SULFONIUM SALT SOLVOLYSIS

PART V. MODEL SYSTEMS FOR BIOLOGICAL TRANSMETHYLATION

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ABSTRACT

The rates of solvolysis of a series of sulfonium salts which may be considered as models for the biologically important sulfonium salt, S-adenosylmethionine, are discussed in terms of a possible anchimeric role of the carboxyl group of methionine in transmethylation reactions.

INTRODUCTION

In a previous paper in this series (1) the apparent enhancement of the nucleophilicity of the acetate anion in the solvolysis of dimethyl *t*-butyl sulfonium acetate in low-polarity solvents suggested the possibility of a similar role for the carboxylate group in biological transmethylations.



While transmethylation in the biological system normally involves S^+ to N transalkylation, the S^+ to O transalkylation in the solvolysis should be subject to similar assistance from an adjacent participating group, if such an effect is at all operative.

The comparison of the *t*-butyl and methyl group transfers requires explanation. By use of the *t*-butyl group as the transalkylating entity, competition from transfer of the other two groups on the sulfonium sulfur is eliminated. This exclusive transfer of the *t*-butyl entity in preference to either of the other functions was demonstrated by nuclear magnetic resonance (n.m.r.) studies of the products in selected cases. While transmethylation to nitrogen in the biological system cannot take place through a free methyl carbonium ion the possibility does exist for a free *t*-butyl carbonium ion in the solvolysis. However, in the low-polarity medium (0.75 mole fraction ethanol), the carbonium ion will be unstable and participation by such entities as an adjacent carboxyl group will be favored. If a *t*-butyl carbonium ion is envisaged, participation in its transfer by the carboxyl group could be envisaged as a very specific type of solvation if not actual covalent participation. The difference between the *t*-butyl and methyl cases is therefore one of degree of development of the δ^+ charge on the transferring alkyl group and participation might be expected to be operative in both cases.

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To investigate further this type of role for the carboxyl group in transalkylation reactions, we report here a rate study of a series of model compounds of the type:



The function $X-(CH_2)_n$ was varied by changing the value of n and by identifying X as methyl, carboxylic acid, and carboxylic ester groups.

RESULTS

The rate constants for the solvolysis (transalkylation to ROH) of the model sulfonium salts used are presented in Table I. These rate constants were obtained using a conductimetric technique with an initial concentration of the appropriate sulfonium iodide of $2 \times 10^{-3} M$ in 0.750 mole fraction ethanol in water. The rate constants quoted in Table I are the average values of three determinations reproducible to better than $\pm 2\%$.



DISCUSSION

It would appear from the rate data presented in Table I that the carboxyl group is significantly involved in the solvolysis of the model sulfonium salts. The carboxyl group may interact with the reactive center at the positively charged sulfur or with the developing positive charge at the *t*-butyl carbon atom:

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If the predominant interaction of the carboxyl group is with the sulfonium sulfur, the initial state should be stabilized and the reaction rate reduced relative to the case where (X) is an alkyl group. If, on the other hand, the interaction is with the developing center of positive charge at the *t*-butyl carbon atom (i.e. anchimeric assistance) the transition state will be stabilized and the reaction rate should be relatively faster compared to that with an alkyl substituent. As can be seen from Table I the latter interpretation is favored since the apparent rate of solvolysis is increased 5.6 times when (X) is changed from methyl to carboxyl.

Assuming that the interaction of the carboxyl group assists in the delocalization of the developing positive charge on the tertiary carbon atom, it can be seen (Table I) that the rate of solvolysis of the carboxyl sulfonium salts are correlated with the size of the ring formed in the transition state of these sulfonium salts. Thus the solvolysis of the sulfonium salt which involves a six-membered ring, I, is 2.5 times the solvolysis rate of the sulfonium salt which must proceed through a seven-membered ring, II. Since III must form an eight-membered ring for similar participation in the transition state to be operative, the carboxyl group would not be expected to function in this manner to any large extent. In fact III solvolyzes only 20% faster than the alkyl sulfonium salt VI in which no COOH participation is possible.

It should be noted that in the simple hydrocarbon chains, where (X) is methyl, alkyl chain lengthening results in an increase in the rate of solvolysis (VIII < VII < VI). This may be due to a dominant entropy effect in these cases where no participation of the terminal entity of the alkyl chain can take place.

Under the conditions of the reaction the carboxyl group will be predominantly in the protonated form, and the anchimeric role of the carboxyl group is likely to be through the participation of the lone pairs of electrons on the carbonyl oxygen. Thus any factor which would increase the availability of these electrons should increase the amount of anchimeric assistance and therefore the rate of solvolysis of the sulfonium salt. Since the ethyl group would be expected inductively to donate electrons to the carboxyl group more readily than hydrogen, it is not surprising that the sulfonium salt with the ester substituent (IV) solvolyzes more rapidly than the corresponding acid (II).

