A Kinetic and X-Ray Diffraction Study of the Solid State Rearrangement of Methyl *p*-Dimethylaminobenzenesulfonate. Reaction Rate Enhancement Due to Proper Orientation in a Crystal[1a]

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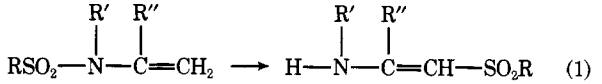
Abstract: Methyl *p*-dimethylaminobenzenesulfonate rearranges in the solid state, as a melt, and in solution to a zwitterionic product, *p*-trimethylammoniumbenzenesulfonate. By a combination of kinetic and field desorption mass spectrometric techniques, we have found that the reaction is intermolecular and that it proceeds at a considerably faster rate in the crystal than it does either in the melt or in solution. The structure of the starting sulfonate has been solved by single crystal x-ray diffraction, and this study revealed that the molecules in the crystal are nearly ideally oriented for reaction in the solid state. Powder diffraction studies have shown that due to the constraints of the starting crystal lattice, the product is initially formed in a metastable crystalline form which slowly reverts to its thermodynamically most stable crystalline modification.

I. Introduction

A. Background. The molecular forces which control both the inter- and intramolecular arrangement of atoms and molecules in a chemical reaction are reasonably well understood. Experimentally, however, few techniques are available which may effectively be used to generate and control those molecular orientations most favorable for chemical reaction in a given system. Perhaps the most spectacular examples of "geometrically" or topochemically controlled reactions are those catalyzed by enzymes. Nature has devised catalysts which appear to be perfectly designed to minimize both the entropic and enthalpic contributions to the free energy of the reaction transition state.[2] Thus, an understanding of possible ways of controlling the reaction geometry for nonenzymic reactions would be of great value.

In this regard, the relative rigidity of the solid state has generated much speculation[3] that it could be an ideal way to simulate orientation dependent catalytic effects. In principle one could imagine two kinds of systems that would have a critical dependence on molecular orientation within a crystal. In one case, crystal packing forces could be used to constrain molecular conformation and either favor or disfavor a particular unimolecular reaction. A second possibility would be systems in which intermolecular interactions could be controlled by the relatively fixed positions of molecules within the crystal matrix.[4]

The question of intermolecular orientational effects has been the subject of much investigation. Many thoroughly studied examples of crystal directed product formation can be found in the area of solid state polymerization.[5] In a wide variety of cases it has been shown that the relative orientation of monomer units dictates both the kinetics of polymerization and the nature of the polymer product. A similar use of crystal packing to propagate a more discrete chemical reaction is postulated in the radiation induced free radical isomerization of *N*-alkyl-*N*-vinylsulfonamides to *N*-alkyl-2-sulfonylvinylamines (eq 1). It was observed[6] that varying R could result in situations

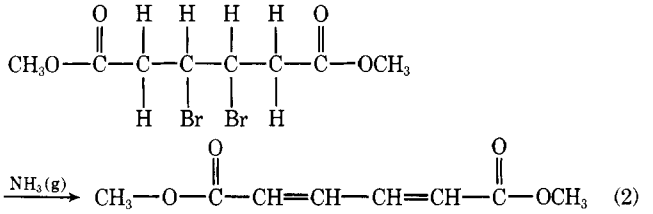


(1)

where crystallinity either enhanced or retarded the observed isomerization. It was further shown that the reaction was a chain process and the authors speculated that the orientation of molecules with respect to their nearest neighbor in the crystal could either enhance or retard the propogation of the radical chain.

A classic case of topochemical control in bimolecular processes is the work of Schmidt and co-workers[7] on the photodimerization of a variety of cinnamic acid derivatives. They were able to show that the relative orientation of starting material monomers could precisely predict the stereochemistry of the dimeric product.

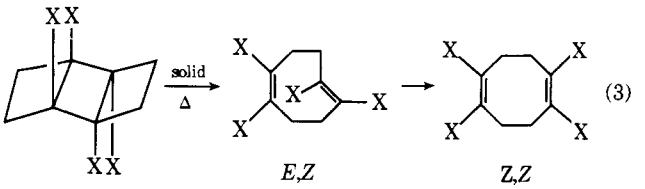
The effect of crystal structure on molecular conformation has also been treated in a variety of systems. A good example of this effect is the base-catalyzed elimination of HBr from dimethyl *meso*-$\beta\beta'$-dibromoadipate[8] (eq 2). In solution one



(2)

obtains a mixture of cis-trans, trans-trans, and cis-cis dienes as well as a variety of side products. However, if the reaction is allowed to proceed in the conformationally fixed crystal, one isolates only the trans-trans diene, the product expected by inspection of the crystal structure of the starting material.

A different kind of system that may demonstrate the constraints a crystal can impose on a unimolecular reaction is seen in the work of Bellus et al.[9] on the following reaction sequence:



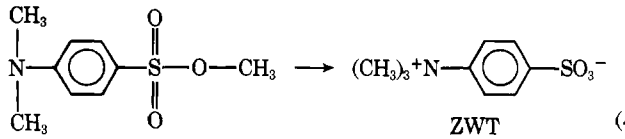
(3)

X = H, $COOCH_3$, CN

When X = H or $COOCH_3$, only the *Z,Z* isomer is isolated. However, when X = CN the reaction can be cleanly stopped at the relatively *unstable E,Z isomer*. The authors speculate that the crystal structure of the tetracyano starting material is such that only minimal motion is needed to go to the *E,Z* isomer. The reaction is stopped at that point by constraints imposed on it by the crystal lattice which forbid the more severe motion needed to go to the final product.

Such considerations raise the rather ironic possibility that when trying to use the solid state as an orienting medium for chemical reactions a problem that is the very opposite of that faced in solution may arise. Is the medium so rigid as to inhibit those molecular motions necessary for product formation? This very general question of the mobility of organic molecules within a crystal has been treated in a number of very elegant studies. McBride and co-workers have obtained considerable information on discrete atomic and molecular motions of very reactive intermediates (free radicals) in the decomposition of various peroxides and azo compounds.[10] Gougoutas[11] has looked at some rare examples of topotactic reactions in which a crystalline starting material goes to a crystalline product whose structure can be analyzed and correlated, by postulated molecular motions, to the structure of the starting material.

B. Statement of Problem. In the course of our work on the solvolysis of a variety of alkyl benzensulfonate esters[12] we noticed a report by Kuhn and Ruelius,[13] later confirmed by Brand and Rutherford,[14] of the following reaction:



MSE ZWT (4)

They indicated that gradually, on standing at room temperature, or more rapidly at higher temperatures, solid methyl *p*-dimethylaminobenzenesulfonate (methyl sulfonate ester, MSE) was cleanly converted to the *p*-trimethylammonium-benzenesulfonate zwitterion (ZWT).

