Absence of S_N1 Involvement in the Solvolysis of Secondary Alkyl Compounds

Thomas J. Murphy
Department of Chemistry, DePaul University, Chicago, IL 60614; *tmurphy@depaul.edu*

One of the more complex and difficult topics in introductory organic chemistry is the mechanism of nucleophilic substitution reactions at saturated carbons. The complexity is due in large part to the occurrence of two different reaction mechanisms termed S_N1 and S_N2 and the variety of conditions that can affect the course of these reactions. Fortunately, reactions under normal conditions at methyl, primary, and tertiary carbons are straight forward: methyl and primary substrates react only via the S_N2 mechanism and tertiary substrates react only via the S_N1 mechanism. The difficulty occurs for reactions at secondary carbons, as demonstrated by the treatment of this topic in different introductory textbooks. For example, *Organic Chemistry* by Solomons and Fryhle *(1)* states, "...only tertiary halides react by an S_N1 mechanism", while *Organic Chemistry* by Bruice *(2)* states that typical secondary compounds can react by either or both mechanisms. Bruice illustrates this in an example problem with a rate law for determining how much 2-bromobutane reacts by an S_N2 mechanism and by an S_N1 mechanism at 30 °C in 75% ethanol. The equation,

$$\text{Rate} = \left(3.2 \times 10^{-5}\right)[\text{RBr}][\text{OH}^-] + \left(1.5 \times 10^{-6}\right)[\text{RBr}]$$

predicts that a solvolysis reaction run in neutral or acid solution, with no hydroxide or other nucleophile present, would go exclusively by the S_N1 mechanism.

Clearly the descriptions in these textbooks cannot both be correct about the course of this reaction. Other textbooks typically take an intermediate approach, including significant S_N1 involvement in the nucleophilic substitution reactions of many saturated secondary systems. One of the downsides of the current situation, in addition to dealing with the complexity of competing mechanisms, is that students using the Solomons and Fryhle textbook versus the Bruice textbook would probably answer examination questions based on this topic differently. Confusion over the course of these reactions dates to the early work by Edward Hughes, Christopher Ingold, and their co-workers. A review of their experiments, results, and interpretations, and also of more recent evidence for the mechanistic course followed in nucleophilic substitution reactions at secondary carbons could serve to resolve the complexities and give a more definitive answer to this topic.

Hughes, Ingold, and Co-Workers

In the late 1930s, Hughes, Ingold, and their co-workers published a number of papers describing their investigations on the mechanisms of substitution reactions at saturated carbons. They concluded that these reactions occurred by two different mechanisms, initially distinguished by their kinetic order. They proposed mechanisms to explain the kinetics and products of these reactions: (i) the S_N1 mechanism, eq 1, for first-order reactions that involved a slow ionization of the substrate, RX, to form a carbenium ion, R^+, and its rapid reaction in a second step with a nucleophile, N^-, to form the substituted product, RN, and (ii) the S_N2 mechanism, eq 2, that involved the reaction of a nucleophile and the substrate in the transition state of a one-step reaction leading to a substituted product.

$$\text{R—X} \longrightarrow \text{X}^- + \text{R}^+ \quad \text{then} \quad \text{R}^+ + \text{N}^- \longrightarrow \text{R—N} \quad (1)$$

$$\text{N}^- + \text{R—X} \longrightarrow \text{N—R} + \text{X}^- \quad (2)$$

The hypothesis of Hughes and Ingold and their collaborators was that alkyl substrates underwent nucleophilic substitution by these two different mechanisms and that as we pass along the series from methyl to primary to secondary and then to tertiary substrates there is a change in mechanism from S_N2 to S_N1. In 1969 this variation in mechanism, kinetic order, and rate was illustrated in the Ingold textbook with a diagram (*3,* p 430) showing the different relative proportions of mechanisms for the four classes of alkyl compounds. The diagram indicated that methyl compounds typically underwent substitution ≈98% by S_N2, primary compounds ≈80% by S_N2, secondary compounds ≈45% by S_N2, and tertiary compounds ≈15% by S_N2, with the remainder in each case going via the S_N1 mechanism. With the caveat that the detailed placing of the points would depend on the nucleophile, leaving group, and the solvent, "...the dividing line between S_N1 and S_N2 is usually located between the primary and secondary alkyl groups."