In this case the substitution of the ethyl group for hydrogen also may give rise to a steric factor similar to the type found for the alkyl substituents. This type of explanation for the increase in rate of solvolysis for the ester group is also suggested in the case of the trifluoro ester, although differences in intramolecular inductive effects will also be important (see later). The salt V solvolyzes more rapidly than the hydrogen analogue, while the prediction based on electronegativity effects on the electron availability at the carboxyl oxygen would be a decrease in rate. Further work will be necessary to separate these various factors in the systems under study.

While the rationalization of the data to this point has been based upon an anchimeric assistance role for the various remote substituents, the possible effect of long range

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intramolecular inductive influences cannot be unambiguously excluded. The magnitude of such effects, and in particular the manner in which they vary with the remoteness of the substituent from the reaction center, can be estimated using the Hammett-Taft type treatment, i.e. log $k_{\rm X}/k_{\rm H} = \rho^* \sigma^*$ (2) Values for the appropriate ρ^* and σ^* constants are not available for the sulfonium salt systems under study here but values for log $k_{\rm X}/k_{\rm H}$ can be calculated from the observed data as shown in Table II. The value of $k_{\rm H}$ for the case where two methylene groups are interposed between the COOH substituent and the reaction center is estimated from the rate values for the substituent one and three methylenes removed respectively, i.e., substrates VIII and VII. The highest possible value, namely that for VII is used in Table II. Inductive effects are frequently assumed to decrease by a factor of 1/2 per additional methylene interposed between substituent and reaction center (3). Depending upon the precise value of $k_{\rm H}$ for the case of two methylenes interposed, the decrease in log $k_{\rm X}/k_{\rm H}$ and hence $\rho^*\sigma^*$ caused by increasing the number of CH_2 groups from two to three is at least of this magnitude and is probably larger. Increasing the number of methylenes interposed from three to four, however, results in a five-fold decrease, much larger than is predicted by the Hammett-Taft treatment. It should be noted that lack of knowledge of the appropriate values for ρ^* and σ^* in this argument is not restrictive since ρ^* is assumed constant for the reactions and hence the change in log $k_x/k_{\rm H}$ is a true measure of the change in the inductive effect σ^* . Our explanation of this observation is that in the substrates with two and possibly three interposed methylenes anchimeric assistance of the type discussed previously enhances the accelerating role of the substituent through the formation of more or less stable transient ring structures. Such participation is unlikely in the case of four interposed methylenes. The result of such additional anchimeric assistance in the case of two or three interposed methylenes will be to increase k_x and make the $k_x/k_{\rm H}$ ratios greater than predicted from purely inductive effects. While such an argument cannot be claimed to be conclusive evidence for the dominant role of anchimeric assistance it does indicate that long range inductive effects do not appear to account for all of the observed rate changes.

TABLE II						
Rate ratios for	COOH a	and	unsubstituted	sulfonium s	alts	

Substrates compared	Number of interposed CH2 groups	$\log k_{\rm X}/k_{\rm H}$	Rate change (decrease)
Estimated from VIII and VII vs. I	2	$\log \frac{13.5}{>2.4} > 0.75$	1 /0
VII vs. II	3	Log $\frac{5.4}{2.4} = 0.35$	1/2
VI vs. III	4	$Log \frac{3.2}{2.7} = 0.07^{1}$	1/5

This type of anchimeric assistance by a carboxyl function is not unusual; for example Winstein *et al.* (4) have shown that anchimeric assistance is important in the acetolysis of trans-2-acetoxycyclohexyl brosylate. It might be argued that in the present study the presence of the bulky t-butyl group might prevent participation of the type suggested. We are not, however, insisting that a covalent bond is formed between the carboxyl oxygen and the developing *t*-butyl carbonium ion, but rather that the ester or acid function is a good 'solvent' stabilizing the formation of the incipient carbonium ion. This may be

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particularly important in view of the fact that the oxygen is in a preferred configuration for interaction compared with water or ethanol which must be taken from the surrounding solvation shell.

The effect of actually attaching the carboxyl group to the sulfonium salt, as opposed to having it available as a separate molecular entity, may be assessed by comparing the rate of solvolysis of the sulfonium salt I ($13.5 \times 10^{-4} \, s^{-1} \, at \, 60^\circ$) with the rate constant for the internal ion-pair attack by acetate ion ($1.5-3.0 \times 10^{-4} \, s^{-1} \, at \, 60^\circ$) as estimated from the value obtained in the previous paper of this series (1). The favorable entropy effect of actually attaching the participating acetate group to the reacting molecule results in a rate enhancement of some 4 to 8 times.

