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Selectivity in the Transfer of Specified Diastereotopic Methyl Groups from a Dimethylsulfonium Ion

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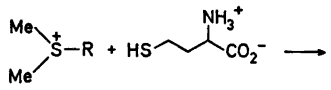
Dedicated to Professor K. A. Jensen on his 70th birthday

By specific ^{14}C-labelling it is demonstrated that the prochiral methyl groups present in the (*RS*)-dimethyl(1-methylpropyl)sulfonium ion are transferred to an acceptor molecule, the 4-methylbenzenethiolate ion, with greatly different rates. Only to a minute extent, however, is the observed rate difference attributable to the diastereotopic character of the two methyl groups, whereas a surprisingly large composite isotope effect of 1.16 ± 0.02, slightly surpassing the highest previously reported values for primary $^{12}C/^{14}C$-isotope effects, accounts almost entirely for the observed rate difference. This observation, pertaining to transmethylation from a dimethylalkylsulfonium ion, deserves attention and may, in certain cases, be of consequence for biochemical methodology.

As part of the synthetic sequence, the relative configuration of one of the diastereomeric (carboxymethyl)methyl(1-methylpropyl)sulfonium perchlorates has been established. The crystal structure was solved from single crystal X-ray data. *Crystal data:* orthorhombic $P2_12_12_1$, $a = 6.725(1)$, $b = 7.287(1)$, $c = 24.382(2)$, and $Z = 4$. The 166 parameters of the derived structural model were refined *versus* 828 structure factor amplitudes to a linear, unweighted R-value of 0.042. Although the structure is partially disordered, the obtained relative configuration at the two chiral centers of the sulfonium ion is uniquely determined as (R_cS_s), or (S_cR_s).

Though unrivalled as a general, biological methylating agent, *S*-adenosyl-L-methionine shares with the naturally occurring dimethylsulfonium compounds, *S*-methylmethionine (*1*) and the thetin (*2*), the capacity to convert homocysteine (*3*) into methionine (*4*) in certain enzyme-catalyzed processes.[1,2] Regardless of the C_1 or C_s-substrate character prevailing in *1* and *2*, respectively, the enzymic methyl transfer reactions are expected to proceed stereospecifically; experimental evidence to this effect, however, is lacking. In contrast to the thetin (*2*), which possesses enantiotopic methyl groups, the methionine derivative (*1*) must, in principle, exhibit selectivity in transfer of its diastereotopic methyl groups to an achiral acceptor even under non-enzymic conditions. We



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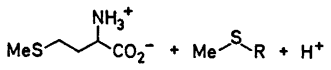

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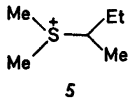

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Scheme 1. Compound *1*, R = $(CH_2)_2CH(NH_3^+)$-CO_2^-; *2*, R = $(CH_2)_2CO_2^-$.

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have attempted to verify this prediction, yet, for experimental reasons, employing the dimethyl(1-methylpropyl)sulfonium ion (*5*) as C_1-donor.[3]

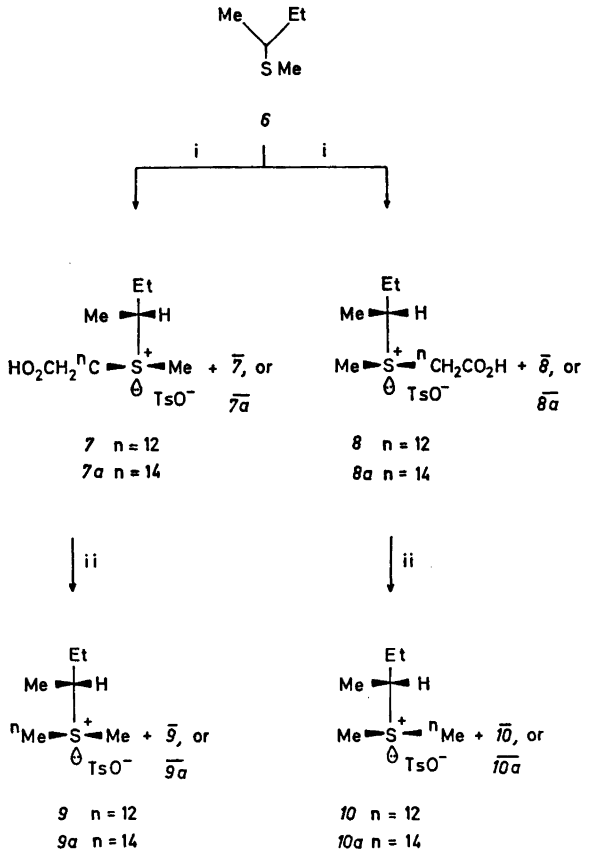
RESULTS

Reactions designed to assess the diastereoselectivity of the transmethylation from *5* to an acceptor must, of course, proceed under conditions mild enough to preclude pyramidal inversion of the sulfonium ions. The 4-methylbenzenethiolate ion admirably meets the requirements as a smoothly reacting acceptor and was employed for this purpose throughout the present work.

The diastereomeric, racemic [*methyl*-^{14}C]-[*methyl*-^{12}C](1-methylpropyl)sulfonium salts, (*9a*,$\overline{9a}$ * and *10a*,$\overline{10a}$), required as donor species, were synthesized as outlined in Scheme 2.

