65. On the Methyl-Transfer Reaction in Crystalline Methyl 2-(Methylthio)benzenesulfonate: a Thermally Induced Non-Topochemical Solid-State Reaction

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(20.II.91)

The rearrangement of methyl 2-(methylthio)benzenesulfonate (1) to the zwitterionic 2-(dimethyl-sulfonium)benzenesulfonate (2) is known to proceed in solution by intermolecular Me transfers. The same rearrangement has been observed to occur in crystalline 1, but the crystal structure shows that the molecular packing is not conducive to intermolecular Me transfer. The reaction has been carried out with mixed crystals composed of 1 and deuteriomethylated (D_6)-1. By fast-atom-bombardment mass spectroscopy, it has been shown that the product consists of a 1:2:1 mixture of the non-, tri-, and hexadeuterated species, the mixture expected, if the solid-state reaction proceeds by intermolecular Me transfers. From this result, together with the slower rates of conversion in the single crystal compared with the melt, it can be concluded that the reaction must occur not topochemically but rather at defects such as microcavities, surfaces, and other irregularities in the ordered crystal arrangement.

Bergman and coworkers [1] have shown that the Me-transfer reaction of methyl 2-(dimethylamino)benzenesulfonate (3) to the corresponding zwitterionic trimethylammon-ium sulfonate (4) proceeds much faster in the crystalline state than in solution or in the melt. They determined the crystal structure of 3 and showed that it contained a particularly favourable arrangement of molecules for intermolecular Me transfer; the rate acceleration in the crystal was then explained as a topochemical effect [2]. During a sabbatical leave in Zürich, one of us (*K.V.*) noticed that the atomic displacement parameters obtained in the crystal structure analysis of 3 indicated a librational motion of the molecules that could move the reacting centers along the putative reaction coordinate (an indication that has recently been confirmed by a redetermination of the crystal structure at 193 and 255 K [3]). Following this observation, *K.V.* became interested in the question of determining the crystal structure of methyl 2-(methylthio)benzenesulfonate (1) and studying its solid-state behaviour. It was already known from the Zurich study of S_N reactions involving endo-cyclic transition states [4–6] that the Me-transfer reaction leading from 1 to the zwitter-ionic product 2-(dimethylsulfonium)benzenesulfonate (2) proceeds not intra- but intermolecularly in solution. A request to the Zurich group for a sample of 1 led to the finding that solid material labeled as 1 in 1968 had completely rearranged to 2 on standing at room temperature for *ca.*16 years. After reconversion to 1 by sublimation of 2, as described in *Tenud*'s dissertation [5], it was shown in Bangalore that partial reaction of

solid **1** to **2** occurs within *ca.* 1 week at 40°. However, the crystal structure analysis of **1**, also done in Bangalore, revealed that the molecular packing was quite unsuitable for a topochemical intermolecular Me transfer, as had been envisaged by analogy with the corresponding solid-state reaction **3** → **4**, even allowing for rotations of the MeOSO$_2$ group about the exocyclic C–S bond and of the Me group about the S–O bond.