A series of thirteen papers by Hughes, Ingold, and their coworkers were published together in the *Journal of the Chemical Society* in 1937; pp 1177–1291. These papers discussed the results of a number of their studies dealing with nucleophilic substitution and elimination at saturated carbons, and constituted much of their evidence for the mechanisms by which these transformations took place. The tenth paper in this series, "Relation of Steric Orientation to Mechanism in Substitutions Involving Halogen Atoms and Simple or Substituted Hydroxyl Groups" *(4),* presents a discussion and conclusions on the mechanisms for substitution at secondary carbons. Their conclusions rely on results reported in other papers in this series and on prior papers, particularly Hughes et al. *(5)* and Cowdrey et al. *(6).*

Their scheme to determine the partitioning of substitution in secondary substrates between S_N1 and S_N2 mechanisms involved running the reaction with and without added nucleophile. In these studies, bromide ion was their usual leaving group and hydroxide was the common nucleophile. *They assumed that the reaction in ethanol/water mixtures in the absence of a nucleophile that followed first-order kinetics went via the S_N1 mechanism:*

> In acid solution the two bimolecular reactions {substitution and elimination} became negligible, leaving the unimolecular substitution (S_N1) in control. *(7)*

The reaction that occurred with a nucleophile present then involved both the second-order reaction with the nucleophile and the first-order reaction with the solvent and was kinetically

more complicated. However, by using the data from the reaction without hydroxide present, Hughes et al. were able to determine both the first- and second-order rate constants. The overall rate of the reaction then was a linear combination of the first- and second-order reactions as in the example above from Bruice *(2)*. Their data for the determination of the first- and second-order rate constants for the solvolysis of 2-bromooctane in 60% ethanol/40% water at 80 °C *(8)* are shown in Figure 1.

The confusing and complicating issue with these papers is that they equate the kinetic order of a reaction with the molecularity of the reaction transition state. Thus all kinetically first-order reactions are *assumed* to follow the S_N1 mechanism:

> ...because it is our view that the rate determining process of all of them {substitution and elimination} is one and the same, viz., the electrolytic dissociation of the alkyl halide. (*8,* p 1193)

Interestingly, at the same time Hughes and co-workers were equating first-order reactions with the unimolecular mechanism, they were fighting a vigorous defense in print *(9)* of the distinction between kinetic order and molecularity against a continuing adversary, William Taylor *(10)*.

Solvolysis reactions, "pseudo first-order" reactions, were not mentioned or discussed in the other papers where "S_N1" is exclusively used to refer to nucleophilic substitution reactions of secondary substrates in neutral or acidic alcohol or aqueous solvents. In subsequent work Hughes, Ingold, and co-workers did discuss the possibility of distinguishing S_N1 and S_N2 reactions using techniques that they had developed and reported earlier in support of their mechanistic proposals. These involved the stereochemistry of the reactions at chiral centers *(4,* p 1259; *11)*.

In the paper that is probably the cause of much of the confusion about substitution at secondary carbons, Hughes et al. *(5)* reported the results of the solvolysis reaction of optically active 2-bromooctane with hydroxide in initially neutral 60% ethanol/water. They reported that the alcohol product showed an enantiomeric excess (ee) of 66% of the inverted product, when corrected for racemization of the starting material before reaction (Figure 2). This result is not consistent with their assumption that solvolysis reactions go via an S_N1 mechanism and yield essentially racemic products. They did not discuss the observed stereospecificity of this solvolysis reaction and when they mentioned it, they used the uncorrected 35% ee (Figure 2) result.

There were a number of complications in this experiment, however, only some of which Hughes et al. were aware of and claimed to correct.

1. The reaction was run before they had a good rate constant from the racemic mixture. The reaction had an overall half-life of about 3.7 hours at 80 °C *(8),* but they ran the reaction for a total of 72 hours at 80 °C, >19 half-lives.

Table II.