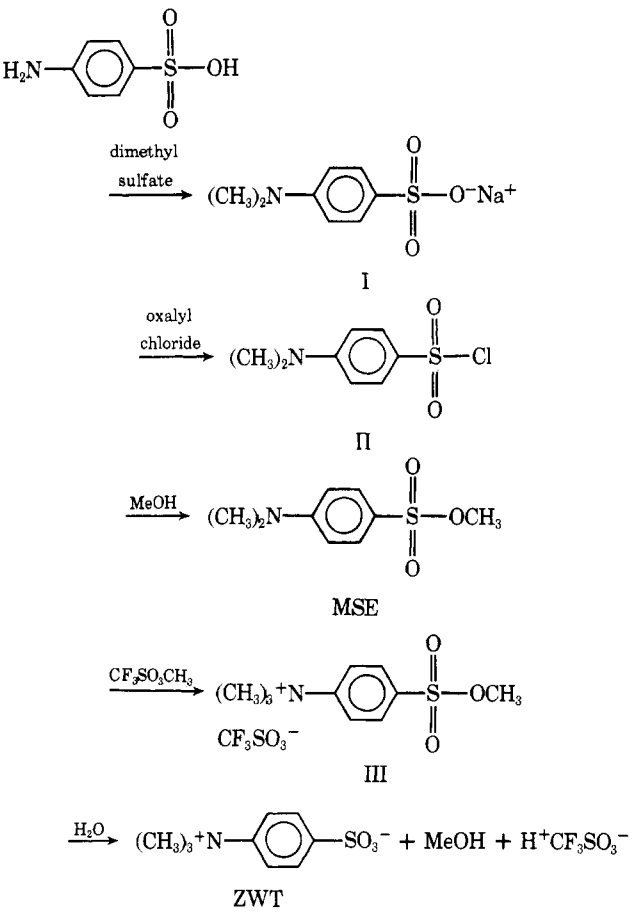
A few years later a report appeared by Valyashko and coworkers[15] in which they claimed that this apparent chemical transformation was in fact only a reorientation of MSE molecules from one crystalline modification to another. They based their conclusions primarily on UV data and the ability to recrystallize the "reaction product" and regenerate starting material.

This controversy was of interest to us not only because modern spectroscopic techniques should easily determine whether the MSE → ZWT conversion was a real chemical transformation, but also because it presented an interesting opportunity for a study of molecular motion in a solid state reaction. We therefore undertook a detailed investigation of this reaction in the hope of answering the following questions: (1) Is the reaction a real chemical transformation and if so what is the mechanism of methyl transfer? (2) How does the structure of the starting MSE relate to the structure of the product and could we say anything about the kinds of molecular motion the crystal would allow? and (3) What role, if any, does the nature of the crystal lattice play in promoting the observed transformation?

II. Results and Discussion

We independently synthesized both MSE and ZWT by the route outlined in Scheme I.[16] It should be noted that ZWT could also be obtained from the solvolysis of other alkylated

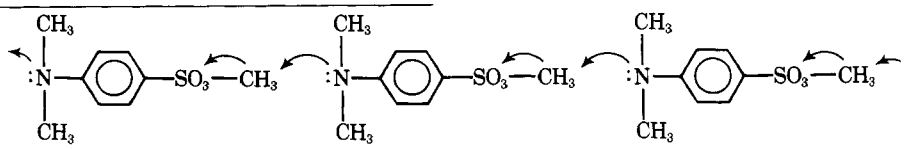
Scheme I



sulfonate esters [see Experimental Section and ref 12].

Even the most concentrated solutions of MSE in a variety of organic solvents were unchanged on standing at room temperature for long periods of time (months or more). However, under these conditions solid MSE, on standing at room temperature, was cleanly converted to ZWT which was identical in every respect with material obtained by solvolysis. Furthermore, we were unable to regenerate any MSE by the reported[15] recrystallization of ZWT from aqueous ethanol. We thus concluded that the reaction was in fact proceeding as initially reported[13,14] and turned our attention to the mechanism of methyl migration.

There are two general mechanisms that might convert MSE to ZWT. One possibility would be a simple intramolecular shift of the ester methyl to the dimethyl amino group. While this is a straightforward process, it is difficult to believe that the transition state for such a transfer would not involve very severe molecular distortion. Alternatively one might suggest an intermolecular chain reaction as shown in eq 5, or at least a dimeric process as in eq 6, or some variation on this intermolecular theme.



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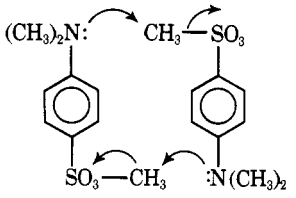
The basic question of inter- vs. intramolecularity was amenable to solution by a "double label scrambling" experiment. Therefore, using commercial perdeuterated dimethyl

Table I. Results of Field Desorption Mass Spectrometry

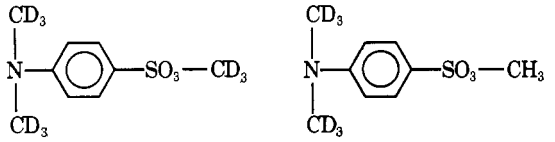
Entry	No. Scans	Relative molar ZWT comp d_0	d_3	d_6	d_9	Observed peaks[a,b] 215	218	221	224
1		1	0	0	0	100			
2	9	0	1	0	0	46	100	45	3
3	9	0	0	1	0	3	41	100	51
4		0	0	0	1				100
5	24	MSE-d_0 and MSE-d_9 reaction mix				43	100	101	46
6	9	1	1	1	1	44	100	98	46
7	14	1	0	0	1	61	100	94	65
8	8	2	1	1	2	49	100	101	54
9	12	1.74	1	1	1.74	47	100	98	52
10	18	1.6	1	1	1.6	46	100	99	47
11	10	0.7	1	1	0.7	44	100	96	39
12	12	0.3	1	1	0.3	37	100	98	34

[a] Intensities normalized so that peak at 218 = 100 (except entries 1, 3, 4). [b] Average standard deviation = ±5 units.