The question was, therefore, raised (by *K.V.*), whether the solid-state reaction might then, after all, be *intramolecular* – a suggestion that could hardly fail to stir the Zürich group into activity. From it, 20 years ago [4], had come the proposition that suggestions of this kind, however attractive they might appear to be, have an excellent chance of being wrong and call, in any case that might arise, for specific experimental proof[1]). Moreover, the reaction in question involved not just any system chosen for whatever reasons but one of the two model compounds chosen to illustrate the mechanistic postulate in the earlier
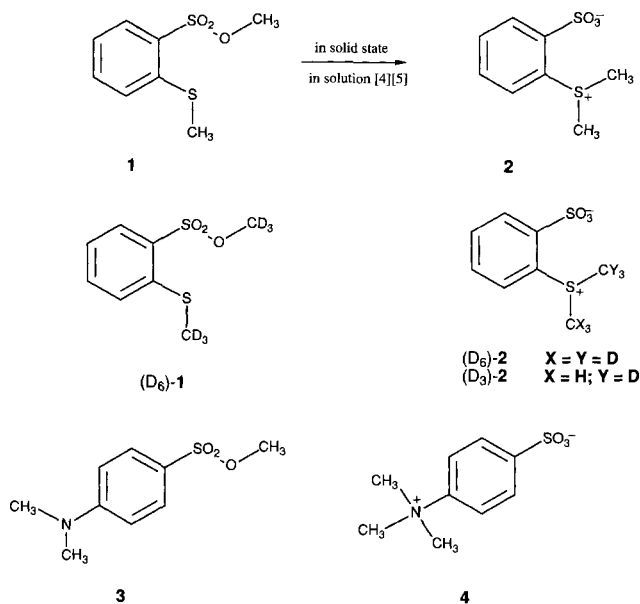
[1]) This translated extract does not quite succeed in conveying the essence of the German original text [4].: 'Es erscheint zwingend, das Ausweichen der Transmethylierungsreaktionen I → II and XI → XII auf den intermolekularen Reaktionsweg als Ausdruck der Eigenschaft des gesättigten Kohlenstoffs aufzufassen, bei S_N2- Reaktionen den Angriff des Nucleophils von der Rückseite her zu fordern. *Die generelle Erfahrung der kinetischen Überlegenheit von intramolekularen gegenüber intermolekularen Reaktionswegen unter topologisch günstigen Voraussetzungen ist nicht einfach auf endocyclische S_N-Prozesse kritischer Ringgrösse extrapolierbar.* Mechanistische *ad-hoc*-Vorschläge dieser Art, so attraktiv sie formal auch erscheinen mögen, haben eine ausgezeichnete Chance, unkorrekt zu sein; gegebenenfalls, erfordern sie einen spezifischen experimentellen Beweis.' Here XI is our **1** and XII is our **2**. Note that the type of intramolecular process repudiated here is exactly equivalent to the 6-*endo-tet* process disallowed in *Baldwin*'s subsequent set of rules [7] for ring-closure reactions.

Zurich study [4]. While the intermolecular nature of the Me-transfer process had been established for the other model compound by crossing experiments, this had not been possible at that time for the **1** → **2** process as FAB-MS (fast-atom-bombardment mass spectrometry) did not yet exist. The intermolecular nature of this reaction in solution rested therefore on kinetic analysis alone. If the solid-state **1** → **2** reaction were indeed to turn out to be intramolecular, it would be the first authenticated example of an endocyclic S_N reaction occurring through a six-membered ring transition state in an associative mechanism.

In view of this situation, it seemed necessary to study the solid-state reaction of **1** in more detail, and, in particular, to establish, by a suitable isotopic labelling experiment, whether the methyl transfer proceeded inter- or intramolecularly in the crystal.

Crystal Structure of 1. – The crystal structure of **1** was first established in Bangalore at room temperature using $\mathrm{Cu}K\alpha$ radiation for data collection and later repeated in Zurich at –80° at higher resolution with $\mathrm{Mo}K\alpha$ radiation. As there are no important differences between the results of the two analyses, we restrict ourselves here to those of the more accurate low-temperature one; crystal data are given in *Experimental*. *Figs. 1* and *2* show
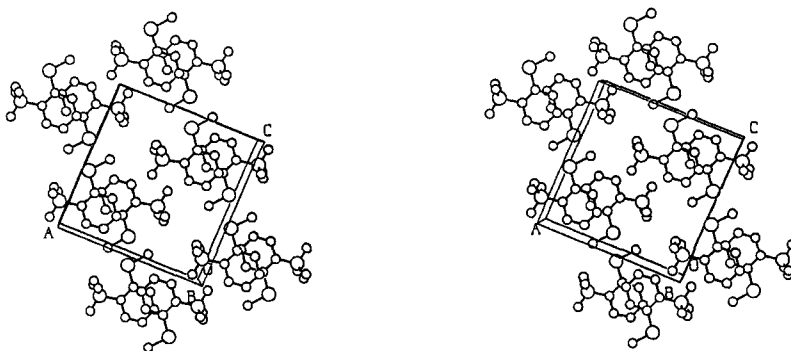

