Quantitation of Proximity Effects on Rate. A Case Study Involving Dyotropic Hydrogen Migration within *syn*-Sesquinorbornene Disulfones Carrying Central Substituents Having Different Spatial Demands

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Abstract: The *syn*-sesquinorbornadiene that is produced upon Diels-Alder reaction of (*Z*)-1,2-bis(phenylsulfonyl)ethylene with tricyclo[5.2.1.$0^{2,6}$]deca-2,5,8-triene has been regiospecifically reduced at its central double bond with diimide. Allied reactions take a parallel course, thereby allowing for the fusion of oxirane, aziridine, cyclopropane, and methylcyclopropane subunits in the central region of this molecule. All of these products undergo clean dyotropic migration of their endo α-sulfonyl protons to the proximal double bond. The distances involved have been quantified by X-ray crystallographic analysis in each case. Following up on this, the kinetics of these isomerizations were measured in order to establish a relative reactivity scale. A very good correlation is seen between reaction rate and the average intracavity distance. These extensive data are in agreement with the notion that reactivity is primarily dependent upon distance in a series where gross structural modifications need not operate at the transition-state level. In the present investigation, modulation of the intracavity distance to an extent slightly in excess of 0.3 Å is reflected in a rate spread greater than 10^4.

Intramolecular reactions often exhibit remarkably enhanced rates. Considerable interest has arisen in these processes because of the belief that the consequences of intramolecularity can be utilized to better understand mechanisms of enzyme action.[1] However, rate accelerations stemming from covalently enforced proximity have proven difficult to analyze from the mechanistic vantage point. As a result, the area has been fraught with controversy. Koshland's early proposal[2] that high rates are a direct consequence of optimal orbital alignment within a reactant, the so-called "orbital steering theory", met almost immediately with opposition.[3-12] The need to imply force constants for partly formed bonds that exceed those of covalent bonds is viewed as particularly unrealistic.[3] The Milstein-Cohen "stereopopulation control" proposal for lactonization[8] was subsequently counteracted by calculations showing that nucleophilic attack by methanol on formic acid has very loose angular requirements.[10b] Other evidence has subsequently been gained to show that neither phenomenon can be a major contributor to overall kinetic acceleration.[13,14]

In fact, scant information exists on the *precise* manner in which geometric disposition affects reactivity. The critical importance of distance to rate has been championed by both Bruice[15] and Menger.[16] As matters have turned out, Menger's "spatiotemporal hypothesis" has been criticized by Houk who has claimed that no necessary relationship exists between the distance separating the reacting atoms in the starting material and the reaction rate.[17] However, Houk's "transition-state modeling" approach has more recently also come under fire.[16d]

This exasperating state of affairs has arisen because of the necessary interplay of several ancillary factors during intramolecular reaction, depending on the precise nature of the chemical event. Certainly there are known cases where the freezing of a single rotation has led to substantitive (ca. 10^4) rate enhancements.[8,16b] However, without accompanying kinetically relevant structural changes, only a 5-fold increase in k can be anticipated from this type of favorable energy contribution.[18,19] Nonetheless, calculations do exist that predict the possibility for attaining accelerations as high as 10^7 under the proper circumstances.[20] These do not include examples where a decrease in distance would be accompanied by a substantial strain increase elsewhere in the reactant. As Houk points out, there is need to give serious thought to the ease of achieving transition-state geometries in addition to the geometric details in the substrate molecule.[17] Failure to do so may ignore the adverse energetic effects associated with precompression.

In light of the above, it occurred to us that definitive information concerning proximity effects on rates could be acquired if the systems under study were inherently free of as many assumptions

