

Table I. Effect of Functional Amino Groups on the Spontaneous Hydrolysis of Methyl *p*-Nitrobenzenesulfonate<sup>a</sup>

Methyl <i>p</i> -nitrobenzenesulfonate, <i>M</i>	Amino acid (concn, <i>M</i> )	$k_{\text{exptl}} \times 10^4$ $\text{sec}^{-1}$
$4.17 \times 10^{-5}$	None	1.77
$5.16 \times 10^{-5}$	Isoleucinamide ( $8.01 \times 10^{-4}$ )	1.61
$4.14 \times 10^{-5}$	N-Acetyl-L-methioninamide ( $5.44 \times 10^{-4}$ )	1.73
$4.14 \times 10^{-5}$	N-Acetyl-L-serinamide ( $1.74 \times 10^{-3}$ )	1.67
$4.14 \times 10^{-5}$	Imidazole ( $5.00 \times 10^{-2}$ )	2.88

<sup>a</sup>The buffer used was 0.1 *M* sodium phosphate, pH 7.94. Methyl *p*-nitrobenzenesulfonate was dissolved in  $\text{CH}_3\text{CN}$ . The amino acid derivatives were in aqueous solutions. The decomposition of the ester was measured at 253 m $\mu$  at 25°.

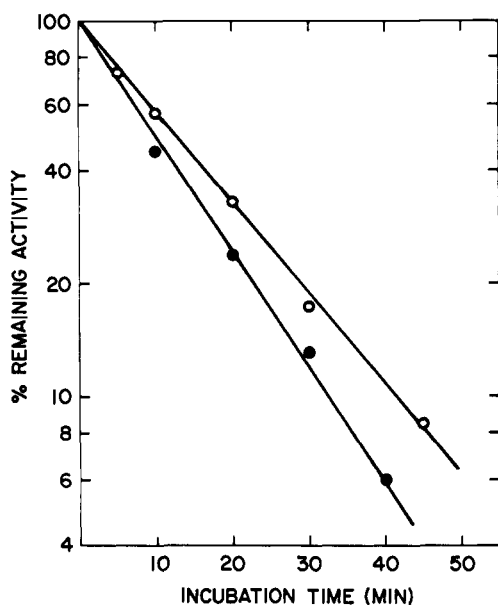


Figure 1. Loss of  $\alpha$ -chymotrypsin activity upon incubation with methyl *p*-nitrobenzenesulfonate. Purified  $\alpha$ -chymotrypsin in 0.1 *M* sodium phosphate buffer, pH 7.93 ( $3.65 \times 10^{-4}$  *M*), was incubated with methyl *p*-nitrobenzenesulfonate ( $2.86 \times 10^{-3}$  *M*) at 25°. The concentration of  $\text{CH}_3\text{CN}$  was 9.9%. The remaining activity was measured by *N-trans*-cinnamoylimidazole titration (full circles) and by a rate assay method with *N*-acetyl-L-tryptophan methyl ester ( $2.48 \times 10^{-4}$  *M*, open circles).

taneous hydrolysis rate of the methyl ester with imidazole at pH 7.94 was  $2.2 \times 10^{-3} \text{ M}^{-1} \text{ sec}^{-1}$ . The highest inhibition rate of  $\alpha$ -chymotrypsin at the same pH was  $41.5 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$ . Thus the inhibition rate of  $\alpha$ -chymotrypsin is at least 190-fold faster than the spontaneous hydrolysis of the ester with imidazole. When histidine was incubated with the methyl ester at pH 7.9 for 48 hr, most of the histidine was unattacked, and a small amount of 1-amino-2-(1-methyl-5-imidazolyl)propanoic acid (1-methylhistidine) and a trace amount of 1-amino-2-(1-methyl-4-imidazolyl)propanoic acid were detected by an amino acid analysis.

The results lead us to conclude that the methyl ester in order to inhibit the enzymatic activity must be oriented in a position similar to that of a substrate on the surface of the enzyme. From the experimental data the enzyme truly catalyzed the reaction of this ester at N-3 of histidine-57. Histidine-57 is known to be present in the active site of  $\alpha$ -chymotrypsin from X-ray crystallographic data.<sup>12</sup> It thus appears from the loss of activity found in the rate

assay (Figure 1) that the hydrogen atom at position 3 of this histidine is essential to the mechanism of hydrolysis of substrates by the enzyme.