Fig.1. *Stereoview of* **1** *at 190 K along a direction nearly normal to the benzene ring planes*
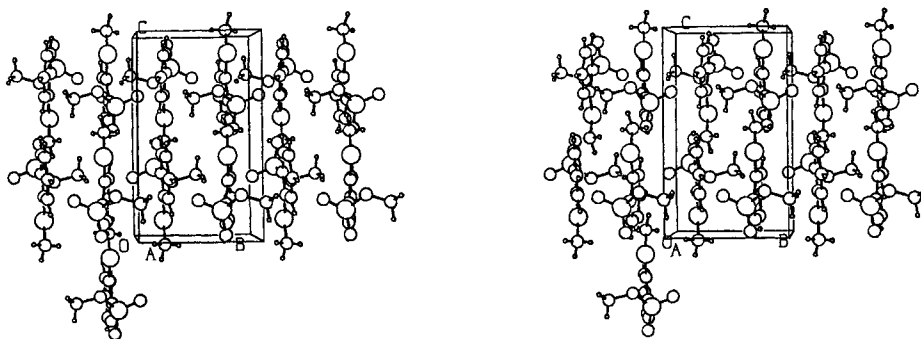

Fig.2. *Stereoview of* **1** *at 190 K along the* a *axis direction*

stereoviews of the molecular packing. Molecules related by the 2_1 symmetry operation form stacks running parallel to the b axis in which aromatic rings of neighbouring molecules are nearly parallel and $ca.$ 3.5 Å apart. There is also a close contact (3.42 Å) between a sulfonyl O-atom O(2) of one molecule and the methoxy C-atom C(7) of the b translation related molecule, the next but one in the stack. From inspection of $Figs.$ 1 and 2, the crystal structure does not look suitable for a topochemical intermolecular S_N2 type transfer of the sulfonyl Me group to the nucleophilic divalent S of a neighbouring molecule; intermolecular $H_3C\cdots S$ distances are at least 5.25 Å, and the linear O–C$\cdots$S requirement is not even remotely satisfied for any neighbouring pair of molecules. Even when rotations about the S(1)–O(3) and S(1)–C(1) bonds are allowed, it does not seem possible to achieve a juxtaposition of the groups suitable for the intermolecular transfer without major disruption of the crystal structure; the $H_3C\cdots S$ distances are too long, and the approach angles are wrong. In the observed molecular structure, the non-bonded intramolecular $H_3C\cdots S$ distance is 3.76 Å and the O—C$\cdots$S angle is 48°. Rotation about the S(1)–O(3) bond alone can reduce this distance to 2.0 Å with an O–C$\cdots$S angle of 122°, and further rotations about this bond and about S(1)–C(1) are all that is necessary to bring the methyl group within bonding distance of the mercapto sulphur atom in a six-membered ring. But the angle in question cannot be increased much past this value without altering the other bonding parameters, and the linear O–C$\cdots$S requirement would not be even remotely fulfilled in a hypothetical transition-state structure with a C$\cdots$S distance of 2.3 Å. Without better knowledge of the structure and energy surface of the corresponding S_N2 transition state, it is hardly possible to make a reliable estimate of the activation energy and rate of this alternative intramolecular reaction.