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(1) Czarnik, A. W. In *Mechanistic Principles of Enzyme Activity*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers, Inc.: New York, 1986.
(2) (a) Storm, D. R.; Koshland, D. W., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *66*, 445. (b) Koshland, D. E., Jr.; Carraway, K. W.; Dafforn, G. A.; Gass, J. D.; Storm, D. R. *Cold Spring Harbor Symp. Quant. Biol.* **1971**, *36*, 13. (c) Storm, D. R.; Tjian, R.; Koshland, D. E., Jr. *J. Chem. Soc. D* **1971**, *15*, 854. (d) Storm, D. R.; Koshland, D. E., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5805, 5815. (e) Dafforn, A.; Koshland, D. E., Jr. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 779.
(3) (a) Bruice, T. C. In *Annual Review of Biochemistry*; Annual Reviews, Inc.: Palo Alto, CA, 1976, Vol. 45, pp 352-357. (b) Bruice, T. C. In *The Enzymes*; Boyer, P. D., Ed.; Academic Press: 1970; Vol. 11, Chapter 4. (c) Bruice, T. C.; Benkovic, S. J. In *Bioorganic Mechanisms*; W. A. Benjamin, 1970; Chapter 4.
(4) (a) Bruice, T. C.; Brown, A.; Harris, D. O. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 658. (b) Bruice, T. C. *Cold Spring Harbor Symp. Quant. Biol.* **1971**, *36*, 21. (c) Bruice, T. C. *Nature (London)* **1972**, *237*, 335.
(5) Jencks, W. P.; Page, M. I. *Biochem. Biophys. Res. Commun.* **1974**, *57*, 887.
(6) Capon, B. *J. Chem. Soc. B* **1971**, 1207.
(7) Hoare, D. G. *Nature (London)* **1972**, *236*, 437.
(8) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158.
(9) Herschfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 6788.
(10) (a) Halgren, T. A.; Lipscomb, W. N. *J. Chem. Phys.* **1973**, *58*, 1569. (b) Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770.
(11) Moriarty, R. M.; Adams, T. *J. Am. Chem. Soc.* **1973**, *95*, 4070, 4071.
(12) Mihel, I.; Knipe, J. O.; Coward, J. K.; Schowen, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 4349.
(13) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996.
(14) Gandour, R. D. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 529-552.
(15) Bruice, T. C. *Ann. Rev. Biochem.* **1976**, *45*, 331.
(16) (a) Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1985**, *107*, 4706. (b) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128. (c) Menger, F. M. *Adv. Mol. Model.* **1988**, *1*, 189. (d) Sherrod, M. J.; Menger, F. M. *J. Am. Chem. Soc.* **1989**, *111*, 2611.
(17) (a) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698. (b) Dorigo, A. E.; Houk, K. N. *Adv. Mol. Model.* **1988**, *1*, 135.
(18) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678.
(19) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(20) Delisi, C.; Crothers, D. M. *Biopolymers* **1973**, *12*, 1689.

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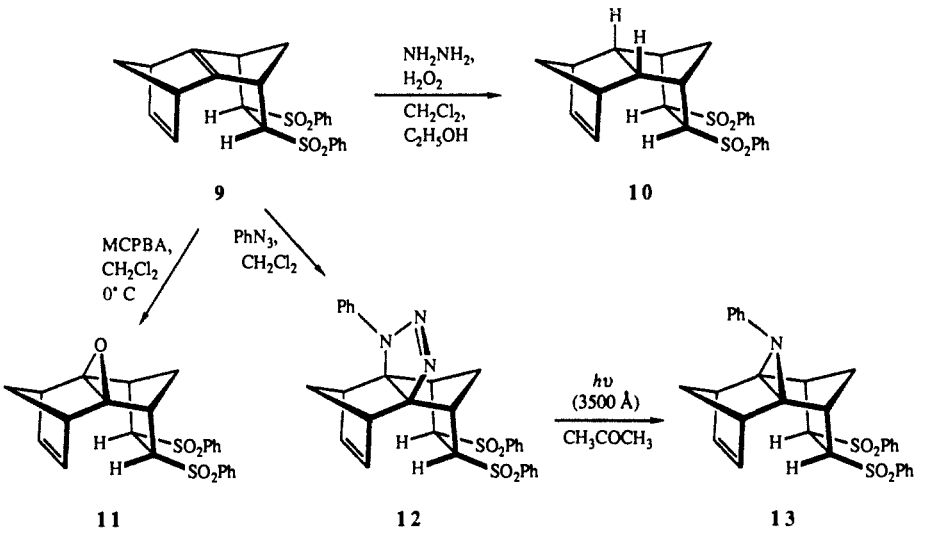
Scheme I



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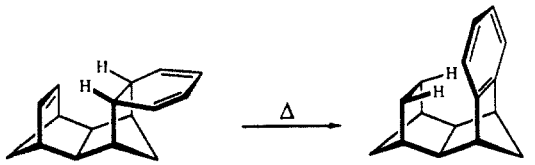
as possible. A detailed appreciation of all relevant structural and mechanistic issues is especially necessary. Also, since the "spatiotemporal hypothesis" necessitates that activation energy be a very steep sigmoidal function of distance, the critical distance must not be exceeded or E_a will no longer decrease with decreasing interatomic distance. The other criteria alluded to above must also be met.