**Acknowledgment.** We thank Professors F. J. Kézdy and E. T. Kaiser of the University of Chicago for many valuable suggestions and discussions. We also acknowledge Professor F. C. Neuhaus of our department who made available the use of a high-voltage electrophoresis apparatus. Y. N. expresses his thanks to Miss Judith A. Domin for amino acid analyses. A grant (HE-11119) from the National Heart Institute supported our amino acid analyzer facility.

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Received November 14, 1968

## The Structure of an $\alpha$ -Sulfonyl Carbanion

Sir:

Conformationally unconstrained  $\alpha$ -sulfonyl carbanions are virtually unique among the reactive intermediates of organic chemistry in their ability to retain asymmetry under a wide variety of experimental conditions.<sup>1</sup> This fact, discovered independently by three groups of workers about 7 years ago,<sup>2-4</sup> has since stimulated much interest in the structures and stereochemical capabilities<sup>5</sup> of these species. The structural discussion has, from the beginning, followed two main lines: (1) the carbanion carbon is *pyramidal*, i.e., **1**, **2**, or **3**, and there is a high barrier to inversion of the *stable* structure; (2) the carbanion carbon is *planar*, and there is a high barrier to rotation. If the latter were correct, then the observed asymmetry would require that the structure be **4** rather than **5** and, further, that proton transfer to **4** (or its microscopic reverse) must occur largely from one face of

(1) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

(2) (a) D. J. Cram, W. D. Nielsen, and B. Rickborn, *J. Am. Chem. Soc.*, **82**, 6415 (1960); (b) D. J. Cram, D. A. Scott, and W. D. Nielsen, *ibid.*, **83**, 3696 (1961).

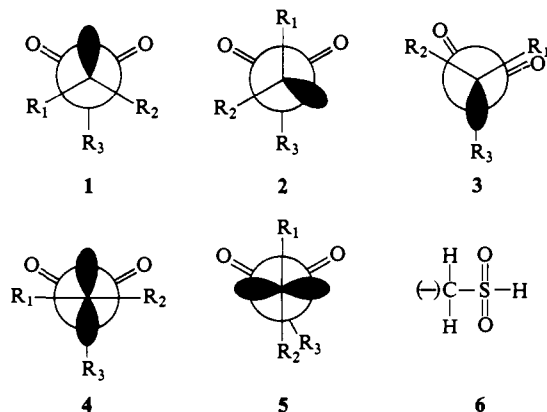
(3) E. J. Corey and E. T. Kaiser, *ibid.*, **83**, 490 (1961).

(4) H. L. Goering, D. L. Townes, and B. Dittmer, *J. Org. Chem.*, **27**, 736 (1962).

(5) (a) E. J. Corey, H. König, and T. H. Lowry, *Tetrahedron Letters*, 515 (1962); (b) E. J. Corey and T. H. Lowry, *ibid.*, 793 (1965); (c) E. J. Corey and T. H. Lowry, *ibid.*, 803 (1965); (d) D. J. Cram and A. S. Wingrove, *J. Am. Chem. Soc.*, **85**, 1100 (1963); (e) D. J. Cram and T. A. Whitney, *ibid.*, **89**, 4651 (1967); (f) D. J. Cram, R. D. Trepka, and P. St. Janiak, *ibid.*, **88**, 2749 (1966); (g) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, **89**, 357 (1967); (h) A. Ratajczak, F. A. L. Anet, and D. J. Cram, *ibid.*, **89**, 2072 (1967); (i) F. G. Bordwell, D. D. Phillips, and J. M. Williams, *ibid.*, **90**, 426 (1968).

(12) P. B. Sigler, D. M. Blow, B. W. Matthews, and R. Henderson, *J. Mol. Biol.*, **35**, 143 (1968).

the anion. Definite evidence has been obtained in one case<sup>5b,c</sup> that proton transfer to an  $\alpha$ -sulfonyl carbanion takes place from the direction *syn* to the oxygen atoms, and this result has since formed the basis for discussions of the stereochemistry of the Ramberg-Bäcklund<sup>6</sup> and related<sup>7</sup> reactions.