Initially, [β-*n*-$C_8H_{17}Br$] ~ *N*/20 and [NaOH] = 0. [β-*n*-$C_8H_{17}Br$] expressed in c.c. of 0·025*N*-$AgNO_3$ per 10 c.c. of reaction mixture; k_1 is in hours^{-1}.

t (hrs.)	0·00	0·65	1·00	1·71	2·40	3·90	5·40	6·90	8·65
[β-*n*-$C_8H_{17}Br$]	20·55	18·30	16·90	14·90	13·20	9·90	7·60	5·60	4·00
10^3k_1	—	178	195	188	184	187	184	188	189

The Total Second-order Reaction.—The method of calculating the second-order constant from observations of the total reaction is the same as that described for the *iso*propyl halides (J., 1936, 225; this vol., p. 1177). In Table III, k_2 is the bimolecular "constant" calculated from the formula

$$K_2 = \frac{1}{t(b-a)} \cdot \log_e \frac{b(a-x)}{a(b-x)}$$

where *a* and *b* are the initial concentrations of β-*n*-octyl bromide and sodium hydroxide respectively, and *x* is the decrease in concentration after time *t*. "Corr. k_1" = $k_1(b-x)$ signifies the correction (due to the simultaneous unimolecular reaction, rate constant = k_1) which must be applied to K_2 in order to deduce the true second-order constant k_2. K_2 and k_2 are in l./g.-mol.-hour.

Table III.

Initially, [β-*n*-$C_8H_{17}Br$] ~ 0·05*N* and [NaOH] = 0·8*N*. [β-*n*-$C_8H_{17}Br$] and [NaOH] expressed in c.c. of 0·025*N*-$AgNO_3$ per 10 c.c. of solution.

t (hrs.).	[β-*n*-$C_8H_{17}Br$].	[NaOH].	K_2.	"Corr. k_1."	k_2.	*t* (hrs.).	[β-*n*-$C_8H_{17}Br$].	[NaOH].	K_2.	"Corr. k_1."	k_2.
0·00	20·75	321·00	—	—	—	0·250	11·20	311·45	3·13	0·24	2·89
0·050	18·45	318·60	2·96	0·23	2·73	0·300	9·90	310·15	3·14	0·24	2·90
0·100	16·20	316·45	3·12	0·24	2·88	0·367	8·50	308·75	3·10	0·24	2·86
0·133	15·00	315·25	3·07	0·24	2·83	0·483	6·45	306·70	3·10	0·24	2·86
0·160	13·80	314·05	3·09	0·24	2·85	0·633	4·70	304·95	3·02	0·25	2·77
0·200	12·70	312·95	3·11	0·24	2·87	0·750	3·40	303·65	3·32	0·25	3·06
										Average	2·86

Figure 1. Kinetic data for the reaction of 2-bromooctane in 60% ethanol/40% water (vol; X_{water} = 0.68) at 80°, without and with hydroxide present. k_1 (h^{-1}) is the first-order rate constant determined for the reaction with [NaOH] = 0.0 M; K_2 (L g-mol^{-1} h^{-1}) is the overall rate constant for the reaction with initial [NaOH] = 0.8 M; k_2 (L g-mol^{-1} h^{-1}) is the second-order rate constant for the hydroxide substitution reaction. It is K_2 corrected for the simultaneous first-order reaction. (Note that g-mol is equivalent mol.) (Hughes, E. D.; Shapiro, U. G. *J. Chem. Soc.* **1937,** 1192–1196. Reproduced by permission of The Royal Society of Chemistry).

2. In general, Hughes and Ingold published the kinetic data for most of their reactions, as in Figure 1, allowing one to check their conclusions, to use their experimental data to test other hypotheses, and so forth. For instance, in this series of 13 papers, they included detailed experimental kinetic data on more than 75 reactions. This is one of the few, perhaps the only, significant reaction in their papers for which they did *not* publish experimental data to demonstrate the effectiveness and thoroughness of the numerous necessary corrections required.
3. The starting 2-bromooctane undergoes an S_N2 reaction with the product bromide ions, causing racemization before hydrolysis. The rate of this second-order reaction is zero at the start of the reaction, $[Br^-] = 0$, and increases as the solvolysis reaction proceeds and the bromide ion concentration increases. It reaches a maximum rate at one half-life when the substrate and bromide concentrations are equal and declines slowly thereafter.