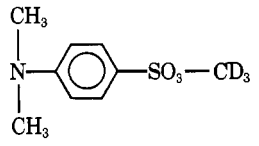
(6)

sulfate and CD_3OD, we synthesized the deuterated MSE isomers MSE-d_9, MSE-d_6, and MSE-d_3. If the reaction were



MSE-d_9

MSE-d_6



MSE-d_3

intramolecular, then a mixture of MSE-d_0 and MSE-d_9 would react to give only ZWT-d_0 and ZWT-d_9, while a random intermolecular transfer of the ester methyl group should produce a 1:1:1:1 ratio of ZWT-d_0:ZWT-d_3:ZWT-d_6:ZWT-d_9. While this seems relatively straightforward, the problem we initially encountered was that the only way to analyze for the ratio of deuterated ZWT isomers is by mass spectrometry. This was problematic since ZWT could not be volatilized in a conventional electron impact mass spectrometer even with the direct solid inlet probe at 500 °C and 10^{-8} Torr. We therefore resorted to field desorption mass spectrometry (FDMS) to carry out these analyses.[18-20]

Authentic samples of ZWT-d_0 (mol wt = 215) and ZWT-d_9 (mol wt = 224), prepared from the appropriate MSE precursors, each gave a FDMS which showed a parent molecular ion and little else. However, a not unexpected[20,21] complication arose when an equimolar mixture of separately generated ZWT-d_0 and ZWT-d_9 (a necessary control experiment) gave, instead of two equal intensity peaks at 215 and 224, partially scrambled labeled methyl groups. In fact, any sample containing a mixture of CH_3 and CD_3 methyl groups gave results which showed some scrambling of possible isomers. Fortunately, the isotope randomization was not complete, and the results were sensitive enough to variations in zwitterion ratios that we still were able to successfully analyze our data (Table I).

The actual experiment involved cocrystallizing a sample containing equal amounts of MSE-d_0 and MSE-d_9 from a homogeneous solution and allowing it to undergo solid state conversion to zwitterion. This mixed product was analyzed by FDMS (entry no. 5) and shown to be identical, within experimental error, with the expected intermolecular product, equal amounts of ZWT-d_0, d_3, d_6, d_9 (entry no. 6). Further controls were carried out (entries 7–12) to determine the limits of detection of an intramolecular reaction component. "Synthetic" potential product isomer mixtures with d_0:d_3:d_6:d_9 ratios of 1:0:0:1, 2:1:1:2, 1.74:1:1:1.74, and 1.6;1:1:1.6, which correlate to 0, 67, 73, and 76% intermolecularity, respectively, were prepared and analyzed. These data revealed that the observed reaction is ≥76% intermolecular (95% confidence limit).

Having established the (at least predominant, but most likely complete) intermolecularity of the rearrangement, we now could view the role of the crystal in this reaction in two ways: either as a very concentrated reaction medium enhancing the reaction rate by allowing close (but isotropic) approach of the reacting molecules, or as a very specifically designed environment that aids the progress of the reaction by *orienting* reactive sites in such a way as to facilitate reaction. Either view would be consistent with the observed stability of MSE solutions relative to solid MSE. To test the importance of ordered crystallinity in this system, we compared the rate of the reaction in the solid with the rate of the reaction in an unoriented medium, the pure melt. Since the melting point of MSE is 91 °C and plunging it into a 95 °C oil bath melts the entire sample within 15 s, we were able to conveniently measure the rate of conversion of MSE to ZWT both as a crystal and a melt.

The data from this kinetic study are given in Table II, and representative plots of percent conversion vs. time at 81 and 95 °C are shown in Figure 1. Because the concept of a rate constant in the crystalline state is somewhat ill defined, we have presented our velocity data in simple concentration vs. time form. The initial rates are probably those which should be attributed to the reactivity of the crystalline compound; as reaction proceeds, and the crystal becomes contaminated with additional amounts of ZWT, the rate of conversion tends to decrease (see Figure 1). In all of the reactions, MSE and ZWT were the only detectable species and the percent conversion of starting material to product was usually measured by partitioning the reaction mixture between $CDCl_3$ (dissolves only MSE) and D_2O (dissolves only ZWT) and integrating their respective NMR spectra.

As previously reported,[13,14] the rate of rearrangement increases at higher temperatures (comparing ambient temperature, 81 and 88 °C) but our results indicate that *this is only true for temperatures below the melting point of MSE.* Melting the starting material introduces a sharp *decrease* in

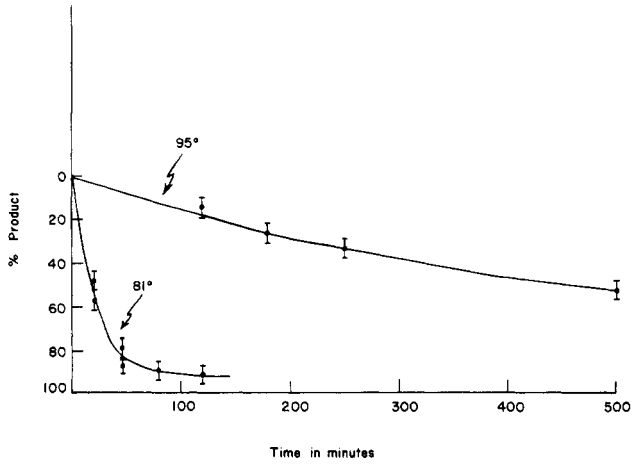


Figure 1. Time dependence of the percent of product observed in the thermal conversion of methyl *p*-dimethylaminobenzenesulfonate (MSE) to *p*-trimethylammoniumbenzenesulfonate (ZWT) at two different temperatures.

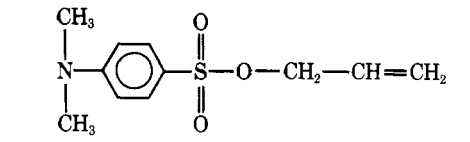
Table II. Conversion vs. Time Data for Conversion of MSE → ZWT[e]

Temp, °C	Reaction time	% product
Amb	1 day	3.3[a,d]
Amb	3 days	21.9[a,d]
Amb	8 days	49.3[a,d]
Amb	17 days	78.8[a,d]
81	20 min	49[b]
81	20 min	55[c]
81	46 min	80
81	46 min	87[c]
81	80 min	88[b]
81	120 min	90
88	10 min	37[b]
88	20 min	55[b]
95	120 min	15[d]
95	120 min	16
95	180 min	26
95	250 min	34
95	500 min	53

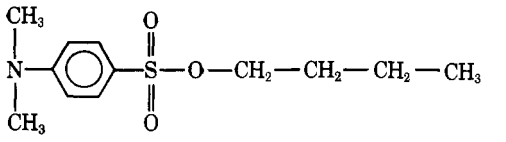
[a] Data from ref 13. [b] All glassware EDTA and base washed. [c] MSE crystallized from MeOH before use. [d] Analyzed by weighing recovered MSE and ZWT. [e] Unless otherwise indicated all samples were powder obtained by rapid removal of solvent from a filtered solution of MSE in ether.

rate of conversion. Two striking examples of this comparison of crystal to melt are: in *10 min* a crystal at 88 °C attains a higher degree of conversion to product than the 95 °C melt attains in over *4 h;* a melt takes *500 min* to achieve the same degree of conversion to product that a crystal at 81 °C (14 °C cooler than melt) attains in *20 min.* This entire set of data seems to show that, at least in terms of initial rates of conversion, the crystal reacts between 25 and 40 times faster than the melt. This indicates that the solid state is providing more than just a high concentration medium for the intermolecular reaction.