In the non-labelled series, treatment of racemic 2-(methylthio)butane (*6*)[4] with bromoacetic acid afforded a *ca.* 1:1 mixture of the diastereomeric salts (*7*,$\overline{7}$ and *8*,$\overline{8}$) individually recognizable by ^{1}H NMR spectroscopy. Repeated recrystallization of the mixture from acetonitrile yielded a product containing more than 96 % of one of the diastereomeric 4-methylbenzenesulfonates. An X-ray analysis of the corresponding perchlorate, prepared by an alternative route (see Experimental), served to establish its identity as the perchlorate of the (R_cS_s/S_cR_s)-sulfonium ion (*7*,$\overline{7}$).

* The designation $\overline{i}$ denotes the mirror image of *i*, produced in the ratio 1:1.



Scheme 2.

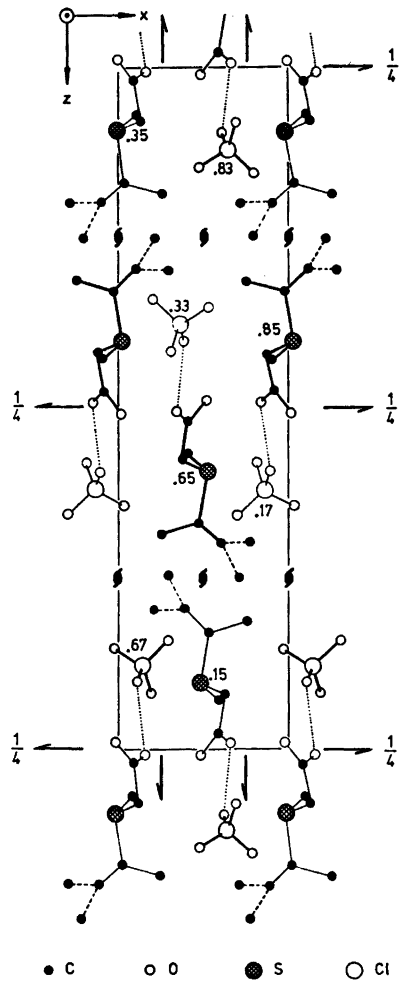


Fig. 1. Molecular packing diagram for the crystal structure of one of the diastereomeric (carboxymethyl)methyl(1-methylpropyl)sulfonium perchlorates. The dotted lines denote the intermolecular hydrogen bonds (O(5)···O(2)), while the dashed lines indicate the covalent bond from C(4) to the alternative positions of C(5). Only nonhydrogen atoms are included. The numbers given are the approximate y-coordinates for the nearest sulfur or chlorine atoms.

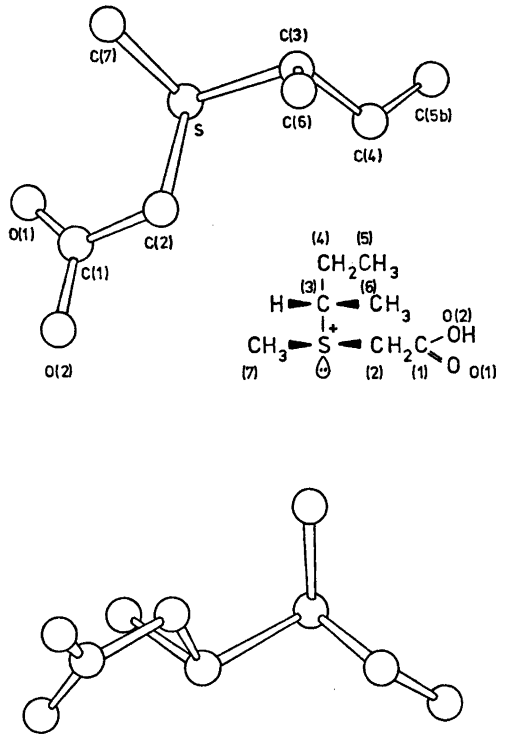


Fig. 2. Molecular geometry of one of the diastereomeric (carboxymethyl)methyl(1-methylpropyl)sulfonium perchlorates, viewed perpendicular and parallel to the plane through the three carbon atoms adjacent to the sulfur atom; hydrogen atoms are not included.

X-Ray structure determination. The molecular packing obtained for the crystal structure of the perchlorate is shown in Fig. 1. The structure can be envisioned as built up by layers of about 12 Å thickness perpendicular to the c direction (*e.g.* the layers $-1/4 < z < 1/4$ and $1/4 < z < 3/4$, respectively). Within these layers the ionic molecules are held together mainly by hydrogen bonds as well as by conventional electrostatic interactions between the ions. Between the layers (across the planes $z = 1/4$ and $z = 3/4$, respectively) there are only relatively weak van der Waals interactions. The lack of any larger intermolecular forces across these layers is most probably of relevance for the observed disorder of the terminal methyl group of the 1-methylpropyl grouping and also for the comparatively large thermal vibrations indicated for this group. Thus, the carbon atom C(5) (*cf.* Fig. 2) was found to be distributed, with almost equal probability, among two different positions labelled C(5a) and C(5b), respectively. Such a disorder appears to be a rather common feature of 1-methylpropyl substituents,[5] possibly caused by the circum-

Table 1. Intermolecular contact distances (Å) less than 3.4 Å between the nonhydrogen atoms.