Reactivity of 1 in the Solid State and in Solution. – Powdered samples of **1** were kept at various temperatures between 36 and 49° (m. p. 54–55°) for various periods. The ratio of **2** to **1** was estimated by ^{1}H-NMR measurements of the product dissolved in (D_6)DMSO (signals of the Me groups of **1** at 3.71 and 2.58 ppm, signal of the Me_2S^+ group of **2** at 3.25 ppm) with allowance for the slow decomposition of **1** in this solvent at room temperature (the amount of decomposition occurring in 10–20 min is negligible). In one experiment, $ca.$ 12–13% transformation of **1** to **2** occurred after 28 days (14 days at 36° and 14 days at 49°); in another, 32% transformation occurred after 20 days at 45°. Whatever the origin of such differences may be (presumably, mainly differences in size and surface area of the powder particles prepared by crushing the crystalline material), the transformation in the powdered material is appreciably faster than was found to occur in single crystals ($ca.$ 6% after 28 days at 49°) and much slower than was found to occur in the melt. On holding the material above the melting point (54–55°) for a few hours, it partially re-solidifies because of the much higher melting point of the zwitterionic product (272–274°). In different experiments, more than 90% transformation was found to occur after 8 h at 70° and virtually 100% transformation after 3 days at 56°. These results alone might appear to cast doubt on the topochemical possibility.

Double-Labelling Experiments. – A distinction between the inter- and intramolecular mechanisms for the solid-state Me transfer reaction can be made by analysis of the reaction product obtained from a crystalline mixture of protio- and deuteriomethylated **1**.

Intramolecular transfer leads to the same distribution of label as in the starting material, *i.e.*, to a mixture of pure (D_0)-**2** and (D_6)-**2**, whereas intermolecular transfer should produce a 1:2:1 mixture of (D_0)-**2**, (D_3)-**2**, and (D_6)-**2**. FAB(+)-MS (fast-atom-bombardment mass spectroscopy) is indicated as the most suitable method for making such analyses, but only if the possibility of isotopic scrambling during the MS experiment can be eliminated. To examine this possibility, various mixtures of (D_0)-**1**, (D_6)-**1**, and of (D_0)-**2**, (D_3)-**2**, and (D_6)-**2** were prepared (by mixed crystallization or by mechanical mixing) and their spectra measured (*Table 1* and *Fig. 3*)[2]. The spectra of **1** are dominated by the molecular ions (m/z 218, 224), those of **2** by the protonated molecular ions (m/z 219, 222, 225). The observed spectra show that neither transformation of **1** into **2** (or **2** into **1**) nor of any significant amount of intermolecular methyl exchange occurs under the conditions of the MS experiment. In particular, the intensity at m/z values attributable to scrambling of Me groups in the mixed samples was never large enough to correspond to any significant amount of this process. On the other hand, the spectrum of the product **2** obtained by the solid-state reaction both in powdered and crystalline samples showed the peaks at m/z 219, 222, and 225 in the approximate ratio 1:2:1, as expected for intermolecular Me transfer (*Table 2, Fig. 4*).

Table 1. *Relative Intensities in the FAB(+)-MS of Artificial Mixtures of* **1**/(D_3)-**1**/(D_6)-**1** *and* **2**/(D_3)-**2**/(D_6)-**2**

No. of scans	Rel. mol. composition			Relative intensities at m/z		
	(D_0)	(D_3)	(D_6)			
	Educt mixture				218	221　224
1	1	0	0	100.0	9.0	0.7
1	0	0	1	1.6	2.6	100.0
1	1	0	1	100.0	10.9	99.2
	Product mixture			219	222	225
1	1	0	0	100.0	4.6±0.4	1.8±0.4
5	0	1	0	1.7±0.1	100.0	3.7±0.0
1	0	0	1	1.2±0.4	0.7±0.4	100.0
4	1	0	1	100.0	1.7±0.2	99.0±2.6
5	1	2	1	57.1±4.5	100.0	56.1±2.4

Table 2. *Comparison of Averaged Intensities of the Artificial 1:2:1-Mixture of* **2**, (D_3)-**2**/(D_6)-**2** *with the Reaction Products of Runs* A *and* B