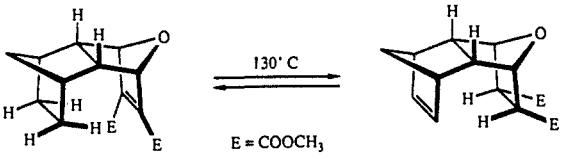
***syn*-Sesquinorbornenes and Hydrogen Dyotropy.** Although the least-motion transfer of two hydrogen atoms from eclipsed ethane to ethylene is symmetry-allowed if concerted, a surprisingly large barrier (71 kcal/mol) has been calculated for this process.[22] The analogous reaction involving diimide and ethylene, which profits from a very large energy lowering due to nitrogen evolution,[23] has an estimated activation energy of approximately 27 kcal/mol.[24] In related fashion, development of a sizable proportion of the resonance energy of naphthalene (61 kcal/mol) at the transition state forms the basis for the ability of *cis*-9,10-dihydronaphthalene to transfer its two central hydrogen atoms.[25]

When the suprafacial dyotropic reaction[26] is made intramolecular as in **1**,[27] advantage can continue to be taken of aromatic ring formation. Furthermore, the rigid positioning of the two migrating hydrogens in close proximity to the double bond facilitates the 2-fold migration still more.[28-30] In 1981, Vogel



1 2

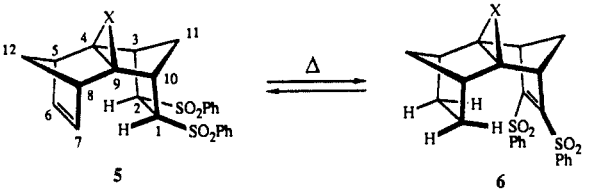
recorded the important observation that these processes need not depend on the formation of aromatic compounds for their operation.[31] Thus, **3** undergoes reversible pericyclic isomerization to give **4** at 130 °C. The equilibrium constant for **4**:**3** in C_6D_6 solution at this temperature is 1.1–1.2.



3 4

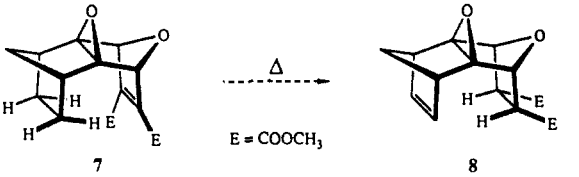
These uncatalyzed intramolecular hydrogen migrations are seen to involve the synchronous translocation of two C–H σ bonds. A totally symmetrical transfer mode is, as usual, not strictly required. In principle, the distances involved are ascertainable by X-ray crystallographic analysis of starting material and product. In **3** and **4**, the compressed molecular topographies guarantee that the traversed distance is short. However, precise structural information is not available.

Herein we describe the synthesis of *syn*-sesquinorbornene disulfones of general type **5**, where the distance separating the pair



5 6

of α-sulfonyl protons and the double bond is progressively altered by the introduction of suitable structural subunits across the C(4)–C(9) bond from its exo surface. X-ray crystallographic data have been obtained for all six starting disulfones and for one of the dyotropisomers **6**. The *exo*-5,10-epoxide included in this group was found to respond well to thermal activation. This observation contrasts with the reported failure of **7** to rearrange into **8**.[31] At 180 °C, **7** purportedly undergoes slow decomposition.



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(21) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1971; pp 141–144.

(22) Feller, D. F.; Schmidt, M. W.; Ruedenberg, K. *J. Am. Chem. Soc.* **1982**, *104*, 960. As noted by a referee, the differences between experimental and calculated values would undoubtedly decrease with the use of high-level basis sets and post-Hartrees–Fock calculations that can be accomplished today with the use of supercomputers.