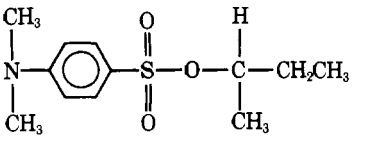
In the hope of extending the scope of this arrangement we prepared compounds IV, V, and VI. However, none of these gave any indication of rearranging to the corresponding zwitterionic species even though one might have predicted that the kind of S_N2 process we envisioned for MSE might be equally possible. Particularly disappointing was the lack of reaction in IV, where one might have predicted a relatively unhindered S_N2'-like process. Clearly the facility of the MSE



IV



V



VI

→ ZWT rearrangement is controlled by factors other than just the normal reactivity of its functional groups.

All of the above evidence pointed toward the hypothesis that the crystal structure of MSE must play an important role in its reactivity. We therefore undertook a determination of the single crystal structure of MSE using x-ray diffraction techniques.

Satisfactory crystals of MSE were obtained from methanol or from a methanol–water mixture. Preliminary precession and Weissenberg photographs suggested the monoclinic space group $P2_1/c$ and gave approximate unit cell dimensions. A least-squares fit to twelve 2θ values measured on a diffractometer yielded more accurate cell parameters: a = 8.942 (2) Å, b = 10.507 (3) Å, c = 11.232 (2) Å, and β = 90.88 (2)°. With four molecules per unit cell the calculated density is 1.43 g cm^{-3}.

Intensity data were measured on a Datex-automated General Electric diffractometer using nickel-filtered Cu K_α radiation. Reflections were collected by the θ–2θ scan technique between 5 and 120° 2θ using a scan spread of 2° min^{-1} and a scan range varying linearly from 2.5° at 2θ = 5.0° to 3.0° at 2θ = 120°. A 20-s background count was measured on both sides of the scan range. After two days of data collection at ambient temperature, the intensities of three standard reflections monitored at 30 reflection intervals decreased anisotropically 40, 45, and 60%, respectively. The data set used in this structure analysis consisted of three subsets, individually corrected for decay using an average, linear correction from the three standard reflections, but collectively scaled together, yielding 750 reflections whose intensities were greater than 3σ (I).

The structure was solved by direct methods with the program MULTAN. Several cycles of the isotropic full-matrix least-squares refinement on the heavy atoms were followed by a difference Fourier wherein all the hydrogen atoms, except those about C(9), were easily located. The hydrogen atoms about C(9) appeared to be disordered and were approximated by six half-populated atoms for structure factor calculations. Anisotropic refinement for the heavy atoms and isotropic refinement for the ordered hydrogen atoms including a secondary extinction parameter gave a residual [= $\Sigma(||F_o| - |F_c||)/\Sigma|F_o|$] of 0.098, and a goodness-of-fit [= $[\Sigma w(|F_o|^2 - |F_c|^2)^2/(M - S)]^{1/2}$ for M = 750 observations and S = 210 parameters] of 4.13 for the $\geq 3\sigma$ data. The final value of the secondary extinction parameter, g,[22] was 2.4(5) × 10^{-6}. The high residual is primarily due to the isotropic correction for the anisotropic intensity decay curve.

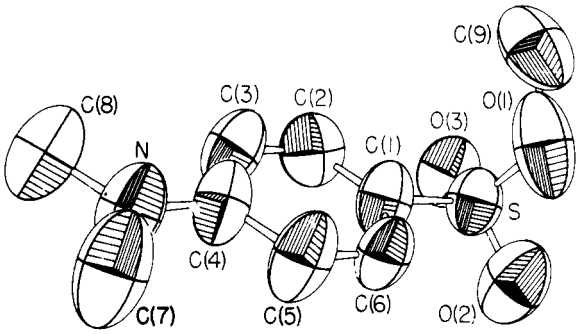


Figure 2. ORTEP drawing of a single molecule of crystalline *p*-dimethylaminobenzenesulfonate (MSE).

Table III. Interatomic Distances and Angles for Methyl *p*-Dimethylaminobenzenesulfonate (MSE)[a]

Distances, Å		Angles, deg	
S-C(1)	1.74	C(9)-0(1)-S	118
S-0(1)	1.50	C(1)-S-0(1)	106
S-0(2)	1.41	C(1)-S-0(2)	109
S-0(3)	1.40	C(1)-S-0(3)	111
0(1)-C(9)	1.49	0(1)-S-0(2)	113
N-C(4)	1.37	0(1)-S-0(3)	101
N-C(7)	1.42	0(2)-S-0(3)	106
N-C(8)	1.47	S-C(1)-C(2)	119
C(1)-C(2)	1.40	S-C(1)-C(6)	121
C(2)-C(3)	1.36	C(1)-C(2)-C(3)	120
C(3)-C(4)	1.39	C(2)-C(3)-C(4)	121
C(4)-C(5)	1.41	C(3)-C(4)-C(5)	118
C(5)-C(6)	1.35	C(4)-C(5)-C(6)	121
C(6)-C(1)	1.37	C(5)-C(6)-C(1)	121
		C(6)-C(1)-C(2)	120
		C(3)-C(4)-N	119
		C(5)-C(4)-N	123
		C(4)-N-C(7)	122
		C(4)-N-C(8)	123
		C(7)-N-C(8)	114

[a] The estimated standard deviation for distances involving sulfur are 0.01 Å; they are 0.02 Å for all other distances. For all of the angles esd's are 1°.