   Hughes et al. demonstrated the ability to correct for this racemization of the starting material in the solvolysis of 2-bromopropionic acid and methyl 2-bromopropionate *(6).* In the reaction of the acid, the rate constant (28.8 L g-mol^{-1} h^{-1}) for the bromide-induced racemization determined in 0.27 M sulfuric acid at 100 °C was 88 times faster than the solvolysis rate constant (0.33 h^{-1}) measured under the same conditions. In the reaction of the bromo ester in methanol, the bromide-induced racemization rate constant (2.7 L g-mol^{-1} h^{-1}) determined at 100 °C was 250 times faster than the solvolysis rate constant (0.011 h^{-1}) measured under the same conditions.

   In the solvolysis of the 2-bromooctane they said that they corrected for this racemization of the starting material, "We omit also all description of the methods of calculation, since these were quite similar to those illustrated in Part III" *(6).* There was no discussion or mention of data from the reactions of optically active 2-bromooctane in *(6),* and they did not include the value of the rate constant determined for the reaction of bromide ion with the 2-bromooctane.
4. We do not know how many kinetic measurements Hughes et al. made during the reaction, when they made them, or what the results were. In the experimental results reported for other experiments, Hughes et al. typically began with 10–15 samples of the reaction mixture, quenching and analyzing one of them at periodic intervals during the course of the reaction. About half of the determinations were made before half of the substrate reacted, and the last determination was typically made after 85–90% reaction (after about 3 half-lives for first-order reactions). The infinity determinations were often made separately. This implies that the expected half-life for the solvolysis of the optically active 2-bromooctane was about 24 hours (= 72/3), at 80 °C with the first sample quenched and analyzed at about 2.4 hours ($t_{1/2}$/10). If the bimolecular rate constant of the S_N2 reaction of bromide ion with the starting 2-bromooctane was 88 times the solvolysis rate constant, the 2-bromooctane would have been half racemized (ee = 50%) in 0.48 h and 90% racemized (ee = 10%) after 0.89 h. If the S_N2 reaction was 250 times the solvolysis rate (as for the methyl 2-bromopropionate), the 2-bromooctane would have ee = 50% in 0.29 h and ee = 10% after 0.52 h.

TABLE II.

Hydrolysis of β-n-Octyl Bromide.

Solvent.	Concn. of KOH, HBr, etc. (*N*). Initial.	Final.	Proportions of simultaneous reactions. S_N2 (%).	S_N1 (%).	Bromide, $[\alpha]_D^{20°}$.	Alcohol, $[\alpha]_D^{20°}$. Obs.	Corr. to pure halide.	Retention of optical purity (%).* Uncorr.	Corr.
60% Aqueous EtOH	1·23	0·91 KOH	88	12	+29·78°	− 7·73°	− 8·78°	− 89	− 93
	0·00	0·31 HBr	0	100	−24·54	+ 2·54	+ 3·46	− 35	− 66
	(Calculated)		100	0	+33·80	− 9·50	− 9·50	− 96	− 96

Ethyl Alcoholysis of β-n-Octyl Halides.

				Halide, $[\alpha]_D^{20°}$.	Ether, $[\alpha]_D^{20°}$. Obs.	Corr.		
β-n-Octyl bromide.								
60% Aqueous EtOH	1·23	0·91 KOH	95	5	−30·28	+13·93	+15·53	− 91	− 95
	0·00	0·31 HBr	0	100	−24·54	+ 4·90	+ 6·74	− 39	− 74
	(Calculated)		100	0	+33·80	−15·98	−15·98	− 94	− 96
EtOH	2·18	1·67 NaOEt	100	0	−24·54	+12·41	+17·10	−100	−100
β-n-Octyl chloride.									
EtOH	2·18	1·67 NaOEt	100	0	+29·79	−13·30	−17·10	−100	−100

* The negative sign signifies that configuration is inverted.

Figure 2. Hydrolysis and alcoholysis of optically active 2-bromooctane in 60% ethanol/40% water at 80°. The columns listed "Proportions of simultaneous reactions" give the percentages in which hydrolysis proceeds by the second- and first-order reactions, the figures being calculated from the kinetic data. The next three columns record, respectively, the specific rotation of the bromide used, that of the alcohol obtained, and that which the alcohol would have had if prepared from optically pure bromide. In the next column, this rotation is expressed as a percentage of the specific rotation of optically pure alcohol, the observed enantiospecificity of the reaction. In the last column a correction to the observed enantiospecificity is made for racemization of the 2-bromooctane before substitution by the bromide ions liberated in the solvolysis reaction; these numbers thus represent the enantiospecificity of the product alcohol if the 2-bromooctane underwent no racemization prior to substitution. (Hughes, E. D.; Ingold, C. K.; Masterman, S. *J. Chem. Soc.* **1937,** 1196–1201. Reproduced by permission of The Royal Society of Chemistry).