Symmetry code:

None	x,y,z		
(i)	$-x,1/2+y,1/2-z$	(v)	$1/2-x,-y,-1/2+z$
(ii)	$-1/2+x,1/2-y,-z$	(vi)	$-x,-1/2+y,1/2-z$
(iii)	$1/2-x,-y,-1/2-z$	(vii)	$1-x,-1/2+y,1/2-z$
(iv)	$x,y-1,z$	(viii)	$x-1,y,z$

S···O(5 i)	3.298(6)	O(2)···O(5 v)	2.736(7)
O(1)···C(1 ii)	3.178(8)	C(1)···O(6 vi)	3.202(10)
O(1)···C(2 ii)	3.188(8)	C(2)···O(4 vii)	3.399(11)
O(1)···C(7 ii)	3.245(10)	C(2)···O(6 vi)	3.304(12)
O(1)···O(5 iii)	3.342(7)	C(5a)···O(4 viii)	3.166(19)
O(2)···C(7 iv)	3.228(8)	C(5b)···C(6 viii)	3.288(27)

stance that in one of the C(5) positions, C(5a), the atoms C(5)–C(4)–C(3)–C(6) form an energetically favourable (almost staggered) conformation. In the other position, C(5b), a favourable molecular packing can be achieved for the elongated molecules (*cf.* Fig. 2). Apart from the short O(2)···O(5) contact of 2.74 Å caused by an intermolecular hydrogen bond (Fig. 1), most of the other shorter contacts (*cf.* Table 1) are formed between atoms expected to have opposite atomic charges.

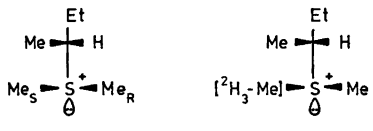
As has been frequently observed in crystals of organic compounds containing perchlorate ions, three [O(3), O(4), and O(6)] of the four oxygen atoms of the perchlorate ions are slightly disordered as judged by their large thermal vibrations. The fourth, not disordered oxygen atom, O(5), is the one involved in the hydrogen bonding to O(2). Apart from the bond distances and bond angles (Table 2) involving the disordered atoms [C(5), O(3), O(4), and O(6)] the general features of the molecular structure agree well with earlier observations on similar compounds.[6] Thus, the sulfur atom and its three adjacent carbon atoms, C(2), C(3), and C(7), form a flattened trigonal pyramid (*cf.* Fig. 2) with the C–S–C bond angles ranging from 102.4 to 104.2° and with the sulfur atom 0.76 Å above the plane through the three carbon atoms. As seen from Fig. 2, the crystal structure determination shows that the configuration of the carboxymethylsulfonium perchlorate building up the crystal is either that of *7* or its enantiomer ($\bar{7}$).

Decarboxylation and transmethylation. Decarboxylation of *7*,$\bar{7}$, or of a mixture of

Table 2. Intramolecular bond distances (Å) and angles (°) between nonhydrogen atoms.

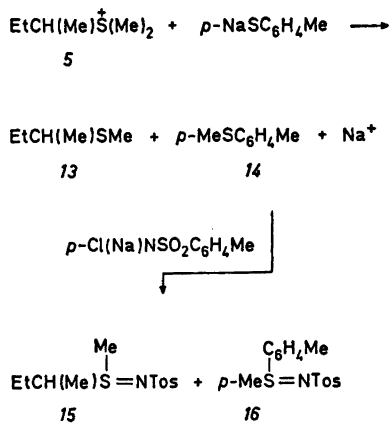
S–C(2)	1.799(6)	C(3)–C(6)	1.510(18)
S–C(3)	1.796(8)	C(4)–C(5a)	1.420(21)
S–C(7)	1.778(8)	C(4)–C(5b)	1.201(27)
O(1)–C(1)	1.198(7)	Cl–O(3)	1.395(9)
O(2)–C(1)	1.328(7)	Cl–O(4)	1.369(9)
C(1)–C(2)	1.500(8)	Cl–O(5)	1.433(5)
C(3)–C(4)	1.528(15)	Cl–O(6)	1.382(7)
C(2)–S–C(3)	104.2(3)	C(4)–C(3)–C(6)	112.6(8)
C(2)–S–C(7)	103.4(3)	C(3)–C(4)–C(5a)	119.2(10)
C(3)–S–C(7)	102.4(4)	C(3)–C(4)–C(5b)	120.0(13)
O(1)–C(1)–O(2)	124.9(6)	O(3)–Cl–O(4)	111.5(5)
O(1)–C(1)–C(2)	124.7(5)	O(3)–Cl–O(5)	108.3(4)
O(2)–C(1)–C(2)	110.4(5)	O(3)–Cl–O(6)	109.6(5)
C(1)–C(2)–S	108.0(4)	O(4)–Cl–O(5)	108.7(5)
S–C(3)–C(4)	108.4(7)	O(4)–Cl–O(6)	108.3(5)
S–C(3)–C(6)	113.6(6)	O(5)–Cl–O(6)	110.4(4)

