Stereoselectivity and Carbon-14 Isotope Effect in Methyl Group Transfer from s-Butyldimethylsulphonium to *para*-Thiocresolate Ion

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Summary The large rate-difference, observed in transfer of the prochiral methyl groups from (*RS*)-s-butyldimethylsulphonium *p*-toluenesulphonate (**1**) to *p*-thiocresolate, is attributed, by stereospecific ^{14}C-labelling, to the compound operation of a small diastereotopic selectivity (<4%) and a large isotope effect.

SEVERAL *S*-methyl sulphonium ions are biologically important methylating agents.[1] In principle, the transfer of diastereotopic methyl groups from a monochiral dimethylsulphonium ion, *e.g.* (*RS*)-s-butyldimethylsulphonium ion (**1**),† to a receptor, *e.g.* the *p*-thiocresolate ion, must proceed with different rates. We report the magnitude of this difference for the methyl groups, Me_S and Me_R, of (**1**).

Conversion (Scheme 1) of the racemic sulphide (**2**) into a nearly 1 : 1 mixture of the salts (**3**)† and (**4**),† followed by fractional crystallization (from MeCN), afforded the (R_CS_S)-(S_CR_S)-salt (**3**),†‡ m.p. 116—119 °C (decomp.), δ (CD_3CN) 2·87 (S*Me*), containing < 4% of the diastereomeric salt (**4**)† [δ 2·80 (S*Me*)]; the structure of (**3**) was established by *X*-ray crystallography of the corresponding perchlorate.[2] Decarboxylation of (**3**) and (**4**) afforded the salt (**1**),†‡ m.p. 80—82 °C; δ (CD_3CN) 2·77 (Me_S) and 2·83 (Me_R).§ Repetition of the same sequence, now with $Br^{14}CH_2CO_2H$, gave, *via* ^{14}C-labelled (**3**), the chiral (R_CR_S)-(S_CS_S)-salt (**5**)† [containing < 10% of (**6**)†§] which was recrystallised to constant activity; this on thermal equilibration (MeCN, 74 °C, 27 h), produced a *ca.* 1 : 1 mixture§ of (**5**)† and (**6**).†

Reaction of (**1**) with sodium *p*-thiocresolate proceeded readily to give an equimolar mixture of sulphides, converted, for the sake of convenient analysis, into the corresponding *N*-*p*-toluenesulphonyl sulphimides, that could be cleanly separated by chromatography into (**7**)[3] and (**8**)[4] (Scheme 2); the former was a mixture of diastereomers. Repetition of the same sequence, starting, in one series, from (**5**)† [containing < 10% of (**6**)†], and, in the other, from the equilibrium mixture of (**5**)† and (**6**),† produced radioactive specimens of (**7**) and (**8**), which were crystallized to constant specific activity (Table).

† Only one enantiomer is depicted.

‡ Combustion analyses of these compounds were within 0·4% of theory.

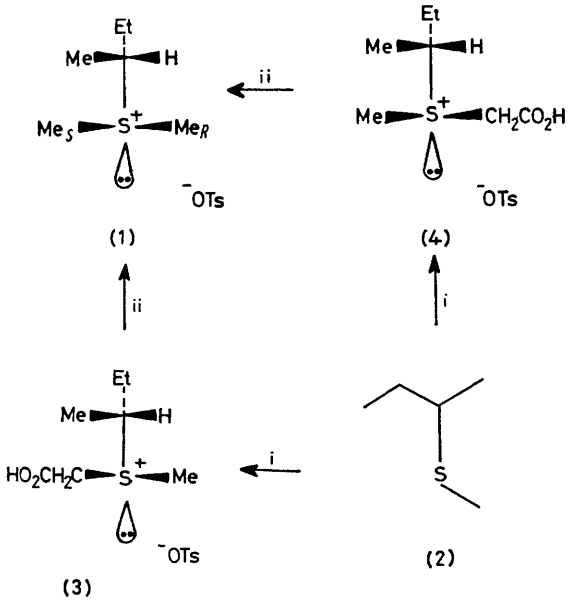
§ Established by ^1H n.m.r. comparison with (R_CS_S)-(S_CR_S)-s-butylmethyl-[$^2H_3$]methylsulphonium *p*-toluenesulphonate, produced by exchange of (**3**) with D_2O, followed by decarboxylation in $(CD_3)_2CO$.