Two simulations of the stereochemical details of the solvolysis of 2-bromooctane are shown in Figure 3, illustrating the effectiveness of the bromide ion in out-competing solvent molecules for the substrate. Panel A shows the results where the racemization rate constant is 40 times the solvolysis rate constant, and Panel B has the ratio of the rate constants equal to 200. The rapid decline in the ee of the starting bromide is apparent. The initial alcohol product should be of inverted configuration and have a high ee. As the reaction proceeds, this early product will be diluted with product of lower ee than with racemic product, resulting in a final inverted product of low ee.

While Hughes et al. reported no experimental data for this reaction it seems that, at best, the first sample was taken toward the end of the bromide ion-catalyzed racemization of the 2-bromooctane. We do not know whether sufficient product was present in that sample to permit isolation and determination of its rotation with sufficient precision to accurately correct for the bromide ion-catalyzed racemization. Since they were expecting a long reaction and had only 10–15 samples to monitor its full course, it seems unlikely that a second kinetic measurement was made before the starting halide was essentially all racemized by the bromide ion, but we have no information on this. The one value reported, the 35% inverted ee of the product does not permit the stereospecificity of the solvolysis reaction to be determined. In response to an inquiry, a chemist whose career overlapped with Ingold's indicated that none of the experimental data or records from the work of Hughes and Ingold survive *(12)*.

5. The product alcohol is subject to racemization catalyzed by the strong acid (HBr) product as the reaction proceeds. The time weighted average acid concentration was 0.11 M HBr. Since the reaction was run for an extended period at 80 °C beyond 99% completion, this could have decreased the percent ee of the product alcohol. The plethora of infinity determinations they must have made on this reaction, however, should have allowed them to observe and correct for this reaction if it had occurred.

Thus while the experimental design, execution, workup, and documentation of individual experiments were usually impeccable in their other studies, these attributes were not apparent in this most important experiment. It is surprising, that based on the significance of this experiment to understanding the reactions of secondary substrates and the uncertainty of these results owing to inappropriate experimental conditions, that Hughes et al. did not repeat this reaction to obtain definitive results for the rate constants and for the stereochemistry of the products. The critical question—did any of this solvolysis reaction proceed via an S_N1 mechanism, and if so how much—remained unanswered.

Hughes and co-worker's results for the reactions of the optically active 2-bromooctane are shown in Figure 2 *(5)*. After correcting for the enantiomeric purity of the starting material, they determine the enantiospecificity of the reaction (retention of optical purity; next-to-last column). In the last column they show the results of the corrections for racemization of the starting 2-bromooctane by the bromide ions released in the solvolysis. This correction for the S_N2 reaction with bromide ion increased the optical purity of the product from 89 to 93%, and of the reaction in acid (72 hour solvolysis) from 35 to 66%. They also added a row of data: "...calculated from the experimental data in the first two rows." for a 100% S_N2 reaction. They do not explain how they did the calculation nor why their result

