference approaches zero.

The significant result regarding the data in Table 1 is that the addition of acetone to a 60% aqueous ethanol mixture brings about an increase in substrate selectivity, $i.e.$ the relative nucleophilicity of water compared to ethanol toward all substrates studied is enhanced in the less polar media. This is discernible in a plot of log S against % acetone shown in Figure 1.

This solvent effect on selectivity may now be examined in the light of the three possible explanations (a)—(c), proposed earlier to rationalize this behaviour.

The possibility that effect (a) is responsible, $i.e.$ that

[6] J. A. Bone and M. C. Whiting, *Chem. Comm.*, 1970, 115.

the change in selectivity results from changes in substrate stabilization in solvents of variable polarity may be eliminated. This is because for adamantyl derivatives the observed change in substrate selectivity is in the opposite direction to that predicted on the basis of reactivity–selectivity considerations. Additions of acetone to aqueous ethanol mixtures brings about a reduction in solvent polarity, which is expected to destabilize the ion pair intermediate and consequently to reduce the observed selectivity (k_{W}/k_{E}). This is directly opposed to the experimental observation. Clearly some other factor is responsible for the increased selectivity observed in less polar media.

As was mentioned earlier, the choice of adamantyl derivatives was made in order to ensure predominant product formation from one intermediate only. This choice rules out the possibility that the variation in substrate selectivity in different media is due to a change in the proportion of various solvolytic species undergoing attack to form products [effect (b)].

We conclude therefore that two of the three possible explanations proposed earlier to rationalize the selectivity dependence on solvent may be eliminated by the study of adamantyl derivatives. Consequently, it appears that at least for adamantyl substrates it is effect (c), the variation in the relative nucleophilicity of water and ethanol, that brings about the observed change in substrate selectivity. What this means is that the addition of acetone to aqueous ethanol enhances water nucleophilicity relative to ethanol nucleophilicity and that the selectivity variation is entirely due to a solvent effect.
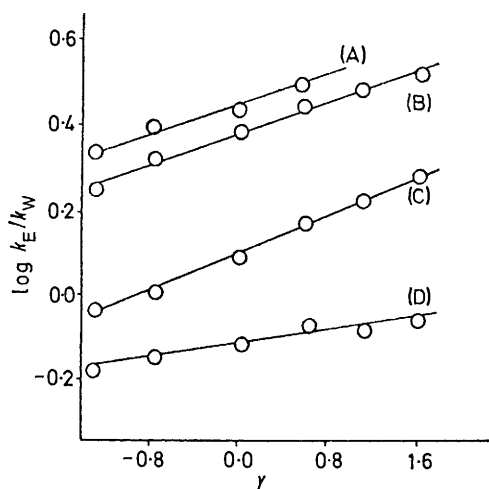

FIGURE 2 Plot of the logarithm of selectivity against Y values of aqueous ethanol mixtures for (A) diphenylmethyl chloride; (B) benzyl chloride; (C) octyl chloride; (D) 1-methylheptyl chloride (data from refs. 1 and 2)

It is hazardous to attempt to ascertain the precise nature of this effect. The fact that the variation in selectivity is not a direct function of solvent polarity, for example, may be shown by examination of the data in Table 2. It is apparent that changing the composition of the aqueous ethanol system has no marked

effect on the selectivity observed for all substrates studied. The selectivities observed in 50 and 95% aqueous ethanol are almost the same with a consistent tendency for all substrates to show slightly higher selectivity in the intermediate composition range. It would appear therefore that the addition of ethanol to
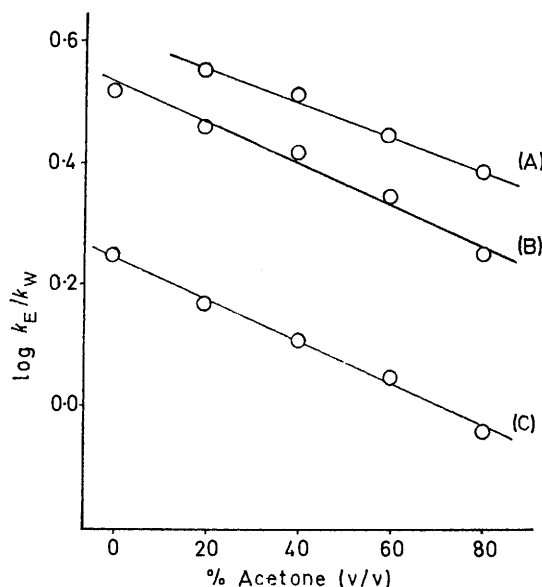

FIGURE 3 Effect of added acetone on the selectivities of (A) diphenylmethyl chloride; (B) benzyl chloride; (C) octyl bromide in 50% aqueous ethanol (data from refs. 1 and 2)

50% aqueous ethanol has little influence on the relative nucleophilicity of ethanol and water. So while we do not wish to speculate as to the precise nature of the interaction which leads to the change in the relative nucleophilicities of ethanol and water on addition of acetone to aqueous ethanol, we believe the selectivity variations themselves may be reliably assumed to be due to a solvent effect rather than to a substrate–solvent interaction.