7,*7̄* and *8*,*8̄*, under closely controlled conditions, yielded the monochiral, racemic sulfonium salt (*11*,*11̄*), the ^{1}H NMR spectrum of which exhibited signals at δ 2.83 and 2.77 (in CD_3CN). These could be attributed to the *pro*-(*R*) and *pro*-(*S*) *S*-methyl-groups of *11* [or, to be sure, the *pro*-(*S*) and *pro*-(*R*) of *11̄*], respectively, by comparison with the spectrum of the trideuteriomethyl analogue (*12*,*12̄*). The latter was produced by exchange of the carboxymethylsulfonium salt (*7*,*7̄*) with D_2O, followed by decarboxylation, performed in $(CD_3)_2CO$ under non-equilibrating conditions; only the signal at δ 2.83 persisted with unchanged intensity.



11 *12*

Repetition of the above sequence with 2-^{14}C-bromoacetic acid yielded a specimen of the salt (*7a*,*7̄a*), which, after recrystallization to constant specific activity, was converted, by decarboxylation, into the (R_cR_s/S_cS_s) salt (*9a*,*9̄a*). Comparison of the ^{1}H NMR spectrum of the product with that of the deuterated salt (*12*) showed it to be contaminated with less than 10 % of the diastereomeric (R_cS_s/S_cR_s)-salt (*10a*,*10̄a*). In boiling acetonitrile, a specimen of the salt underwent pyramidal inversion, resulting in an equilibrium mixture containing nearly equal amounts of the diastereomeric salts (*9a*,*9̄a* and *10a*,*10̄a*). Its composition was established by comparison of its ^{1}H NMR spectrum with that of the deuterio-ion (*12*). The *ca.* 9:1 and 1:1 mixtures were studied separately as donor substrates in the transmethylation reaction. This proceeded smoothly on treating a dimethylformamide solution of the 4-methylbenzenesulfonate of dimethyl(1-methylpropyl)sulfonium ion (*5*) with sodium 4-methylbenzenethiolate, yielding an equimolar mixture of 2-(methylthio)-butane (*13*) and 1-methyl-4-(methylthio)-benzene (*14*). In order to facilitate their quantitative separation, the sulfide mixture was converted into a corresponding mixture of *S*-methyl-*S*-(1-methylpropyl)-*N*-[(4-methylphenyl)sulfonyl]-sulfimide (*15*)[4] and S-methyl-



S-(4-methylphenyl)-*N*-[(4-methylphenyl)sulfonyl)]sulfimide (*16*).[7] These were separated by liquid chromatography, yielding the two known, crystalline components. As expected, the former derivative consisted of two, non-separated racemates, revealed by the appearance of several, slightly anisochronous signals in its ^{1}H NMR spectrum. The same reaction sequence was subsequently applied to (i) the *ca.* 9:1-, and (ii) the *ca.* 1:1-mixture of the diastereomeric, ^{14}C-labelled salts (*9a*, *9̄a* and *10a*, *10̄a*), yielding the radioactive analogues of *15* and *16*, both of which were recrystallized to constant activity. The distribution of radioactivity in the individual specimens can be calculated from the data presented in Table 3. Arithmetical correction of the experimentally derived 'mean values' (see Table 3), obtaining for the two above mixtures of diastereomers, afforded the values 1.14 ± 0.02 and 1.18 ± 0.03, respectively, for the activity ratio $A_{(15)}/A_{(16)}$ pertaining to the homogeneous isomers (*9a*, *9̄a* and *10a*, *10̄a*).

DISCUSSION

As is apparent from Table 3, the prochiral methyl groups of the racemic ion (*9a*, *9̄a*), exhibit considerable selectivity in their reaction with the attacking nucleophile, the 4-methylbenzenethiolate ion. That only a minute fraction of the observed selectivity is attributable to the topologically conditioned, non-identical reaction rates of the two groups becomes apparent, however, when the data are compared with those obtaining for the diastereo-

Table 3. Relative specific activities, $A_{(n)}$ of compounds n, determined on at least three individually weighed samples, each counted at least four times. Specific activities were within the range 0.3 – 3.2 μCi mmol^{-1}.

$A_{(9a,\ \overline{9a})}$ [a]	$A_{(9a,\ \overline{9a})}+A_{(10a,\ \overline{10a})}$ [b]	$A_{(15)}$	$A_{(16)}$	$A_{(15)}/A_{(16)}$	Mean value
1.000 ± 0.020 [c]		0.527 ± 0.012	0.460 ± 0.011	1.147 ± 0.037	1.144 ± 0.023 [d,f]
1.000 ± 0.018		0.529 ± 0.012	0.464 ± 0.005	1.140 ± 0.028	
	1.000 ± 0.012	0.534 ± 0.006	0.455 ± 0.006	1.174 ± 0.020	
	1.000 ± 0.018	0.525 ± 0.006	0.456 ± 0.009	1.152 ± 0.027	1.160 ± 0.015 [e,f]
	1.000 ± 0.016	0.523 ± 0.011	0.453 ± 0.006	1.155 ± 0.028	