No. of scans	Rel. mol. composition			Relative intensities at m/z		
	(D_0)	(D_3)	(D_6)	219	222	225
5	1	2	1	57.1±4.5	100	56.1±2.4
5	run A (powder)			54.5±1.4	100	52.8±1.3
5	run B (single crystal)			47.6±2.8	100	52.0±2.7

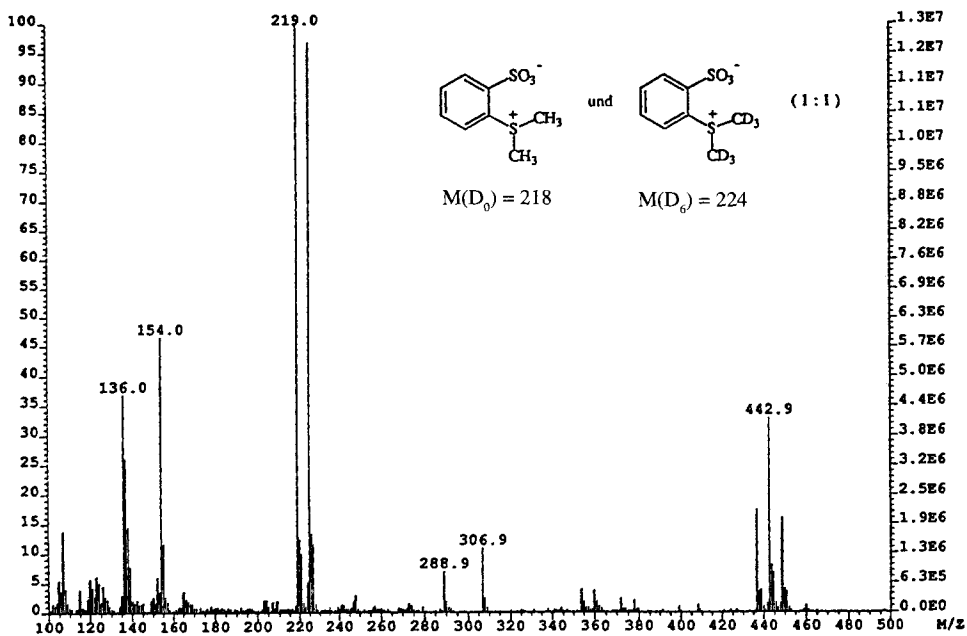[2]　Measured in the laboratories of *Ciba-Geigy AG*, Basel.

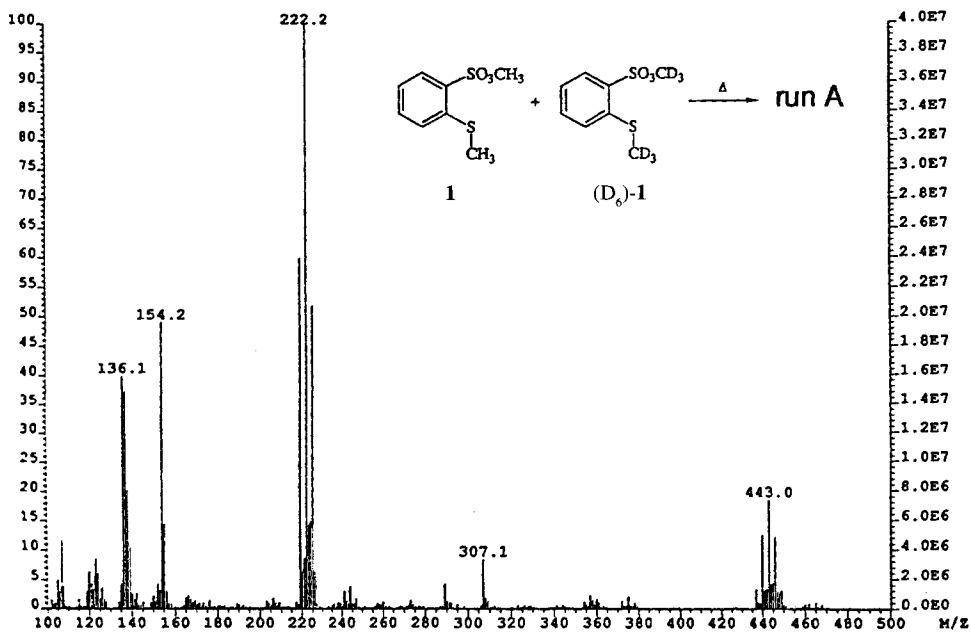Fig. 3. *FAB(+)-MS* (3-NOBA) *of a 1:1 mixture of* 2/(D$_6$)-2