It is of interest to probe theoretically the structure of an  $\alpha$ -sulfonyl carbanion. Intuitively one expects d-orbital conjugation to be important, and the problem then appears to provide an opportunity to study the stereochemistry of 3d-orbital conjugation with an adjacent electron pair. Koch and Moffitt<sup>8</sup> discussed 2p-3d conjugation in aryl sulfones in terms of the relative stabilities of conformations in which a carbon 2p orbital is directed along the bisector of the OSO angle (e.g., 4, case II in their nomenclature), and in a direction perpendicular to this (e.g., 5, case I in their nomenclature). They concluded that greater stability would be attained by case I delocalization, a result which predicts no asymmetry for an  $\alpha$ -sulfonyl carbanion. More recently, Lipscomb and his coworkers<sup>9</sup> carried out extended Hückel-type calculations on  $F_2NSO_2NF_2$  with the  $NF_2$  groups oriented so as to give  $C_{2v}$  (case II) and  $C_s$  (case I) geometry. They found the case II conformation to be more stable than the case I conformation by 9.54 kcal/mol and concluded that this stability arises almost completely from the d-orbital interactions. Apparently, in the case I conformation the nitrogen lone pair has to compete more with the oxygen lone pairs for the sulfur d orbitals.

We have shown<sup>10</sup> that it is possible to perform *non-empirical* molecular orbital calculations on sulfur-containing systems and that such calculations provide a detailed picture of the properties of  $\alpha$ -sulfonyl carbanions. This work has now been extended to the  $\alpha$ -sulfonyl carbanion 6, hydrogen methyl sulfonyl carbanion ( $HMSO_2^-$ ).<sup>11</sup>

As in the earlier work<sup>10</sup> the calculations were performed by the LCAO-MO-SCF method using a minimal basis set of Gaussian-type functions (GTF). The geometrical

(6) L. A. Paquette, *Accounts Chem. Res.*, 1, 209 (1968).

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(10) (a) S. Wolfe, A. Rauk, and I. G. Csizmadia, *ibid.*, 89, 5710 (1967); (b) A. Rauk, S. Wolfe, and I. G. Csizmadia, *Can. J. Chem.*, 47, 113 (1969); (c) A. Rauk and I. G. Csizmadia, *ibid.*, 46, 2105 (1968).

(11) As shown in Figures 16 and 17 of ref 10b, the form of the potential energy surface of an  $\alpha$ -sulfonyl carbanion is the same whether hydrogen or methyl is attached to sulfur.

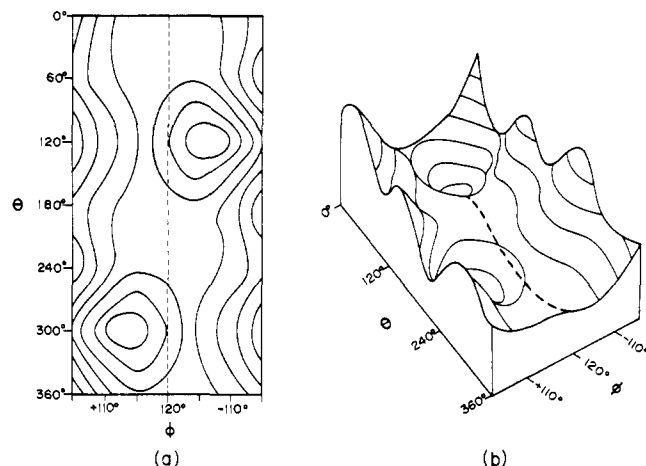


Figure 1. (a) An energy contour diagram showing the total energy of  $HMSO_2^-$  as a function of rotation about the S-C bond ( $\theta$ ) and inversion of the carbanion angle ( $\phi$ ). (b) A projection of the three-dimensional energy surface.