In the light of this conclusion it is of interest to re-examine the selectivity behaviour exhibited by octyl,[1] benzyl,[1] and diphenylmethyl [2] derivatives in different solvent mixtures. This is illustrated for variable aqueous ethanol mixtures in Figure 2 and for acetone–aqueous ethanol mixtures in Figure 3.

It is apparent that all systems show remarkably similar behaviour within either solvent system. For example, in Figure 3 the selectivities of diphenylmethyl, benzyl, and octyl chlorides respond almost identically to the addition of acetone to a 50% aqueous ethanol solution. Since the species involved during product formation for these three substrates differ considerably both in structure and in energy it appears unlikely that the change in selectivity results from changes in solvent stabilization of the solvolytic species undergoing product formation [effect (a)]. This is because such stabilization would be expected to differ significantly for each substrate. Similarly, it appears unlikely that the variation in selectivity in different solvents is due to effect (b),

i.e. a change in the quasi-equilibrium established between the solvolytic species which undergo product formation. It would be remarkably fortuitous for the variation in all substrates to be so similar as illustrated in Figures 2 and 3, since entirely different solvolytic species are involved during the solvolysis of each substrate. We therefore do not accept Harris' contention [4] that a change in selectivity with solvent composition constitutes proof for the intervention of at least two solvolytic intermediates such as those illustrated in the Winstein solvolysis scheme [equation (1)]. Rather, we believe that the behaviour we have noted is evidence for a change in the relative nucleophilicities of ethanol and water as the solvent composition is varied. We conclude therefore that for the substrates examined in this and earlier studies that solvent effects are primarily responsible for the variations in selectivity that are observed.

One final point requires clarification. Whereas the influence of acetone on substrate selectivity is identical for all substrates including adamantyl derivatives, the influence of variations of ethanol and water in the binary mixtures is different for adamantyl derivatives compared to those substrates illustrated in Figure 2. While octyl, 1-methylheptyl, benzyl, and diphenylmethyl derivatives responded in such a way that ethanol nucleophilicity increased in more aqueous mixtures, the adamantyl derivatives showed little variation over the entire composition range (Table 2). This discrepancy may be explained by the fact that nucleophilicity is not a fixed property but is greatly dependent on the nature of the species with which the nucleophile reacts, and that even the order of relative nucleophilicity is substrate dependent. What this means is that nucleophilicity is determined by a large number of parameters and that the relative importance of these parameters changes considerably from substrate to substrate. The nucleophilic properties of ethanol and water are quite different when attack takes place from the front side of the substrate *via* collapse of the solvent separated ion pair and when back side displacement occurs. This is most simply demonstrated by the observation that when attack occurs from the front side, water exhibits

the greater nucleophilic character, while during back side attack the reverse is true. It appears that the greater acidity of water relative to ethanol is largely responsible for this inversion in the normal nucleophilic order, due to the increased ability of water to stabilize the leaving group by hydrogen bonding.[4,7] We may thus speak about back and front side nucleophilicity as quite different parameters which are not simply correlated and which are influenced by a different set of molecular properties. Under such circumstances the effect of solvent changes on back and front side nucleophilicities need not be identical and there is no real contradiction in the observation that adamantyl selectivities (determined by front side nucleophilicity, $k_W/k_E > 1$) and the selectivity of benzyl, diphenylmethyl, and octyl substrates (determined by back side nucleophilicity, $k_W/k_E < 1$) respond differently to solvent changes.

EXPERIMENTAL

Materials.—Adamantyl bromides were commercially available. 1-Adamantyl chloride was prepared by reaction of 1-adamantanol and thionyl chloride.[8] 2-Adamantyl tosylate was prepared by reaction of 2-adamantanol and tosyl chloride.[9] Lutidine was distilled and stored over potassium hydroxide pellets or molecular sieves. Analytical grade absolute ethanol and acetone (Merck) were stored over molecular sieves and used directly.

Product Determination.—Reactions were performed in pressure tubes containing substrate (0.01M), lutidine as base (0.013M), and solvent (5 ml). Reactions were conducted in thermostatted oil-baths (± 0.05 °C) for 10—20 half-lives. For all materials, product ratios were established as stable under the reaction conditions. 2-Adamantyl product ratios were determined by response calibrated g.l.c. on a 1.5 m × 1/4 in glass column packed with a mixture of 3% OV 17 and 0.3% Carbowax 20M on 80—100 mesh Chromasorb WAW DMCS. 1-Adamantyl product ratios were determined on a 1.5 m × 1/4 in copper column packed with 5% SF 96 on Anakron ABS. Results are the average of between two and four determinations on at least duplicate runs. An error of 5% is estimated for product ratios.

[7] A. Pross, *Tetrahedron Letters*, 1975, 637.

[8] P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, **83**, 2700.

[9] M. Fieser and L. F. Fieser, ' Reagents for Organic Synthesis ', Wiley, New York, 1967.