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Application of the Endocyclic Restriction Test to the Rearrangement of Methyl 2-Mercaptobenzoate to 2-(Methylthio)benzoic Acid

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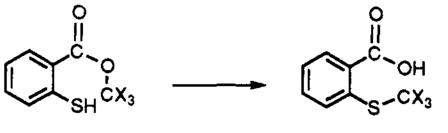
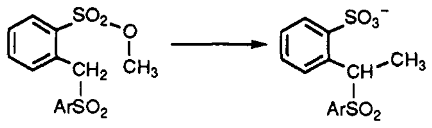
Bimolecular nucleophilic substitution at saturated carbon, the S_N2 mechanism, is thought to proceed with inversion of configuration through a trigonally bipyramidal transition state with the entering and leaving groups colinear with the carbon atom.[1] Therefore, it was surprising that the rearrangement of methyl 2-mercaptobenzoate (**1**) to 2-(methylthio)benzoic acid (**2**), initiated by heating **1** in basic media, was reported to be largely, perhaps exclusively, intramolecular.[2] If this reaction follows an S_N2 pathway, the S–C–O angle in a hypothetical six-membered cyclic transition state would be far from the approximate value of 180° usually assumed for this mechanism.

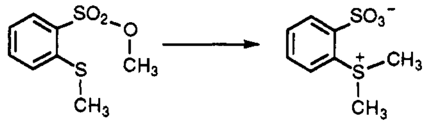


1, X = H; **1**-**d_3**, X = D **2**, X = H; **2**-**d_3**, X = D

Eschenmoser[3] and King[4] probed the angular requirements for an S_N2 mechanism using the endocyclic restriction test.[5] Eschenmoser found that a six-membered cyclic transition state was not involved to any measurable extent in the rearrangement of the α-sulfonyl carbanion of **3** to **4** or of **5** to **6**; *i.e.*, the methyl group was transferred inter- and not intramolecularly. Later, King found that a dilute solution of **7b** (5×10^{-3} M) rearranged to **8b** with 16% of the reaction being intramolecular. The angular requirements of an S_N2 mechanism were accommodated by a nine-membered cyclic transition state. A similar transformation of **7a** to **8a** which, if it were intramolecular, would have involved an eight-membered cyclic transition state was exclusively intermolecular. Martin showed that a 17° deviation from linearity was allowed in an S_N2 substitution reaction involving S–C–S atoms.[6] Perhaps endocyclic reactions with transition states deviating greatly from linearity are possible but not detected because of competing intermolecular processes in which the transition states have more favorable geometries.[7] However, attempts to detect bimolecular substitution proceeding through four-centered transition states and/or with retention of configuration have been unsuccessful.[8,9] With these results and ideas in mind, it was of interest to see if the rearrangement of **1** to **2** was intramolecular as reported.



3 **4**



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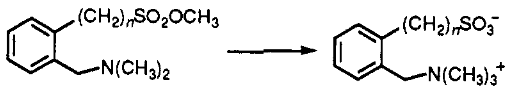

7 **8**

a, $n = 1$; **b**, $n = 2$

Table I. Relative Intensities of Mass Spectral Peaks

compds	m/z	intensity	compds	m/z	intensity
10 + **10**-d_3	202	100[a]	**10** + **10**-d_3	206	95.1 ± 13.9
	204	37.1 ± 3.9		208	43.6 ± 6.6
	205	94.9 ± 6.8	**2** + **2**-d_3	169	100[b]
	207	34.7 ± 2.9		170	10.9 ± 1.3
10 + **10**-d_3	203	100[b]		172	133 ± 18
	205	45.4 ± 7.7		173	13.7 ± 1.1

[a] EI, M^+ normalized to 100%; average of six spectra ± sample standard deviation. [b] CI, MH^+ normalized to 100% average of 19 spectra ± sample standard deviation.