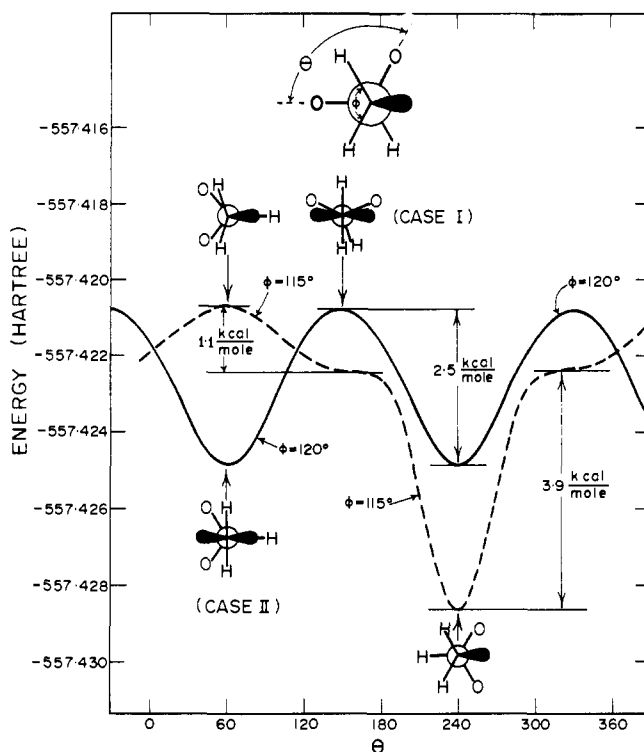


Figure 2. Cross sections of the energy surface of Figure 1 through the planar carbanion ( $\phi = 120^\circ$ ; solid line) and through the energy minimum ( $\phi = 115^\circ$ ; dashed line).

parameters were:<sup>12</sup> S-O, 1.43 Å; C-S, 1.80 Å; S-H, 1.329 Å;<sup>13</sup> C-H, 1.08 Å; CSO, 104°; OSO, 110°; CSH, 104°. Rotation about the carbon-sulfur bond ( $\theta$ ) and inversion of the carbanion angle ( $\phi$ ) were treated as variables. Figure 1 shows the resulting three-dimensional energy surface and Figure 2 shows two cross sections of the surface, one through  $\phi = 120^\circ$  (the planar carbanion)

(12) H. J. M. Bowen, *et al.* (Compilers), "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 11, The Chemical Society, London, 1958.

(13) This is the bond length found for mercaptans.<sup>12</sup> It is noteworthy that the C-S bond length is essentially the same in dimethyl sulfide ( $1.82 \pm 0.01$  Å), dimethyl sulfoxide ( $1.83 \pm 0.04$  Å), and dimethyl sulfone ( $1.80 \pm 0.02$  Å).

and the other through the energy minimum ( $\phi = 115^\circ$ ).

It is evident from Figure 1 that one structure is clearly favored. This structure corresponds to a pyramidal carbanion with the electron pair on carbon directed along the acute bisector of the OSO angle, *i.e.*, **1**. Figure 2 shows this more clearly. *The case II conformation is more stable than the case I conformation, but neither planar conformation is as stable as the pyramidal carbanion with the lone pair directed along the bisector of the OSO angle.*

A set of six GTF were used in the calculations to describe the d orbitals of sulfur, and for each of the molecular orbitals this set of functions could be transformed to a single 3s-type and a set of five 3d-type orbitals. The 3s-type orbital appears as an s-type function in the sulfur 1s and 2s cores, and the five d-type functions appear as a set of five nearly degenerate *antibonding* molecular orbitals. Thus, as in the earlier calculations,<sup>10</sup> and in contrast to the semiempirical results,<sup>9</sup> the nonempirical calculations appear to show no significant contribution to the structure of the carbanion from the d orbitals of sulfur. It must be noted, however, that ours is a *minimal* basis set calculation. Further work is now under way with improved (near Hartree-Fock) basis sets.

The present calculations suggest that the asymmetry of  $\alpha$ -sulfinyl and  $\alpha$ -sulfonyl carbanions need not be related to a possible existence of 3d-orbital conjugation. Rather, we now believe that the two species adopt an asymmetric structure as a consequence of the stereochemical requirements of two adjacent electron pairs or an electron pair and an adjacent dipole. This concept, which appears to have broad implications, will be examined in more detail in a forthcoming communication.<sup>14</sup>

**Acknowledgments.** The authors thank Professor D. J. LeRoy for his encouragement and the National Research Council of Canada for continuous financial support of this work and for the award of a special grant. Grateful acknowledgment is also made to the Institute of Computer Science of the University of Toronto and to the Department of Computing and Information Science of Queen's University for generous allocation of computing time.

(14) S. Wolfe, A. Rauk, and I. G. Csizmadia, in preparation.