EXPERIMENTAL

Compounds which could be characterized by literature references were prepared by standard procedures and are listed below with the pertinent physical properties and references. Procedures for preparing new compounds are listed with the physical properties, analyses, and yields. Nuclear magnetic resonance spectra were obtained for all intermediate compounds and sulfornium salts using a Varian A-60 Spectrometer. These spectra (available on request) leave little doubt as to the nature of the products, although the analytical data for some of the sulfonium salts are not in as good agreement with theory as is normally expected. These discrepancies are probably due to the instability of the salts. The salts decomposed readily and were recrystallized immediately before use. All other reagents were "reagent grade" chemicals.

Previously Prepared Compounds

5-Bromopentanoic acid.-Boiling point 110-115° at 2 mm; lit. b.p. 125-131° at 6 mm (5). Yield 50%.

4-Bromobutanoic acid.-Boiling point 92-96° at 2 mm m.p. 31-31.5°, lit. m.p. 32° (6). Yield 90%.

S-Bromopropanoic acid.-Melting point 61-61.5°, lit. m.p. 59.5-61° (7), 62.5° (8). Yield 75%.

Ethyl-(4-bromo)-butanoate.—Boiling point 93–95° at 02 mm; lit. b.p. 96–100° at 20 mm (9), 85–87° at 14 mm (10). Yield 40%.

Dimethyl t-Butyl sulfonium iodide.-Melting point 160-160.5°, lit. m.p. 159-160.2° (11).

Intermediates

2,2,2-Trifluoroethyl-(4-bromo)-butanoate

An ether solution of 4-bromobutanoic acid was dropped into thionyl chloride (100% mole excess) and the mixture refluxed for 1 h, and distilled; b.p. of the acid chloride, 87–89° at 20 mm. The acid chloride was added to 2,2,2-trifluoroethanol (100% mole excess) over a period of 1 h at 0°. The solution was allowed to stand for 1 h at room temperature, then poured into water, extracted with ether, washed with water, sodium carbonate, and water, dried with Drierite, and distilled; b.p. 86–88° at 17 mm. Overall yield 45%.

t-Butyl-n-propyl Sulfide

Sodium hydroxide (0.22 mole) was dissolved in 50 ml of dry ethanol. The *t*-butyl mercaptan (0.11 mole) and then 1-bromopropane (0.1 mole) were added dropwise. The mixture was refluxed for 1 h and then one-half of the ethanol was removed by distillation. Water (50 ml) was added and the layers separated. The water layer was extracted twice with ether, the ether layers being added to the original organic layer. The ether solution was dried with Drierite, the ether removed, and the sulfide distilled; b.p. 133–136° at 660 mm. Yield 50%.

t-Butyl n-Butyl Sulfide

The same procedure as above, using sodium hydroxide (0.22 mole), t-butyl mercaptan (0.11 mole), and 1-bromobutane (0.1 mole), was followed; b.p. $159-164^{\circ}$ at 660 mm. Yield 55%.

t-Butyl δ-Carboxy-n-butyl Sulfide

Sodium hydroxide (0.375 mole) was dissolved in 50 ml of dry ethanol. The *t*-butyl mercaptan (0.125 mole) and then 5-bromopentanoic acid (0.1 mole) were added dropwise. The mixture was refluxed for 1 h and then one-half of the ethanol was removed by distillation. Water (50 ml) was added and the layers separated. The water layer was extracted with ether twice to remove any ester which formed in the reaction. The water layer was acidified and extracted with ether twice. The ether solution was dried with Drierite, the ether removed, and the sulfide distilled under vacuum; b.p. 110–111° at 0.4 mm. Yield 40%.

t-Butyl y-Carboxy-n-propyl Sulfide

The same procedure as above, using sodium hydroxide (0.375 mole), *t*-butyl mercaptan (0.125 mole), and 4-bromobutanoic acid (0.1 mole), was followed; b.p. $115-122^{\circ}$ at 3 mm. Yield 45%.

t-Butyl β -Carboxyethyl Sulfide

The same procedure as above, using sodium hydroxide (0.375 mole), t-butyl mercaptan (0.125 mole), and 3-bromopropanoic acid (0.1 mole), was followed; b.p. $87-94^{\circ}$ at 3 mm. Yield 45%.

t-Butyl γ -Carboethoxy-n-propyl Sulfide

Sodium hydroxide (0.25 mole) was dissolved in 50 ml of dry ethanol. The *t*-butyl mercaptan (0.125 mole) and the ethyl-(4-bromo)-butanoate (0.1 mole) were added dropwise. The mixture was refluxed for 1 h and then one-half of the ethanol was removed by distillation. Water (50 ml) was added and the layers separated. The water layer was extracted with ether. The organic layers were combined and washed with water, dried with Drierite, the ether removed, and the sulfide distilled; b.p. 93-97° at 2 mm. Yield 35%.

t-Butyl Carbo-(B,B,B-trifluoro)-ethoxy-n-propyl Sulfide

The same procedure as above, using sodium hydroxide (0.25 mole), t-butyl mercaptan (0.125 mole), and 2,2,2-trifluoroethyl-(4-bromo)-butanoate (0.1 mole), was followed; b.p. 120–122° at 2 mm. Yield 45%.