Fig. 4. *FAB(+)-MS of the reaction product of cocrystallized* (D$_6$)-1 *and* 1 *kept at* ca. *49° for 28 days*

Intermediates. – The intermolecular transformation of **1** to **2** involves a sequence of Me transfers. For the analysis of the solid-state reaction, the reacted crystals containing neutral starting material **1** and zwitterionic product **2** were dissolved in a mixture of H_2O and CH_2Cl_2. On separation of the aqueous and organic phases and evaporation to dryness, the educt and product could be obtained separately and their ^1H-NMR spectra measured (in $CDCl_3$ and D_2O, respectively). Not more than traces of intermediates such as **5** and **6** could be detected.

As a check that intermediates were not destroyed during the chemical separation, reacted crystals were also dissolved in (D_6)DMSO (which dissolves ionic as well as neutral species) and analysed directly by ^1H-NMR spectroscopy. Here as well, not more than traces of intermediates could be detected[3]). When the reaction **1** to **2** occurs in solvents such as CF_3COOH the concentration of the ionic intermediates $cf.$ [4] does not rise past a few percent.

Conclusions. – Since the crystal packing is quite unsuitable for intermolecular Me transfer, one can infer that the reaction in the solid-state reaction proceeds not topochemically but rather at defects such as microcavities, surfaces, and other irregularities in the ordered crystal arrangement. This is also suggested by the observation that the transformation in powdered samples is faster than in single crystals but slower than in the melt.

There remains the possibility that the primary reaction **1** to **2** is intramolecular, and that the isotopic scrambling occurs in a subsequent reverse step where **2** is reconverted to **1** intermolecularly. In such a situation, the observed 1:2:1 ratio of the products (D_0)-**2**, (D_3)-**2**, and (D_6)-**2** could result from long equilibration of the labelled reactants and products. Against this possibility speaks the fact that the labelled products were obtained under conditions where equilibrium had not yet been reached, $i.e.$, where the amount of product was still increasing with time. For a reaction in solution or in the gas phase, this would indicate that the reaction was proceeding under kinetic rather than under thermodynamic control. However, for a solid-state reaction one can never be quite certain that one is observing the result of a kinetically controlled process. One can imagine a situation where the solid-state reaction proceeds rapidly to local equilibrium in small, isolated pockets, where increase in product concentration merely means an increase in the number or size of such pockets. We do know that, in the solid, the equilibrium lies far on the side of **2**, so that the rate of the back reaction must be many times smaller than the rate of the forward reaction. However, as we do not know the actual rate constants, only their rough ratio, and since we are ignorant of the nature and properties of the local defects that are presumed to exist, we cannot completely exclude this possibility, and hence the possibility that the primary Me transfer occurs intramolecularly via the 'forbidden' endocyclic reaction. Thus, while the result of the labelling experiment is in agreement with the concept of intermolecular Me transfer, it should not be taken as a rigorous proof.

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[3]) As a complication, slow alkylation of (D_6)DMSO to the (D_6)trimethylsulfoxonium cation occurs. Spectra were therefore recorded as soon as possible (within 10 min) after dissolution of the crystals. In this time, only traces of products arising from DMSO alkylation can be detected.

Nevertheless, we believe that the experiment furnishes strong and even convincing support for the intermolecular pathway. The alternative, intramolecular endocyclic process still awaits any evidence whatsoever in its favour.

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