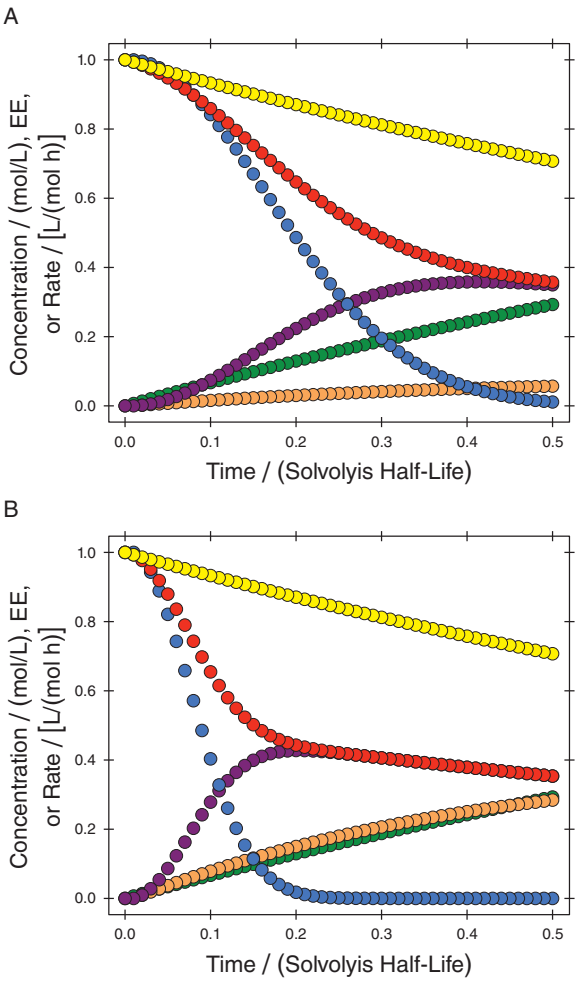

Figure 3. Stereochemical details of a simulated solvolysis of 2-bromooctane in ethanol/water. Starting with one molar 2-bromooctane with ee = 1.00, the progress of the reaction is shown for half of one half-life. Quantities plotted are [2-bromooctane] (yellow); [plus enantiomer] (red); ee of plus enantiomer (blue); [minus enantiomer] (purple); [bromide ion] (green); and the second-order reaction rate (L mol^{-1} h^{-1}) (orange). Panel A is a simulation for a ratio of the racemization to solvolysis rate constants equal to 40; Panel B is for the ratio equal to 200.

of ee = 0.96 is different from the expected ee = 1.00. Note that rather than referring to the reactions in columns 3 and 4 as second- and first-order, they use S_N2 and S_N1. This paper contained little interpretation or discussion of the results presented, "These results will be considered with other data in part VI" *(4)*, but, there was no discussion of these results in part VI.

In 1940 Hughes, Ingold, and their co-workers published another series of papers documenting their continuing work on substitution mechanisms. In their 1940 paper discussing the substitution at saturated carbon atoms, "Mechanisms Operative in the Hydrolysis of Methyl, Ethyl, Isopropyl and *tert*-Butyl Bromides in Aqueous Solutions" *(11)*, in the section on stereochemistry of the reaction, there is this brief statement concerning the stereochemical course of solvolysis reactions at secondary carbons:

> It has been shown that the solvent reactions of *sec*-octyl bromide exhibit in considerable amount the racemization which is diagnostic of the unimolecular mechanism. (*11*, p 933)

This is an exaggeration as the product they reported for this solvolysis reaction is inverted, with an enantiomeric purity of 66%. However, they also state:

> ...we find pure second-order reactions for MeBr and EtBr, a reaction *predominantly of second order* for isopropyl, and an inappreciable second order reaction for *t*-butyl. (*11,* p 932)

These conclusions are strikingly different from the diagram in the Ingold textbook (*3,* p 430) that showed primary substrates went 20% via S_N1 and tertiary 15% by S_N2.

Cowdrey et al. *(6)* reported on a number of different substitution reactions of optically active 2-bromopropionic acid, its methyl ester, and its salt, 2-bromopropionate, in 60% ethanol/water at a variety of temperatures. They determined rate constants for a variety of S_N2 reactions with hydroxide and solvolysis reactions in methanol and water. A most unexpected result was that the solvolysis of the 2-bromopropionate in both water and in methanol yielded product alcohol or ether of *retained* configuration with high enantioselectivity (ee = 90–100%). The authors make little comment on this surprising result other than to explain it by the intermediacy of a chiral, tetrahedral intermediate carbenium ion. Since they assumed that the solvolysis reactions went via an S_N1 mechanism, "...by the *kinetically identified* unimolecular mechanism, S_N1; ..." (*3,* p 524), to get this very stereospecific reaction with retention the S_N1 intermediate must be chiral and must permit (require?) front-side attack. Again, the mechanism molecularity is defined solely by the kinetic order of the reaction.

Most probably this reaction involves an S_N2 displacement of the bromide by the neighboring carboxylate anion, forming a reactive α-lactone intermediate that quickly undergoes a second S_N2 reaction by water or ethanol *(13).* Interestingly, in their summary paper *(6),* Hughes et al. discuss the possible intermediacy of an α-lactone in the solvolysis of 2-bromosuccinic acid with silver salts, but conclude rather that it is a β-lactone.