[a] With a maximum contribution of 10 % of the activity from (*10a*, $\overline{10a}$). [b] An approximately 1:1 mixture of the two diastereometers. [c] Mean errors were calculated from the observed values and include an allowance for a 1 % contribution from possible impurities. [d] Calculated for homogeneous (*9a*, $\overline{9a}$): 1.14 ± 0.02. [e] Calculated for homogeneous (*10a*, $\overline{10a}$): 1.18 ± 0.03. [f] Mean values calculated from values of $A_{(15)}$ and $A_{(16)}$ without any rounding off.

meric racemate (*10a*, $\overline{10a}$). Evidently, the isotope effect plays a predominant role in determining the observed differences in reaction rates. Put into quantitative terms, the contribution, D, arising from the diastereotopic nature of the two *S*-methyl groups of the dimethylsulfonium ion (*11*) can be expressed as follows:

$$D=\frac{k_R^{11}}{k_S^{11}}\equiv\left[\frac{k_{12}^{9a}\,k_{14}^{10a}}{k_{14}^{9a}\,k_{12}^{10a}}\right]^{\frac{1}{2}}\times\left[\frac{k_{14}^{9a}\,k_R^{11}}{k_S^{11}\,k_{14}^{10a}}\times\frac{k_{12}^{10a}\,k_R^{11}}{k_S^{11}\,k_{12}^{9a}}\right]^{\frac{1}{2}}=\left[\frac{k_{12}^{9a}\,k_{14}^{10a}}{k_{14}^{9a}\,k_{12}^{10a}}\right]^{\frac{1}{2}}\times\left[\frac{I_R\,I_R^*}{I_S\,I_S^*}\right]^{\frac{1}{2}}$$

where k_n^i denotes the rate constant relating to the ^{12}C isotope-labelled methyl group in compound No. $i,\bar{i}$; k_R^{11} and k_S^{11} the rate constants pertaining to the prochiral methyl groups in *11*; and I_R,I_S, respectively I_R^*,I_S^*, the primary and secondary isotope effects of consequence in bond-breaking processes to the diastereotopic methyl groups.*

On the reasonable assumption that $I_R=I_S$ and $I_R^*=I_S^*$, and equalling rate constant ratios with activity ratios, it follows that:

$$D=\left[\frac{k_{12}^{9a}\,k_{14}^{10a}}{k_{14}^{9a}\,k_{12}^{10a}}\right]^{\frac{1}{2}}=\left[\frac{1.14\pm0.02}{1.18\pm0.03}\right]^{\frac{1}{2}}=0.98\pm0.02$$

Similarly, the observed, composite isotope effect, I, can be expressed as:

$$I=\left[\frac{k_{12}^{9a}\,k_{12}^{10a}}{k_{14}^{9a}\,k_{14}^{10a}}\right]^{\frac{1}{2}}\equiv\left[\frac{k_R^{11}\,k_S^{11}}{k_{14}^{10a}\,k_{14}^{9a}}\times\frac{k_{12}^{9a}\,k_{12}^{10a}}{k_R^{11}\,k_S^{11}}\right]^{\frac{1}{2}}=\left[\frac{I_S\,I_R}{I_R^*\,I_S^*}\right]^{\frac{1}{2}}$$

Again, inserting the experimentally derived rate constant ratio, one finds:

$$I=\left[\frac{k_{12}^{9a}\,k_{12}^{10a}}{k_{14}^{9a}\,k_{14}^{10a}}\right]^{\frac{1}{2}}=[(1.14\pm0.02)\times(1.18\pm0.03)]^{\frac{1}{2}}=1.16\pm0.02$$

A small, yet probably significant predilection of the 4-methylbenzenethiolate ion for the *pro*-(*S*) *S*-methyl group of *11*, [or, by the same token, the *pro*-(*R*) *S*-methyl group of $\overline{11}$], thus prevails. No conclusions can be drawn from the present study, however, regarding the magnitude of the diastereoselectivity as a function of the donor substrate, the accepting nucleophile, the solvent *etc.*

The composite isotope effect observed in the present work seems among the largest ever reported for ^{12}C/^{14}C-nuclei. It appears of interest, however, that primary isotope effects of comparable magnitude ($\simeq$1.10 – 1.15) have typically been reported for nucleophilic displacement reactions, most likely akin to that involved in the present transmethylation studies.[9]

There is hope that continued studies within this area, encompassing enzymically catalyzed processes, will further clarify the stereospecificity of transmethylation reactions in-

* Large, inverse α-deuterium secondary isotope effects have been reported in the transfer of methyl groups from *S*-adenosylmethionine to 1-(3,4-dihydroxyphenyl)ethane.[8]

volving dimethylsulfonium ions. For the interpretation of such studies, conducted by ^{14}C-labelling technique, the large isotope effect observed in the present study, may serve as a caveat (see *Added in proof*).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope. NMR spectra were recorded on a 90 MHz Bruker HX-90E instrument.

Radioactive measurements were carried out by liquid scintillation technique on a Packard Tricarb Scintillation Spectrometer model 3320; the radioactive components (*ca.* 1 mg) were dissolved in methanol (1.00 ml), and a solution (10.00 ml) of scintillation liquid was added.[10] The efficiency of counting was determined for the individual samples by internal calibration.