Table IV. Distances and Angles Involving Hydrogen Atoms in *p*-Dimethylaminobenzenesulfonate (MSE)[a]

Distances, Å		Angles, deg	
C(2)-H(2)	0.9	C(1)-C(2)-H(2)	123
C(3)-H(3)	0.9	C(3)-C(2)-H(2)	116
C(5)-H(5)	1.0	C(2)-C(3)-H(3)	114
C(6)-H(6)	0.9	C(4)-C(3)-H(3)	123
C(7)-H(71)	1.0	C(4)-C(5)-H(5)	122
C(7)-H(72)	0.9	C(6)-C(5)-H(5)	116
C(7)-H(73)	0.9	C(5)-C(6)-H(6)	117
C(8)-H(81)	0.9	C(1)-C(6)-H(6)	121
C(8)-H(82)	1.0	N-C(7)-H(71)	109
C(8)-H(83)	1.0	N-C(7)-H(72)	110
		N-C(7)-H(73)	114
		N-C(8)-H(81)	108
		N-C(8)-H(82)	112
		N-C(8)-H(83)	109
		H(71)-C(7)-H(72)	103
		H(71)-C(7)-H(73)	118
		H(72)-C(7)-H(73)	109
		H(81)-C(8)-H(82)	115
		H(81)-C(8)-H(83)	103
		H(82)-C(8)-H(83)	108

[a] The estimated standard deviations on the distances and angles are 0.1 Å and 2.0°.

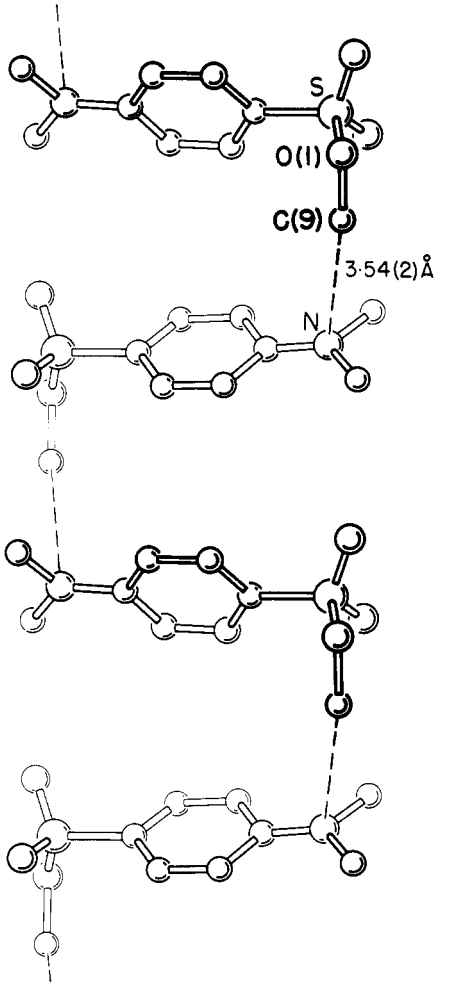


Figure 3. A view of the stacking along one chain of molecules in crystals of methyl *p*-dimethylaminobenzenesulfonate (MSE), as seen perpendicular to the (101) plane. Distance indicated is that between the carbon atom of the methyl group which undergoes transfer in the solid state reaction and the nitrogen atom to which it moves.

The bond distances and angles for the heavy atoms and those involving hydrogen atoms are all within acceptable values and are listed in Tables III and IV. An ORTEP drawing of a single molecule is shown in Figure 2. A view of the stacking of the molecules within a chain in the crystal perpendicular to the (101) plane (Figure 3) is very revealing mechanistically. The molecules stack with alternating dimethylamino and sulfonate groups and with the aromatic rings inclined approximately 76° to each other. Each nitrogen is in alignment with a sulfonate ester methyl group only 3.54 Å away (the sum of the van der Waals radii for CH_3 and N is 3.5 Å); the O(1)-C(9)···N angle is 147° (close to the linear alignment needed for the proposed S_N2-like transition state). The system can therefore readily transfer each ester methyl to its neighboring N atom, and thus the *orientation in the crystal is directly implicated in lowering the entropy of activation of the reaction* by fixing the relative orientation of the reaction sites and facilitating the proposed (5) chain reaction sequence.

A simple formulation of this proposed chain process led us to suspect that it might be possible to actually "see" the propagation of a "reaction front" on a macroscopic scale as has, for example, been observed in some heterogeneous gas-solid reactions by Lin, Curtin, and Paul.[23] We therefore attempted to follow the reaction by recording sequential pictures of a crystal of MSE "reacting" on the stage of a polarizing microscope. Pictures were taken at one day intervals for 2 weeks, and though there was an overall change in crystal appearance,

Table V. Observed *d* Values from Powder Diffraction Study

Calcd MSE	Obsd MSE	MSE +2 days	MSE +6 days	MSE +8 days	Recryst ZWT
7.67	7.69	7.66	7.68	5.77	5.81
6.81	6.84	6.73	6.77	5.23	5.22
5.79[2] [a]	5.81[2]	5.81	5.73	5.11[1]	5.10[1]
5.25	5.26	5.71	5.22	4.77[2]	4.79[2]
4.79	4.80	4.76[1]	5.08	4.51	4.50
4.76[1]	4.76[1]	4.64[2]	4.76[1]	3.65	3.63
4.74	4.72	4.39	4.65[2]	3.49[4]	3.49[4]
4.47	4.49	4.25	4.40	3.12[3]	3.12[3]
4.31	4.32	4.21[3]	4.25	2.00	2.00
4.20[3]	4.21[3]	4.16	4.17[3]		
4.11	4.12	3.84	3.85		
3.88	3.89	3.50[4]	3.50[4]		
3.52[4]	3.53[4]	3.32			
3.34	3.35	3.28			
3.30	3.30	3.26			
3.25	3.25	3.24			
3.13	3.13	3.21			
2.90	2.90	3.12			
2.64	2.63	2.97			
2.46	2.46	2.78			
		2.46			

[a] Superscript numbers indicate the strongest four lines on each film with 1 being the most intense.

consistent with the presence of an ongoing chemical reaction, there was no distinguishable pattern of change relative to the crystal morphology. One might therefore speculate that our proposed reaction is initiated at random points throughout the crystal, akin to random thermal activation in other chemical processes. It is then propagated over microscopically short chains which can be interrupted by random molecular dislocations that are present throughout the crystal in increasing numbers as the reaction progresses.

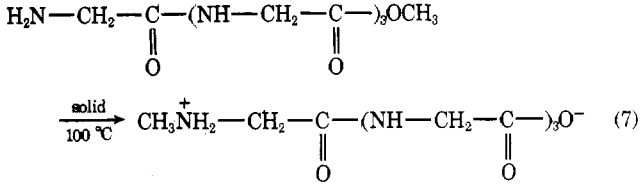
Having demonstrated the absence of uniform long-range molecular motions, we were left with the question of how much molecular motion does go on within the confines of the initial crystal. From our single crystal x-ray work and by simple inspection of the gross crystal morphology of the reaction product, it was obvious that we did not have a clean single crystal → single crystal transformation of the sort that Gougoutas has reported.[11] However, we wondered whether the original MSE structure (a) forces the product molecules into some metastable crystalline state, (b) keeps them relatively amorphous, or (c) allows them enough mobility to reorient themselves into their most stable crystal packing (i.e., the structure they naturally attain when crystallized from solution). We were able to answer this question by inspection of changes in the x-ray powder patterns of MSE as it formed ZWT.