Trideuteriomethyl ester **1**-d_3 and methyl 4-chloro-2-mercaptobenzoate (**9**) were prepared as described[10] from the corresponding acids for use in a cross-over experiment; *i.e.*, the endocyclic restriction test. An equimolar mixture of esters **1**-d_3 and **9** was heated under nitrogen in tri-*n*-butylamine. The resulting mixture of S-methylated acids was examined by electron impact (EI) and chemical ionization (CI) mass spectrometry; the data obtained are given in Table I. If the reaction proceeded with exclusive intramolecular transfer of the *S*-methyl and *S*-trideuteriomethyl groups, **1**-d_3 would have given only **2**-d_3, and **9** would have given only **10**. No crossover products, **2** and **10**-d_3, would have been formed. This analysis assumes that the rates of intermolecular rearrangement of the esters are comparable, although the *p*-chlorobenzoate anion is probably a better leaving group than the benzoate group in S_N2 reactions. α-Isotope effects should have no significant influence on rates, since they are approximately unity in S_N2 reactions.[11]

In the EI mass spectrum, the molecular ion region of **10** had peaks for **10** at $m/z = 202$ (M^+) and **10**-d_3 at $m/z = 205$ (M^+) of almost equal intensity; *i.e.*, **10**/**10**-d_3 = 1.06 ± 0.08. The molecular ion peaks at m/z 204 and 207 for the

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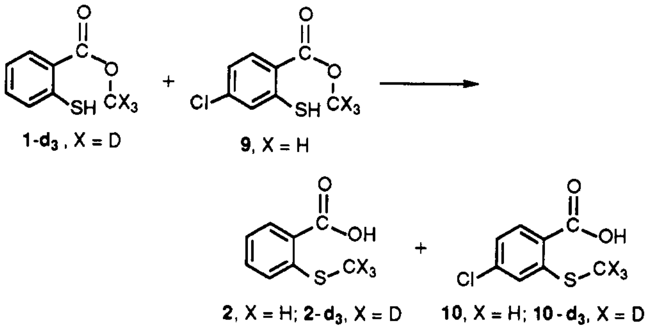
^{37}Cl isotopomers of **10** and **10**-d_3, respectively, are also of almost equal intensity; *i.e.*, the ratio is 1.07 ± 0.10. These results indicate that the transfer of the ester methyl group to the sulfur atom took place almost equally from OCH_3 and OCD_3 groups; the rearrangement of **9** to **10** is largely, perhaps completely, intermolecular. Unfortunately, the molecular ion peaks for **2** at 168 and **2**-d_3 at 171 overlapped with peaks arising from the fragmentation of **10**.



CI mass spectra obtained using methane were of no help, but when isobutane was used, the molecular ion region for **2** and **2**-d_3 appeared to be free of major fragments from **10**. The (MH^+) 203/206 ratio for **10**/**10**-d_3 was 1.07 ± 0.16 and for the corresponding ^{37}Cl isotopomers at 205/208 1.04 ± 0.20. But the (MH^+) ratio **2**/**2**-d_3 was 0.77 ± 0.11 and for the (MH^+ + 1) peaks 0.79 ± 0.08. The deviation of these ratios from unity could be caused by several factors. Any unreacted esters **1**-d_3 and **9** would cause an apparent decrease in **2**/**2**-d_3 and an increase in **10**/**10**-d_3, but such contamination was absent, as shown by TLC, so this possible cause can be excluded. The rates for the reactions of the various nucleophilic species with the various esters should differ, and as a consequence, this would cause the ratios to deviate from unity. Another possible explanation is that a fraction of the reaction was intramolecular; this would cause the ratios to deviate as observed. This formal possibility seems unlikely in view of the **10**/**10**-d_3 ratios and our current conception of the S_N2 mechanism.