Other Investigators

Later, Weiner and Sneen *(14, 15)* also measured the stereochemical course of solvolysis reactions on a substituted 2-octanol: 2-octyl 4-bromobenzenesulfonate (2-octyl brosylate). In water containing from 0 to 75% dioxane, they found that the configuration of the 2-octanol product was inverted with an ee that ranged from 100 to 75%, with the enantiomeric purity inversely related to the dioxane concentration. In an elegant series of reactions with the much stronger nucleophile azide, they demonstrated that the dioxane participated in an S_N2 reaction with the brosylate, yielding an oxonium intermediate with inverted configuration. Water then displaced the dioxane in a second S_N2 reaction, yielding 2-octanol with retained configuration. Thus, all of the reactions went via S_N2 mechanisms with 100% inversion, but the alcohol was of intermediate optical purity because it was formed by two different pathways, one involving one inversion, the other involving two inversions.

When azide was present (0.006–0.06 M), it preferentially displaced the dioxane from the oxonium ion, reducing the yield of alcohol with retained configuration thus increasing the optical purity of the inverted alcohol, 98% inversion when $[N_3^-] = 0.06$ M. The azide ion was also involved in both substitution reactions yielding an azide product of reduced ee. As the azide concentration was increased, the yield of azide product and its optical purity increased as it increasingly out-competed the water and the dioxane for the brosylate. Weiner and Sneen's work also included solvolysis experiments with 2-octyl methanesulfonate in water and in water/dioxane mixtures that gave inverted alcohol product with ee = 1.0 *(14).*

Weiner and Sneen concluded:

> *It is clear that there is nothing borderline about the behavior of 2-octyl sulfonates, even in highly ionizing solvents such as water.* They undergo solvolysis by processes which are S_N2 in character. Apparent racemization in mixed solvents is but the result of competitive but stereospecific displacement processes. *(14)*

A brief comment on this reaction was included as a footnote in the Ingold textbook (*3,* p 529) but the results of the solvolysis of the 2-octyl methanesulfonate were misstated and misinterpreted. He concluded that it was "plausible" that the results of Weiner and Sneen were still consistent with an S_N1 mechanism for this reaction. Ingold continued to be unwilling to acknowledge that secondary substrates could solvolyze via an S_N2 mechanism.

More recent studies by Schleyer and co-workers *(16–18)* on the 2-adamantyl system demonstrated that all secondary substrates most probably undergo solvolysis by the S_N2 mechanism, except under uncommon but predictable conditions. Adamantane is a rigid, molecule that can be viewed as consisting of four cyclohexane rings, all in the least-strained chair conformation. Because of its symmetry, there are only two different types of hydrogen present, those on tertiary bridgehead carbons and those on secondary carbons. More importantly, all of the secondary hydrogens are equivalent, with each being axial to one cyclohexane ring and equatorial to another. A substituent on one of the methylene carbons then will be equatorial to one ring that blocks the backside, precluding displacement in an S_N2 reaction. *Thus 2-adamantyl substrates can solvolyze only via the S_N1 mechanism.* In 1946 Dostrovsky et al. (*19,* p 192) proposed the use of the neopentyl-like 2,2-dimethyl-3-butyl system for the same purpose.

Schleyer and co-workers demonstrated that the 2-adamantyl system is a limiting case for S_N1 nucleophilic substitution of secondary systems. They presented evidence that it solvolyzes without nucleophilic participation in solvents ranging from trifluoroacetic acid to 100% ethanol. This system then allows the extent of nucleophilic participation in the solvolysis of other compounds to be determined *(16).*

For instance, comparison of the solvolysis rate constants of 2-bromo-2-methyladamantane and 2-bromoadamantane–related 3° and 2° systems, in trifluoroacetic shows the 2-bromo-2-methyladamantane to be 3×10^7 times faster, an activation energy decrease of about 46 kJ/mol, similar to the energy difference in the cations in the gas phase *(17).* Conversely, the solvolysis rate ratio of a more typical 3°/2° pair, 2-methyl-2-bromopropane and 2-bromopropane, in 80% ethanol is only 5000, implying nucleophilic rate acceleration: an S_N2:S_N1 ratio, of at least 6000 in the 2-propyl system (only 0.017% of the reaction via S_N1). In acetic acid, this ratio is about 8000 *(18).* The tertiary compounds 2-bromo-2-methyladamantane and the 2-methyl-2-bromopropane have almost identical solvolysis rate constants in 80% ethanol after correcting for inductive effects and were considered to be typical tertiary alkyl systems *(17)* solvolyzing exclusively via S_N1.