Single crystals of ZWT were grown by recrystallization from H_2O solution. By oscillation and Weissenberg photographs these crystals were found to be orthorhombic with a = 10.15 Å, b = 20.55 Å, and c = 9.69 Å, and a calculated density of 1.41 g/cm^3 for eight molecules per unit cell. The density measured by flotation is 1.39 g/cm^3. The space group is either the centric P_{bam} or the acentric P_{ba2}.

An ether solution of MSE was then evaporated to dryness and its x-ray powder pattern recorded. Additional powder patterns taken after 2, 5, 6, 8, 11, and 33 days were used to photographically follow the rearrangement process, and the *d* values from representative patterns are given in Table V. In the first two columns are shown the values observed for MSE, along with those calculated from the single crystal atomic parameters. The observed and calculated diffraction maxima for MSE show excellent agreement, but neither pattern is consistent with that reported by Valyashko et al.[15] The data for days 2 and 6 (columns 3 and 4) are clearly different from each other as well as from either MSE or ZWT (column 6). After 8 days, however, the pattern is identical with that observed for independently prepared and recrystallized ZWT.

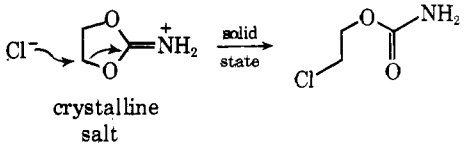
The set of powder patterns therefore clearly indicates the formation of a metastable intermediate, having a different crystalline form (but probably not a different molecular structure) from either MSE or ZWT, after 2 days and the rearrangement of this intermediate into ZWT between 6 and 8 days after the reaction begins. This intermediate lattice is apparently less stable thermodynamically than the final ZWT structure. The diffraction maxima which must be attributed to a structural intermediate in the MSE + 2 days and the MSE + 6 days patterns are the 6.73, 6.77 Å pair, the 5.71, 5.73 Å pair, and the 4.64 and 4.25 Å *d* spacings. The zwitterionic structure obtained at the end of the in situ rearrangement is identical with the structure of the single crystals grown from the water solution as shown in columns 5 and 6 of Table V.

There are other transformations in the literature that may display the same kind of solid state acceleration that we have observed. An interesting example[24] is shown in the following equation:



(7)

Here, too, transfer of a methyl group in a crystalline system results in a stable zwitterionic product. The authors speculate[24] that the rigidity of the crystal lattice may be in part responsible for the behavior of their system, but indicate no attempt to determine the details of the reaction mechanism. There are also many reports in the literature of compounds that are stable in solution but decompose either to known products or intractable tars when isolated in solid form. We suspect that many of these cases (for example,[25] eq 8) may also be examples of nucleophilic attack (or some other process) facilitated by proper molecular orientation within a crystal. These systems merit further investigation.



crystalline salt

(8)

III. Experimental Section

A. General. NMR spectra were obtained on a Varian A60A or T-60 spectrometer. They are reported as: NMR (solvent) chemical shift in units τ (multiplicity, number of protons), etc. IR spectra were recorded either on a Perkin-Elmer Model 257 grating infrared spectrophotometer or on a Perkin-Elmer Model 137 spectrophotometer and are reported in cm^{-1}. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical electron impact mass spectra were obtained on a du Pont 21-492B high-resolution mass spectrometer. All analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

Synthesis. Sodium *p*-Dimethylaminobenzenesulfonate (I). Using a modification of the procedure of Fierz-David and Blangey,[26a] a 1500-ml 24/40 round-bottom flask was charged with 153.8 of sulfanilic acid monohydrate and 69.9 g of sodium hydroxide pellets. Water (700 ml) was added, and the flask was stoppered. While shaking the flask to dissolve all the solid, it became very hot. Dimethyl sulfate (113 g) was added to this hot solution in one portion, and the flask was again shaken (the reaction was *very* exothermic) until the solution was homogeneous. The reaction mixture was allowed to come to room tem-

perature and then placed in the refrigerator overnight. The next day approximately 22 g of wet solid was filtered from the reaction. NaOH (45 g) was dissolved in the supernatant and another 113 grams of dimethyl sulfate were added with shaking. A second crop of 34.5 g of product was recovered the next day.

The products were combined, recrystallized once from water, and dried under reduced pressure at 80 °C to obtain 37 g (21% yield) of clean dry white powder. A similar run using 121.2 g of sulfanilic acid at the start gave 43.5 g (31% yield) of recrystallized material: NMR (D_2O) 7.08 (s, 6 H), 2.74 (AB quart, 4 H).

Sodium *p*-Dimethylaminobenzenesulfonate-d_6 (I-d_6). The procedure was basically the same as for the nondeuterated material except that we used dimethyl-d_6 sulfate (99% deuterated) obtained from Stohler Isotopes, Inc. Sulfanilic acid monohydrate (8.26 g) was mixed with 3.8 g of NaOH pellets and 6 g of Me_2SO-d_6. A second crop was obtained by addition of another 3 g of NaOH and 3 g of Me_2SO-d_6. The total product of 4.4 g of crude material was recrystallized from H_2O and dried to yield 1.1 g of product.

***p*-Dimethylaminobenzenesulfonyl Chloride (II).** A 1000-ml three-neck 24/40 round-bottom flask equipped with N_2 inlet, reflux condensor, mechanical stirrer, and 25-ml addition funnel was charged with 38 g of I (freshly dried at 80 °C under high vacuum) and 410 ml of freshly distilled dry benzene. Oxalyl chloride (17.1 g) was added dropwise over 10 min at room temperature, followed by 1 ml of dry, distilled pyridine. The reaction mixture was refluxed for 3 h at which time the reflux condenser was replaced with a short-path distilling head and the benzene was distilled out (to dryness). Another 100 ml of dry benzene was added to redissolve the product, and the reaction was again distilled to dryness. CH_2Cl_2 was added to dissolve the organic material, and the inorganic salts were filtered off. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$, then with H_2O and saturated aqueous NaCl solution, dried over Na_2SO_4, and then evaporated to dryness. The crude product was recrystallized from ether or an ether/petroleum ether mixture to give 33.8 g of product ranging in color from yellow to emerald green: yield, 90%; mp 109.5–111.0 °C (lit.[27] 110.5–111.5 °C); NMR ($CDCl_3$) 6.9 (s, 6 H), 2.77 (AB quart, 4 H); IR ($CHCl_3$) 1375, 1165, 1090, 810 cm^{-1}. Anal. Calcd for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.55; N, 6.38; Cl, 16.18. Found: C, 43.81; H, 4.42; N, 6.41; Cl, 16.23.