(Carboxymethyl)methyl(1-methylpropyl)sulfonium perchlorate and 2,4,6-trinitrobenzenesulfonate. A solution of 2-(methylthio)butane [4] (*6*) (50 mmol), bromoacetic acid (75 mmol), and silver perchlorate (50 mmol) in acetonitrile (50 ml) was kept at 65 °C for 16 h. After filtering off the silver bromide (49.7 mmol), the filtrate was concentrated to an oil. Trituration with ether left a crystalline mixture of two diastereomeric sulfonium perchlorates, composed, according to the ^1H NMR spectrum (in CH_3CN), of approximately equal amounts. Since separation by fractional crystallization was unsuccessful, the perchlorate mixture (30 mmol) was dissolved in water (20 ml). A solution of the tetrahydrate of 2,4,6-trinitrobenzenesulfonic acid (30 mmol) in water (30 ml) was added, and the solid collected by filtration. Repeated recrystallizations from water (50 – 75 ml), followed by thermal equilibration of the mother liquors (heating to 90 °C for 10 – 15 min) and renewed recrystallization, gave a specimen (6 mmol) of one of the diastereomeric trinitrobenzenesulfonates, m.p. 172 – 175 °C (dec.), contaminated, according to ^1H NMR spectroscopy (DMSO-d_6), by less than 5 % of the other isomer [*Me*-S$^+$: δ 2.91 (major isomer), 2.84 (minor isomer)]. Anal. $C_{18}H_{17}N_3O_{11}S_2$: C, H, N, S. The salt (2.5 mmol) was stirred with sodium perchlorate monohydrate (2.5 mmol) in nitromethane (10 ml) for 1 h. After centrifugation, and concentration of the supernatant, the residue was recrystallized from acetic acid:ethyl acetate to give an analytical specimen of a perchlorate (~0.8 mmol), again containing less than 5 % of the diastereomeric salt. Anal. $C_7H_{15}ClO_6S$: C, H, Cl, S. This preparation was employed for X-ray analysis.

This virtually homogeneous perchlorate (14 mmol) was dissolved in water, and the solution was slowly passed through a column containing 30 ml of Amberlite IRA-400 ion exchange resin, loaded in its 4-methylbenzenesulfonate form. After concentration *in vacuo* and recrystallization from acetic acid:ethyl acetate (1:3), a crystalline sulfonium 4-methylbenzenesulfonate was obtained (10.6 mmol), containing less than 5 % of the diastereomeric salt and identical with the salt prepared directly, as described below.

X-Ray structure determination. Single crystal X-ray diffraction data for the (carboxymethyl)-methyl(1-methylpropyl)sulfonium perchlorate were collected from a selected crystal with the dimensions $0.22 \times 0.12 \times 0.05$ mm by means of a CAD-4 diffractometer using graphite-monochromatized Mo$K\alpha$-radiation. *Crystal data:* Space-group $P2_12_12_1$, $a = 6.725(1)$, $b = 7.287(1)$, $c = 24.382(2)$ Å and $Z = 4$. The crystal structure was solved by direct methods and refined by conventional least-squares techniques to an unweighted linear R-value of 0.042. Atoms other than hydrogens were allowed to vibrate anisotropically, while the hydrogens were given fixed isotropic values of a size comparable to the vibrations of the attached nonhydrogen atoms. Due to disorder not all of the hydrogens within the 1-methylpropyl group could be located, and some of those located were given fixed positions to avoid divergence during the refinement cycles. In the refinement all of the 828 reflexions, having d-values above 0.76 Å and observed net intensities (not corrected for absorption effects) greater than four times their estimated standard deviations, were used. No attempts were made to determine the absolute configuration. The obtained structural parameters * are given in Tables 4 and 5. The atomic labels used are shown in Fig. 2.

(R_cS_s/S_cR_s)-(Carboxymethyl)methyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate (7,7). A solution in acetonitrile (5 ml) of bromoacetic acid (5.4 mmol), 2-(methylthio)-butane (5.4 mmol), and silver 4-methylbenzenesulfonate (5.2 mmol) was kept at 50 °C for 20 h. After removal of silver bromide (5.0 mmol), and concentration of the filtrate, the residue was washed with ether (removing about 0.5 mmol of carboxymethyl 4-methylbenzenesulfonate, according to ^1H NMR spectroscopy) and recrystallized to give 4.7 mmol of a 1:1 mixture (^1H NMR in CD_3CN) of the two diastereomeric salts. Five recrystallizations from acetonitrile (4 – 8 ml), combined with thermal equilibration of the mother liquors, produced 2.0 mmol of one of the salts, contaminated with less than 4 % of the other. M.p. 116 – 119 °C (dec.). ^1H NMR (CD_3CN): δ 2.87 (s) (*Me*–S$^+$); [the (R_cR_s/S_cS_s)-isomer: δ 2.80 (s)]. Anal. $C_{14}H_{22}O_5S_2$: C, H, S. The salt proved identical with that produced from the perchlorate submitted for X-ray analysis (*vide supra*), and hence consists of the (R_cS_s/S_cR_s)-sulfonium-4-methylbenzenesulfonate (*7,7*).