TABLE

A (5)[a]	A (5)+A (6) (1:1)	A (7)	A (8)	A (7)/A (8)	Mean values
1·000		0·527	0·460	1·147 ± 0·037	1·144 ± 0·023[b]
1·000		0·529	0·464	1·140 ± 0·028	
	1·000	0·534	0·455	1·174 ± 0·020	
	1·000	0·525	0·456	1·152 ± 0·027	1·160 ± 0·015[c]
	1·000	0·523	0·453	1·155 ± 0·028	

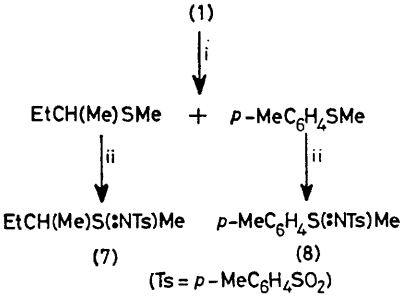
[a] $A(i)$: relative specific activity of compound (i); specific activities were within the range of 0·3—3·2 μCi mmol^{-1}, measured with mean errors varying between 1·2 and 2·2%, including an estimated 1% contribution from possible impurities. < 10% of the activity arises from contamination with (**6**).† Counting efficiencies were separately determined by internal calibration. [b] Corresponding to the value 1·14 ± 0·02 for homogeneous (**5**),† obtained by correction for a content of 10% of (**6**).† [c] Corrected value for homogeneous (**6**),† 1·18 ± 0·03.

The diastereotopic contribution, D, to the observed selectivity, expressed in terms of rate constants, indexed as



SCHEME 1. Reagents: i, $BrCH_2CO_2H$–AgOTs–MeCN, 50 °C, 20 h, 91%; ii, Bu_3N–Me_2CO, 50 °C, 10 min, recryst. (Me_2CO–EtOAc), 70%. Ts = p-$MeC_6H_4SO_2$.

relating to the appropriate ^{12}C- and ^{14}C-methyl groups of the salts (**1**)† (**5**),† and (**6**),† can be expressed as: $D = k_R$ (**1**)$/k_S$-(**1**) = $[k_{12}$ (**5**)$/k_{14}$ (**5**) × k_{14} (**6**)$/k_{12}$ (**6**)$]^{\frac{1}{2}}$ × $(I_R/I_S \times I^*_R/I^*_S)^{\frac{1}{2}}$, where I and I^* denote primary and secondary isotope effects, respectively. On the assumption that $I_R = I_S$ and $I^*_R = I^*_S$, and equalling k_{12} (**5**)$/k_{14}$ (**5**) with 1·14 ± 0·02 and k_{12} (**6**)$/k_{14}$ (**6**) with 1·18 ± 0·03 (Table), it follows that $D = [(1{\cdot}14 \pm 0{\cdot}02)/(1{\cdot}18 \pm 0{\cdot}03)]^{\frac{1}{2}} = 0{\cdot}98 \pm 0{\cdot}02$. For the observed compound isotope effect I one obtains: $I = (I_S \times I_R)^{\frac{1}{2}}/(I^*_S \times I^*_R)^{\frac{1}{2}} = k_{12}$ (**5**)$/k_{14}$ (**5**) × k_{12} (**6**)$/k_{14}$ (**6**)$^{\frac{1}{2}}$ = $[(1{\cdot}14 \pm 0{\cdot}02) \times (1{\cdot}18 \pm 0{\cdot}03)]^{\frac{1}{2}} = 1{\cdot}16 \pm 0{\cdot}02$.



SCHEME 2. Reagents: i, p-MeC_6H_4SNa–DMF, 22 °C, 1 h; ii, p-$MeC_6H_4SO_2(Cl)Na$–DMF, 22 °C, 1 h; chromatographic separation, overall yields: (**7**; 35—65%), (**8**, 50—70%). DMF = dimethylformamide, Ts = p-$MeC_6H_4SO_2$.

We conclude that the large difference observed in the rate of transfer of the methyl groups of the salts (**5**)† and (**6**)† can be accounted for as a combined effect of a small diastereotopic contribution (< 4%) and a compound isotope effect (*ca.* 1·16), the magnitude of which, we believe, has hardly ever been surpassed, though comparable primary ^{12}C/^{14}C-isotope effects have been reported for reactions of presumably analogous type.[5]

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