If the results obtained for the transformation of **1** to **2** and **9** to **10** are general, and there seems no reason to believe otherwise, then rearrangements of this kind are largely, very likely exclusively, intermolecular and not intramolecular as reported earlier.[2]

Experimental Section

General. Mass spectrometry was carried out on a Hewlett-Packard Model 5988-A GC/MS quadrupole spectrometer using electron impact ionization at 70 eV. Chemical ionization was performed using isobutane. Spectra were measured at various ion currents. The molecular ion intensity was normalized to 100% and the intensity of the other peaks measured against it. These intensities were averaged and are reported in the Table I. Peak ratios were obtained from each of the same spectra, averaged, and are reported in the text together with the sample standard deviations. NMR spectra were obtained in $CDCl_3$, unless reported otherwise, at 360 MHz for ^{1}H and at 90.6 MHz for ^{13}C and are reported in ppm from internal TMS. IR spectra were obtained on a Nicolet Model 520 FT spectrometer.

Methyl-*d*$_3$ 2-mercaptobenzoate (1-*d*$_3$) was prepared according to the literature by esterification of 2-mercaptobenzoic acid using methanol-d_3 and gaseous HCl:[10] bp 82–86 °C (0.2–0.3 mm); IR (neat) 2551 (SH), 2256, 2193, 2129, 2087 (CD) cm^{-1}; ^{1}H NMR δ 4.67 (s, 1 H), 7.11–8.10 (m, 4 H); ^{13}C NMR δ 51.5 (septet), 124.7, 125.8, 130.9, 131.7, 132.5, 138.3, 167.2; MS *m/z* (relative intensity) 171 (23, M^+), 136 (M^+ − CD_3OH), 100). **Methyl 4-chloro-2-mercaptobenzoate (9)** was prepared according to the literature:[10] mp 42–44 °C; bp 118–122 °C (0.2–0.3 mm); IR (neat) 2558, 2516 (SH) cm^{-1}; ^{1}H NMR δ 3.86 (s, 3 H), 4.80 (s, 1 H), 7.04–7.92 (ABX, 3 H); ^{13}C NMR δ 52.4, 124.1, 124.9, 130.1, 132.8, 138.6, 140.5, 166.5; MS *m/z* (relative intensity) 202 (18, M^+), 170 (M^+ − CH_3OH, 100).

Rearrangement of 1-*d*$_3$ and 9. A mixture of **1**-d_3 (0.997 g, 5.82 mmol), **9** (1.18 g, 5.82 mmol), and tri-*n*-butylamine (12 g, 65 mmol) was heated to effect solution. The air was replaced with nitrogen, and the solution was heated at 175–180 °C for 6 h and then at 205–210 °C for an additional 5 h. The mixture separated into two layers upon cooling. Each layer was diluted with water and acidified with hydrochloric acid to yield a total of ~2 g of product which was analyzed by MS.

Rearrangement of Methyl 4-Chloro-2-mercaptobenzoate (9) to 4-Chloro-2-(methylthio)benzoic Acid (10). Ester **9** (1.2 g, 5.9 mmol) and tributylamine (6 g, 32.5 mmol) were heated under nitrogen at 175–180 °C for 6 h and at 205–210 °C for an additional 5 h. Workup as described above gave **10** (0.9 g, 75% yield) which was purified by recrystallization from ethanol-hexane to give two crops of crystals (0.42 g, mp 209–211 °C and 0.25 g, mp 208–210 °C) for a 55% yield: IR (KBr) 3300–2500 (b, OH), 1673 (C=O) cm^{-1}; ^{1}H NMR δ (acetone-d_6), 2.48 (s, 3 H), 7.23–8.05 (ABX, 3 H), 11.44 (b, 1H, COOH); ^{13}C NMR (acetone-d_6), δ 15.4, 124.1, 124.8, 126.1, 133.8, 139.4, 147.4, 166.7; MS *m/z* (relative intensity) 202 (100, M^+). Anal. Calcd for $C_8H_7ClO_2S$: C, 47.41; H, 3.48. Found: C, 47.49; H, 3.55.

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