New Sulfonium Salts

Methyl t-Butyl n-Propyl Sulfonium Iodide (VII)

Methyl iodide (10% mole excess) was added to *t*-butyl *n*-propyl sulfide and allowed to stand for 6 h. The resulting mass was recrystallized three times by dissolving the salt in warm ethanol and then adding sufficient ether to turn the solution cloudy. The solution was then placed in the freezer until precipitation was complete. The solution yielded a white crystalline solid, 60%; m.p. 115.5–116°.

Anal. Calcd. C, 35.04; H, 6.98; S, 11.6. Found: C, 35.28; H, 7.11; S, 11.6.

Methyl t-Butyl n-Butyl Sulfonium Iodide (VI)

Methyl iodide (10% mole excess) was added to *t*-butyl *n*-butyl sulfide and allowed to stand for 6 h. The resulting mass was recrystallized four times from an ethanol-ether mixture as described previously. The mixture yielded a white crystalline solid, 45%; m.p. $96-97^{\circ}$.

Anal. Calcd. C, 37.50; H, 7.34; S, 11.1. Found: C, 37.63; H, 7.47; S, 11.1.

Methyl t-Butyl S-Carboxy-n-butyl Sulfonium Iodide (III)

Methyl iodide (20% mole excess) was added to *t*-butyl δ -carboxy-*n*-butyl sulfide and allowed to stand for 4 h. The resulting mass was recrystallized three times from an ethanol-ether mixture as described previously. The mixture yielded a white crystalline solid, 35%; m.p. 106.5-107°. Anal. Calcd. C, 36.15; H, 6.47; S, 9.65. Found: C, 37.37; H, 6.27; S, 9.51.

Methyl t-Butyl γ -Carboxy-n-propyl Sulfonium Iodide (II)

Methyl iodide (20% mole excess) was added to *t*-butyl γ -carboxy-*n*-propyl sulfide and allowed to stand for 4 h. The resulting mass was recrystallized four times from an ethanol-ether mixture as described previously. The mixture yielded a white crystalline solid, 25%; m.p. 116.5-117.5°.

Anal. Calcd. C, 33.97; H, 6.02; S, 10.08. Found: C, 34.19; H, 6.16; S, 9.65.

Methyl t-Butyl β-Carboxyethyl Sulfonium Iodide (I)

Methyl iodide (20% mole excess) was added to *t*-butyl β -carboxyethyl sulfide and allowed to stand for 3 h. The resulting mass was recrystallized three times from an ethanol-ether mixture as previously described. The mixture yielded a white crystalline solid, 25%; m.p. 87.5-89°.

Anal. Calcd. C, 31.59; H, 5.63; S, 10.5. Found: C, 30.11; H, 6.09; S, 9.68.

Methyl t-Butyl γ -carboethoxy-n-propyl Sulfonium Iodide (IV)

Methyl iodide (20% mole excess) was added to *t*-butyl γ -carboethoxy-n-propyl sulfide and allowed to stand for 2 h. The resulting mass was recrystallized three times from an ethanol-ether mixture as previously described. The mixture yielded a slightly yellow crystalline solid, 15%; m.p. 84.5-85°.

Anal. Calcd. C, 38.15; H, 6.70; S, 9.26. Found: C, 38.39; H, 6.65; S, 8.51.

Methyl t-Butyl γ -Carbo-(β , β , β -triftuoro)-ethoxy-n-propyl Sulfonium Iodide (V)

Methyl iodide (20% mole excess) was added to *t*-butyl γ -carbo-(β , β , β -trifluoro)-ethoxy-n-propyl sulfide and allowed to stand for 2 h. The resulting mass was recrystallized four times from an ethanol-ether mixture as previously described. The mixture yielded a slightly yellow crystalline solid, 15%; m.p. 84-84.5°. Anal. Calcd. C, 33.01; H, 5.04; S, 8.01. Found: C, 33.48; H, 5.22; S, 7.44.

Solvents

Ethanol, Reliance Chemicals "100 per cent" grade was dried with magnesium turnings and distilled; $n_{20}^{c}D^{c} = (1.3606, \text{ lit. } n_{20}D = 1.3614 (12).$

+ The water used was doubly distilled, with conductance less than 5 \times 10⁻⁷ mhos.

Rate Determinations

ENT COST

The rate constants were measured conductimetrically using an a-c. bridge at 1 100 c.p.s. as described by Robertson. (13)

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