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Received October 28, 1968

### Static Bridged Carbonium Ions. Direct Nuclear Magnetic Resonance Observation of Stereochemically Distinct Ions

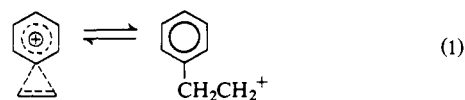
Sir:

Although substituted "ethylenephonium" cations have now been directly observed under specialized conditions, the existing reports<sup>1,2</sup> of nmr observations of these

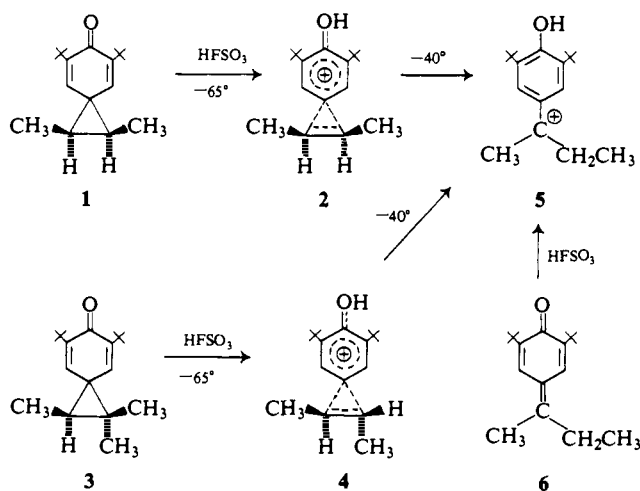
(1) L. Ebersson and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 3506 (1965).

(2) G. A. Olah, M. B. Comisarow, E. Namanworth, and B. Ramsey, *ibid.*, **89**, 5259 (1967).

cations provide no evidence with regard to the question of whether these bridged ions are static or are in rapid equilibrium with the corresponding open ions (see, *e.g.*, eq 1).<sup>3</sup> We wish to report the observation of two stereochemically distinct "ethylenephonium" cations which could in principle interconvert *via* a nonbridged ion but which in actuality fail to do so.



Protonation of *cis*-1,2-dimethyl-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-one (**1**)<sup>4</sup> with fluorosulfonic acid at  $-65^\circ$  affords a species whose nmr spectrum<sup>5</sup> (see Figure 1) is in accord with that expected for the *cis* ion **2**. The most significant features in the spectrum occur at low field where three one-proton singlets are observed at  $\delta$  8.30, 8.04, and 7.80. In deuterated fluorosulfonic acid, the resonance at  $\delta$  8.30 is absent from the spectrum of **2**. These resonances are ascribed to the hydroxyl proton and to the two nonequivalent vinyl protons, respectively.<sup>6</sup> Additionally, resonances at  $\delta$  4.60 (2 H), 1.88 (6 H), and 1.45 (18 H) are observed and ascribed to the methine, methyl, and *t*-butyl protons, respectively, in cation **2**. The spectrum persists unchanged for at least 1 hr at  $-65^\circ$ , and no resonances attributable to the *trans* cation **4** are detectable. However, protonation of *trans*-1,2-dimethyl-5,7-di-*t*-butylspiro[2.5]octa-4,7-dien-6-one<sup>4</sup> (**3**) with fluorosulfonic acid at  $-65^\circ$  does afford a species which has an nmr spectrum<sup>5,7</sup> (see Figure 2) in accord with that expected for the *trans* ion **4**. In particular, a singlet at  $\delta$  8.30 (1 H), a singlet at 7.95 (2 H), a broad singlet at 4.57 (2 H), a broad singlet at 1.79 (6 H), and a



(3) On the basis the chemical shifts observed for these cations, it is clear that they spend the greater fraction of their time bridged. However, one cannot infer from chemical shift measurements whether or not the ions are static or are opening and reclosing rapidly.

(4) G. F. Koser and W. H. Pirkle, *J. Org. Chem.*, **32**, 1992 (1967).

(5) Spectra were recorded on a Varian HA-100 nmr spectrometer and overlapping resonances were resolved and integrated by means of a DuPont 310 curve resolver. Chemical shifts are referenced to tetramethylsilane, using methylene chloride as a secondary internal standard.

(6) The weak coupling which is observed<sup>4</sup> between the nonequivalent vinyl protons in dienone **1** is not clearly resolved in the spectrum of ion **2**.

(7) Since a 3:1 mixture of the *trans* and *cis* dienones was actually used, the resonances previously ascribed to the *cis* cation **2** were observed as well as those of the *trans* cation **4**. The relative ratio of the two ions is the same as the ratio of the two isomeric dienones prior to protonation.