In a concluding paper on the mechanism of solvent assistance in secondary systems Bentley and Schleyer *(20)* concluded:

> This interpretation suggests a variation in the magnitude of nucleophilic solvent assistance in S_N2 transition states with a clear *theoretical* distinction between S_N2 and S_N1 reactions. Few solvolyses should be classified as "borderline".

They also found no support for ion pairs involving carbenium ions as intermediates in the reactions of secondary systems. They conclude that if ion pairs are intermediates in secondary systems, they are an oxonium ion and the anion of the leaving group—as in Weiner and Sneen's solvolysis reactions in dioxane/water *(14, 15)*—rather than a carbenium ion and the leaving group as in tertiary systems.

In addition, Streitwieser and co-workers *(21)* showed that 2-butyl 4-bromobenzenesulfonate (2-butyl brosylate) solvolyzed in ethanol with essentially complete inversion of configuration and 2-octyl 4-toluenensulfonate (2-octyl tosylate) solvolyzed in acetic acid with 100% inversion. Lambert and Putz *(22)* used a number of specifically deuterated cyclohexyl compounds to show that cyclohexyl tosylate solvolyzed in buffered acetic acid, and in the more strongly ionizing formic acid to yield substitution products with *complete inversion* of configuration. Water is one of the best ionizing solvents and it should be a strong promoter of the S_N1 reaction in solvolysis and select for it if there is an S_N1: S_N2 competition. However, Bunton et al. *(23)* studied the oxygen exchange of 2-butanol in water catalyzed by perchloric acid and found that the rate of racemization was twice the exchange rate, indicating that every reaction of the alcohol with water involved backside attack, presumably via an S_N2 mechanism. These additional examples with a diversity of substrates, under a variety of conditions *including conditions that should strongly favor an S_N1 mechanism* are substantial if not conclusive evidence that the nucleophilic substitution reactions of secondary substrates go *only* via the S_N2 mechanism.

All of these results are in agreement with the approach of Solomons and Fryhle *(1)* that secondary alkyl compounds react only via the S_N2 mechanism and greatly simplify the determination of the course of nucleophilic substitution reactions of alkyl compounds. Tertiary substrates (and others that can form stabilized carbenium ions) will react via the S_N1 mechanism under ionizing conditions. This effectively precludes the involvement of the S_N1 reaction in nucleophilic substitution in primary and methyl substrates also, for which there are few claims. Bentley and Schleyer *(20)* conclude that there is a change in nucleophilic participation in the transitions state of the reaction in going from methyl to tertiary, with a significant change between the secondary and tertiary substrates.

This leaves a much simpler, but experiment-based, scheme for nucleophilic substitution than the one promulgated by Ingold *(3)* and discussed in the introduction to this paper. Nucleophilic substitution of methyl, primary, and secondary substrates go *only* via the S_N2 mechanism even with relatively weak nucleophiles such as alcohols, while substitution in tertiary substrates goes only via the S_N1 mechanism. There is no support in the Ingold textbook *(3)* or in the literature for secondary systems exhibiting "borderline" behavior or carbenium ion-type intermediates; for tertiary systems going ≈15% by an S_N2 mechanism; or for primary systems going ≈20% via an S_N1 mechanism.

While conducting numerous elegant experiments on a variety of substrates, with a variety of nucleophiles, under a variety of conditions, over a period of more than 15 years Hughes, Ingold, and their co-workers did much of the experimental science that elucidated the nature of nucleophilic substitution reactions in aliphatic systems. Unfortunately, the reaction critical to understanding the course of nucleophilic substitution in secondary alkyl compounds *(5)* suffers from a number of deficiencies that, despite diverse and abundant evidence to the contrary, including their own, has led to widespread confusion and uncertainty about the mechanism and stereochemistry of these reactions. A reconsideration of their results and the results of later investigators, leads to the conclusion that the nucleophilic substitution of secondary alkyl substrates goes *only* via the S_N2 mechanism, except under rare and predictable conditions.

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