***p*-Dimethylaminobenzenesulfonyl Chloride-d_6 (II-d_6).** The procedure was the same as used for the nondeuterated material, but here 1.1 g of freshly dried sodium sulfonate-d_6 (I-d_6) was mixed with 500 μl oxalyl chloride to give 1.0 g (93% yield) of d_6 chloride (IV-d_6) whose NMR showed no signal at τ 6.9 (<2%).

Methyl *p*-Dimethylaminobenzenesulfonate (MSE). Using a modification of the "Organic Syntheses" procedure for methyl tosylate,[28] 6.45 g of II was dissolved (with vigorous shaking) in 180 ml of reagent grade methanol in a 300-ml round-bottom flask. Sufficient concentrated aqueous NaOH (≈4 ml) was added to make the solution strongly basic, and the reaction was allowed to stand, first at room temperature and then in the refrigerator for 24 h. The first crop of crystals (≈2 g) was collected and washed with water. The water washes and supernatant were combined to yield, after 1 day in the cold, a second crop of 3.3 g of crystals. The combined product of 5.3 g (84% yield) was stored as a solution in ether over Na_2SO_4 and K_2CO_3; NMR ($CDCl_3$) 6.93 (s, 6 H), 6.30 (s, 3 H), 2.78 (AB quart, 4 H); IR (KBr) 1590, 1330, 1210, 1150, 1080, 985, 780, 740 cm^{-1}; mp 90–91 °C (lit. 90–91 °C,[13] 91 °C[14,15]). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.22; H, 6.09; N, 6.51; S, 14.89. Found: C, 50.23; H, 6.16; N, 6.50; S, 14.91. The analytical mass spectrum at 70 eV showed a base peak which was also the parent peak at *m/e* 215, as well as minor peaks at 214, 216, 217.

MSE-d_3, MSE-d_6, MSE-d_9. The procedure used was basically the same as for the nondeuterated MSE. MSE-d_3 was made from 444 mg of sulfonyl chloride (II-d_0) and 14 ml of CD_3OD (99% obtained from Stohler Isotopes, Inc.) using NaOD and D_2O. (The CD_3OD can be recovered (>90%) by vacuum transfer at the end of the reaction.) The MSE-d_6 was prepared from 292 mg of sulfonyl chloride (II-d_6) and 15 ml of CH_3OH using NaOH and H_2O. The NMR's of MSE-d_3 and MSE-d_6 each indicate >98% deuteration in the appropriate methyl groups.

MSE-d_9 was prepared by reacting 309 mg of sulfonyl chloride (II-d_6) with NaOD and D_2O in 10 ml of CD_3OD. The product was a white powder with mp 89.0–90.0 °C. The NMR showed protons on the aromatic ring only. The mass spectrum at 70 eV showed a base peak which was also the parent peak at *m/e* 224. To verify the percentage deuterium incorporation we noted that for MSE-d_0, parent/(parent − H) = 1.93 and for MSE-d_9, parent/(parent − H) + (parent − D) = 1.94. This combined with the NMR spectrum indicated overall deuterium incorporation >98%.

All of the MSE isomers were stored as dilute solutions in ether over anhydrous K_2CO_3 in the cold.

Methyl *p*-Trimethylammoniumbenzenesulfonate Trifluoromethanesulfonate. Approximately 1 g of crude MSE-d_0 was dissolved in CH_2Cl_2 and dried over $MgSO_4$. This solution was filtered, and solvent was removed under reduced pressure. The solid residue was redissolved in 10 ml of spectral grade $CHCl_3$ in a 50-ml round-bottom flask equipped with a magnetic stirrer and an N_2 inlet. Commercial methyl trifluoromethanesulfonate (400 μl) (Cationics Inc.) was added in one portion, and the reaction was allowed to stir under N_2 at room temperature 4.5 h. The reaction was cooled to ≈0 °C in an ice bath, and 20 ml of dry, distilled pentane was added to precipitate the product. The product was filtered under an N_2 atmosphere in a glovebag and exhaustively triturated with fresh pentane to give a clean white powder with the following spectra: IR (KBr) 1485, 1365, 1261, 1193, 1032, 990, 845, 800 cm^{-1}; NMR (D_2O) 6.33 (s, 9 H), 6.20 (s, 3 H), 1.86 (s, 4 H). Anal. Calcd for $C_{11}H_{16}F_3NO_6S_2$: C, 34.83; H, 4.22; N, 3.69. Found: C, 34.54; H, 4.09; N, 3.69.

Allyl *p*-Trimethylammoniumbenzenesulfonate Triflate. The dimethylaminobenzenesulfonate ester was prepared as above for MSE using 1.11 g of sulfonyl chloride (II) dissolved in 25 ml of commercial allyl alcohol and aqueous NaOH, to give 1 g of wet product (IV) which was dissolved in ether and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual solid recrystallized at low temperature from ether, giving clean white crystals: mp 41 °C; NMR ($CDCl_3$) 6.96 (s, 6 H), 5.52 (d, J = 5 Hz, 2 H), 4.72 (m, 2 H), 4.29 (m, 1 H), 2.79 (AB quart, 4 H). Anal. Calcd for $C_{11}H_{15}NO_3S$: C, 54.77; H, 6.22; N, 5.81. Found: C, 54.76; H, 6.17; N, 5.79.

The alkylation of the dimethylamino ester was done as above for MSE using 298 mg of allyl sulfonate ester dissolved in 2 ml of dry distilled benzene and 145 μl of methyl triflate. The product was a white powder that did not dissolve in $CDCl_3$: NMR (CD_2Cl_2) 6.12 (s, 9 H), 5.33 (d, J = 5 Hz, 2 H), 4.52 (m, 3 H), 1.86 (broad s, 4 H). Note: In D_2O solution this material is converted to ZWT and allyl alcohol at room temperature with $T_{1/2} \leq 30$ s. Due to its reactivity, no analysis was obtained for this compound.