* A list of structure factors is available from one of the authors (R.N.) on request.

Table 4. Fractional atomic coordinates for all atoms and isotropic temperature factors for the hydrogens.

	x	*y*	*z*	*U*
S	−0.0173(2)	0.3488(2)	0.0955(1)	
O(1)	−0.0099(8)	0.1847(5)	−0.0103(2)	
O(2)	0.1667(9)	−0.0668(5)	0.0102(2)	
C(1)	0.0845(9)	0.0945(7)	0.0215(3)	
C(2)	0.1300(10)	0.1498(7)	0.0794(2)	
C(3)	0.0272(16)	0.3872(8)	0.1672(3)	
C(4)	−0.1122(22)	0.2630(11)	0.2000(5)	
C(5a)	−0.2075(23)	0.3342(25)	0.2474(7)	
C(5b)	−0.2807(34)	0.3093(30)	0.2082(9)	
C(6)	0.2424(22)	0.3649(14)	0.1836(3)	
C(7)	0.1165(14)	0.5315(8)	0.0643(3)	
Cl	0.3584(2)	0.3269(2)	0.3788(1)	
O(3)	0.2034(14)	0.3191(9)	0.3409(4)	
O(4)	0.5324(13)	0.3814(14)	0.3547(4)	
O(5)	0.3858(9)	0.1473(7)	0.4015(2)	
O(6)	0.3117(13)	0.4511(9)	0.4197(3)	
H(1)	0.136(11)	−0.086(9)	−0.018(3)	5.0
H(2a)	0.292(9)	0.184(8)	0.079(2)	5.0
H(2b)	0.080(9)	0.068(8)	0.108(3)	5.0
H(3)	−0.037(9)	0.527(8)	0.182(2)	5.0
H(6a)	0.28	0.23	0.182	10.0
H(6b)	0.26	0.41	0.224	10.0
H(6c)	0.33	0.44	0.160	10.0
H(7a)	0.269(11)	0.541(8)	0.073(2)	5.0
H(7b)	0.057(9)	0.649(9)	0.080(2)	5.0
H(7c)	0.109(10)	0.516(9)	0.031(3)	5.0

Table 5. Thermal parameters for nonhydrogen atoms. The atoms C(5a) and C(5b) were allowed to vibrate isotropically, the others anisotropically.

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	48(1)	36(1)	72(1)	1(1)	10(1)	−4(1)
O(1)	67(2)	50(2)	62(2)	4(2)	−12(2)	−1(2)
O(2)	90(4)	39(2)	56(3)	15(2)	−2(3)	−10(2)
C(1)	48(3)	32(2)	58(4)	−7(2)	5(3)	1(2)
C(2)	56(3)	36(2)	47(3)	2(3)	8(3)	2(2)
C(3)	122(7)	45(3)	62(4)	0(4)	34(5)	−6(3)
C(4)	213(15)	54(4)	136(9)	−13(6)	122(10)	−8(5)
C(6)	177(10)	83(6)	60(5)	−16(7)	−20(6)	−5(5)
C(7)	76(5)	36(3)	70(4)	−3(3)	5(4)	3(3)
Cl	57(1)	40(1)	49(1)	−3(1)	−2(1)	5(1)
O(3)	195(8)	81(4)	146(6)	−28(5)	−113(6)	25(4)
O(4)	128(6)	146(8)	199(9)	−39(6)	79(6)	35(6)
O(5)	101(3)	58(2)	74(3)	16(3)	−1(3)	17(2)
O(6)	176(8)	99(5)	98(4)	57(5)	−6(5)	−32(4)
C(5a)	78(4)					
C(5b)	97(6)					

(RS)-*Dimethyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate(5)* = *(9,$\bar{9}$)* = *(10,$\bar{10}$)*. The individual, *(7,$\bar{7}$)*, or mixed, *(7,$\bar{7}$* and *8,$\bar{8}$)*, diastereomers of the carboxymethylsulfonium 4-methylbenzenesulfonates (1 mmol), were dissolved in anhydrous acetone (2 ml), containing 1.2 mmol of tributylamine. After standing at 50 °C for 10 min, the solutions were cooled, and the residues were washed with ether. The crystalline product (0.98 mmol), which proved homogeneous on ^{1}H NMR spectroscopy (CD_3CN), was recrystallized from acetone:ethyl

acetate to give an analytical specimen (hygroscopic) of (*RS*)-dimethyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate (*5*) = (*9,9̄*) = (*10,10̄*), m.p. 80 – 82 °C. Anal. $C_{13}H_{22}O_3S_2$: C,H,S. ^{1}H NMR (CD_3CN): δ 2.83 (s) (*pro-(R) Me-S*$^+$) 2.77 (*pro-(S) Me-S*$^+$), as specified in the enantiomer *11*.

Decarboxylation of the corresponding perchlorates proceeded similarly to give the homogeneous, yet non-crystalline dimethyl(1-methylpropyl)sulfonium perchlorate.

Methylation of 2-(methylthio)-butane proceeded readily on keeping it (62 mmol), admixed with methyl 4-methylbenzenesulfonate (60 mmol), at 90 °C for 3 h. Extraction with ether (2 × 40 ml), and recrystallization from acetone:ethyl acetate afforded the pure dimethyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate(*5*) = (*9,9̄*) = (*10,10̄*).