***n*-Butyl *p*-Dimethylaminobenzenesulfonate (V) and *sec*-Butyl *p*-Dimethylaminobenzenesulfonate (VI).** Sulfonyl chloride (1.97 g) (II) was dissolved in 20 ml of dry (distilled from KOH) pyridine in a 50-ml round-bottom flask. *n*-Butanol (0.9 ml, 0.7 g) was added, and the reaction was covered with a drying tube and stored in the refrigerator for 3 days. The reaction mixture was poured onto a mixture of 30 ml of concentrated HCl and 100 g of ice. After the ice melted, 2.2 g of crude reaction product was filtered off and washed with H_2O. The product was twice recrystallized from ether: mp 35.5–37.0 °C; NMR ($CDCl_3$) 9.33–8.04 (multiplets, 7 H), 6.95 (s, 6 H), 6.02 (t, J = 6 Hz, 2 H), 2.82 (ABq, 4 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01, H, 7.44; N, 5.44; S, 12.46. Found: C, 55.89; H, 7.28; N, 5.38; S, 12.43.

The same procedure, using 1.65 g of sulfonyl chloride and 0.7 ml (0.56 g) of *sec*-butanol, gave 1.5 g of crude *sec*-butyl sulfonate ester. Recrystallization gave 0.8 g of clean white needles: mp 46.5–47.5 °C; NMR ($CDCl_3$) 9.18 (t, J = 6.5, Hz 3 H), 8.79 (d, J = 6.0 Hz, 3 H), 8.49 (q, J = 6.5 Hz, 2 H), 6.96 (s, 6 H), 5.53 (q, J = 6 Hz, 1 H), 2.82 (ABq, 4 H). Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44; S, 12.46. Found: C, 56.22; H, 7.11, N, 5.44; S, 12.51.

The above esterification procedure gave no detectable product when used to make either the allyl or methyl esters.

***p*-Trimethylammoniumbenzenesulfonate (ZWT).** This compound was prepared by three independent routes: (1) the thermal rearrangement of MSE at room temperature, 81, 88, and 95 °C; (2) the H_2O solvolysis of alkylated MSE (III); (3) the H_2O solvolysis of alkylated allyl sulfonate ester (alkylated IV). The material isolated from each of these reactions could be recrystallized from water and had the following properties: mp ≫350 °C (no decomposition evident under vacuum); NMR (D_2O) 6.38 (s, 9 H), 2.05 (s, 4 H); IR (KBr) 1500, 1200, 1130, 1100, 1035, 1000, 840, 755 cm^{-1}; field desorption mass spectroscopy = *m/e* 215. Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.22; H, 6.09; N, 6.51. Found: C, 50.08; H, 5.99; N, 6.61.

Deuterated ZWT isomers were prepared by heating the corresponding MSE isomer at 81 °C under vacuum and analyzing the resulting powder by FDMS. ZWT-d_9 gave FDMS = 224 while

ZWT-d_3 and ZWT-d_6 gave scrambling (see text) but with the main peak for d_3 = 218 and d_6 = 221.

C. Field Desorption Mass Spectrometry. The instrument used was a Varian MAT Model CH5 DF. The basic procedure can be summarized as follows: A powdered sample of zwitterion was dissolved in H_2O; this solution was spread on the tungsten wire anode by dipping, and excess solvent was evaporated. The emitter was heated with a 23–27 mA (ca. 250 °C) heating current and maintained at pressures less than 10^{-6} Torr. The high voltage field was applied (typically +3 kV to anode and −8 kV to cathode), and the spectra were recorded on an oscillographic recorder. Multiple scans were averaged to obtain each spectrum, since single scans at approximately 25 amu/s failed to give the desired reproducibility. After each run the anode was cleaned by raising the current through it to 50 mA. A detailed account of the experimental conditions for FDMS is given in ref 19b.

D. Kinetics of the Solid State Reaction. A sample of 29–37 mg of MSE was placed in a 5-ml pear-shaped flask topped with a ground joint and a stopcock. The flask was evacuated and the stopcock closed. The flask was then immersed in an oil bath that had previously been equilibrated to a temperature of 81, 88, or 95 °C. After a known amount of time the sample was removed from the oil bath and plunged into ice water. The vacuum was released, and 1–2 ml each of D_2O and $CDCl_3$ were added using a glass stirring rod to help dissolve all of the sample material in one solvent or the other. After the phases separated they were each pipetted into separate NMR tubes. The NMR of each solution was recorded and integrated using the Varian A-60A spectrometer, and the relative amount of MSE and ZWT was determined by comparing their integration (average of three–five scans) and correcting for the difference in volume of D_2O and $CDCl_3$ used in that run.

Two large scale (70–80 mg) runs were performed in which MSE and ZWT were isolated and weighed. These results were within 3% of the NMR results.

E. X-Ray Single Crystal Structure Determination for MSE. Suitable crystals for x-ray diffraction work could be isolated either directly out of the reaction mixture in which MSE was synthesized, or by recrystallization from methanol or a methanol–water mixture. Clean single crystals of sufficient size for the structural work were selected and mounted on the goniometer head in a capillary tube. The details of this work as well as a listing of the computer programs used can be found in the thesis submitted (1975) by J.B. to the Instituto de Quimica da Universidae Federal do Rio de Janiero, Brazil.

F. Preliminary Single Crystal Work on ZWT. Crystals of ZWT were very easily grown by cooling a saturated aqueous solution. A suitable crystal was chosen and used for oscillation and Weissenberg pictures using a Charles Supper Weissenberg camera. The data from these pictures have been summarized in the above text (Results and Discussion).

G. Photography of the Reaction Through a Polarizing Microscope. A thin, clear single crystal of MSE was placed on the stage of a Bausch and Lomb polarizing microscope. A 35-mm camera was adapted to fit the eyepiece of the microscope, and it was bolted onto the microscope. A remote trigger was used for the camera shutter and pictures were taken at fixed intervals. The entire apparatus (camera and microscope) was left undisturbed for the 2-week duration of the experiment. The resulting slides gave a clear view of the sequence of changes in the way that the light was refracted by the crystal.

H. Powder Diffraction Patterns of MSE and ZWT. The powder pattern (d values and relative intensitites) of MSE was calculated using the atomic parameters determined from our single crystal work and the program "POWDER" written by Dr. G. Mandel (program available on request).

The experimental powder patterns were determined using Cu K_α radiation with a circular powder sample holder and a Guinier camera. Exposure times ranged from 6.5 to 24 h. d values were calculated using distances measured on an optical comparator.

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Supplementary Material Available: Coordinates, thermal parameters, and structure factors for *p*-dimethylaminobenzenesulfonate are listed in the supplementary information (archival edition) following the preliminary communication outlining part of the work described here (ref 1a) (11 pp). Ordering may be done by citing ref 1a and following the ordering information given on any current masthead page.

References and Notes

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