Methylation of sodium 4-methylbenzenethiolate with (RS)-dimethyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate. The transmethylation proceeded rapidly in dipolar, aprotic solvents. In a typical run, a solution of the sulfonium salt (1.0 mmol) and the sodium thiolate (1.1 mmol) in dimethylformamide (2 ml) was kept for 1 h at 23 °C, when ^{1}H NMR spectroscopy revealed a quantitative conversion to the sulfides (*13* and *14*).

Sulfimide derivatives and their separation. A 3 N solution of anhydrous Chloramine T in dimethylformamide (3 ml), prepared from the commercial trihydrate by azeotropic distillation with chlorobenzene,[11] was added to the above sulfide mixture. After standing at 23 °C for 1 h, when conversion was complete according to ^{1}H NMR spectroscopy, most solvent was removed (< 55 °C/10 mm), and the residue was taken up in benzene (10 ml). The solution was washed with sodium hydroxide and water, and the benzene was distilled off.

The residue was applied to a silica gel column ('Merck Fertigsäule, Kieselgel 60, Grösse B') and the column was eluted with ethyl acetate, with continuous UV-detection of the effluate. Fraction 1 (30 – 45 min), and fraction 2 (80 – 120 min) were collected separately. The former yielded 0.5 – 0.7 mmol of *S*-methyl-*S*-(4-methylphenyl)-*N*-[(4-methylphenyl)sulfonyl]-sulfimide (*16*), which was recrystallized from benzene:light petroleum, m.p. 125 – 127 °C (Ref. 7, m.p. 125 – 126 °C), ^{1}H NMR ($CDCl_3$): δ 2.82 (s), *Me* – S (Ref. 12, δ 2.81), whereas fraction 2 afforded *S*-methyl-*S*-(1-methylpropyl)-*N*-[(4-methylphenyl)sulfonyl]-sulfimide (*15*), m.p. 80 – 94 °C (Ref. 4, m.p. 79 – 80 °C). The broad melting point range, in connection with doubling of several of the signals in the ^{1}H NMR spectrum, *e.g.* $\Delta\delta$ 0.005 in the δ 2.52 (s) signals (*Me* – S), is indicative of the derivative being a mixture of two diastereomeric racemates.

Deuterium exchange experiments. The virtually homogeneous carboxymethylsulfonium 4-methylbenzenesulfonate (*7,7̄*) (0.4 mmol) was dissolved in D_2O (1 ml) and the solution was concentrated to dryness *in vacuo*. The procedure was repeated, and the crystalline residue was dried *in vacuo* over phosphorus pentoxide. ^{1}H NMR control revealed a content of more than 95 % of the (R_cS_s/S_cR_s)-[*carboxymethyl*-$^2H_3$]methyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate.

Decarboxylation, carried out in acetone-d_6 (dried over molecular sieve MS 3), as described above, yielded the (R_cR_s/S_cS_s)-[*methyl*-$^1H_3$]-[*methyl*-$^2H_3$] (1-methylpropyl)sulfonium 4-methylbenzenesulfonate (*12,12̄*), containing less than 10 % of the diastereomeric racemate, as estimated from the intensity of the signal at δ 2.77.

Thermal equilibration of the above mixture in acetonitrile-d_3 at 71 °C proceeded as a first order reaction with a rate constant $k_1 = k_{-1}$ of 1.5 × 10^{-4}s.

^{14}C-Labelling experiments. 2-^{14}C-Bromoacetic acid (Amersham Radiochemicals CFA.18) (35 μCi), was employed as an alkylation reagent in experiments identical to those described above, with regard to scale as well as execution. After recrystallization to constant activity, a 40 % yield of the (R_cR_s/S_cS_s)-[*carboxymethyl*-$^{14}C_1$]methyl(1-methylpropyl)sulfonium 4-methylbenzenesulfonate (*7a,7̄a*), containing less than 4 % of the diastereomeric salt, was obtained.

Again, the decarboxylation was carried out precisely as described above. Before recrystallization of the product to constant activity, it was diluted with an equal quantity of non-labelled product.

The transmethylation, derivation, and separation were performed as described.

The combined mother liquors from the recrystallizations of the decarboxylated products in two experimental series were concentrated, redissolved in acetonitrile (10 ml), and heated, in separate experiments, to 74 °C for 2, 4, and 27 h. The specific activity was reduced by 50, 80, and 80 %, respectively, by adding non-labelled material. After recrystallization to constant activity, the three samples were separately taken through the usual sequence of transmethylation, derivation, separation, and radioassay.

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Added in proof. Methyl group transfer from the ion *9,9̄a* to 1-adamantanethiolate ion to give 1-adamantyl methyl sulfide, characterized as *S*-methyl-*N*-[(4-methylphenyl)sulfonyl]-*S*-(tricyclo[3.3.1.1.^{3,7}]decyl)sulfimide, m.p. 176 – 178 °C [Anal. $C_{18}H_{25}NO_2S_2$:C,H,N,S], proceeded

with very similar selectivity: $D = 0.97 \pm 0.02$, and $I = 1.16 \pm 0.03$.

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