(23) Hunig, S. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271.

(24) Pasto, D. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 2290.

(25) Doering, W. von E.; Rosentahl, J. W. *J. Am. Chem. Soc.* **1967**, *89*, 4534.

(26) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129, 131. (b) Reetz, M. T. *Tetrahedron* **1973**, *29*, 2189. (c) Reetz, M. T. *Adv. Organomet. Chem.* **1977**, *16*, 33.

(27) (a) Mackenzie, K. *J. Chem. Soc.* **1965**, 4646. (b) Mackenzie, K. *J. Chem. Soc. C* **1969**, 1784. (c) Mackenzie, K.; Adams, C. H. M. *Ibid.* **1969**, 480.

(28) For a related example, consult the following: Chow, T. J.; Ding, M.-F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1121.

(29) Heterocyclic analogues of **1** have been prepared and studied: (a) Mackenzie, K.; Proctor, G. J.; Woodnutt, D. J. *Tetrahedron Lett.* **1984**, *25*, 977. (b) Mackenzie, K.; Proctor, G. J.; Woodnutt, D. J. *Tetrahedron* **1987**, *43*, 5981.

(30) For the demonstration of a dyotropic reaction in the gas phase, see: Kluft, E.; Nibbering, N. M. M.; Kuhn, H.; Herzschuh, R. *J. Am. Chem. Soc.* **1986**, *108*, 7201.

(31) Hagenbuch, J.-P.; Stampfli, B.; Vogel, P. *J. Am. Chem. Soc.* **1981**, *103*, 3934.

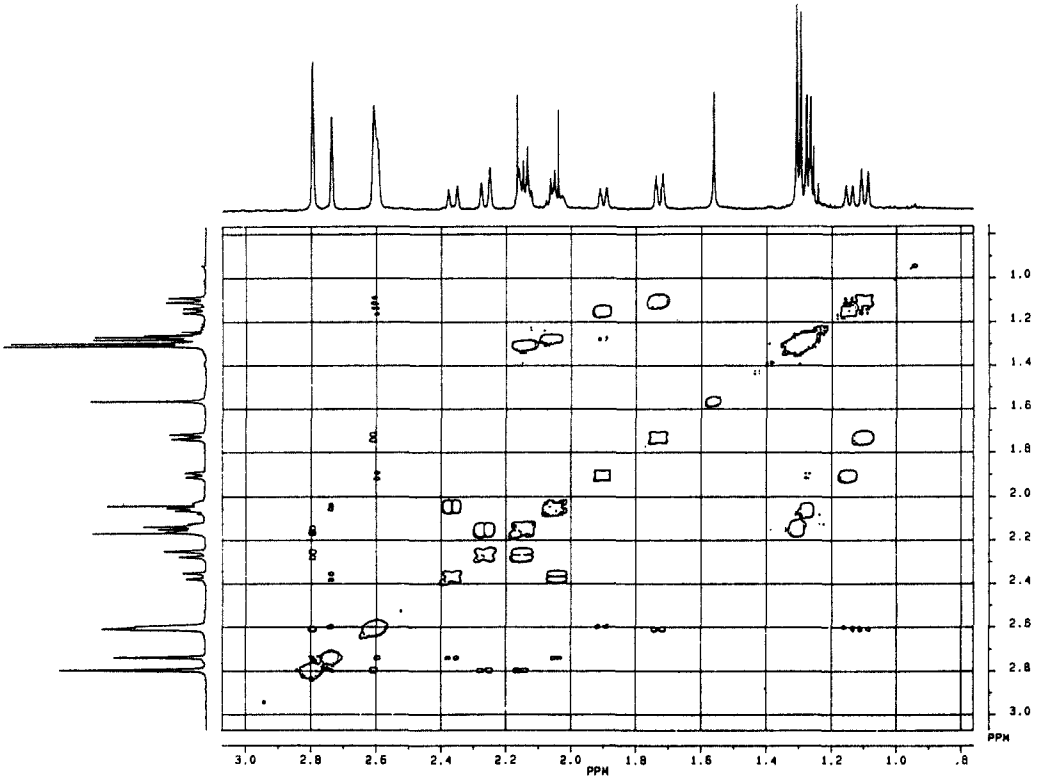


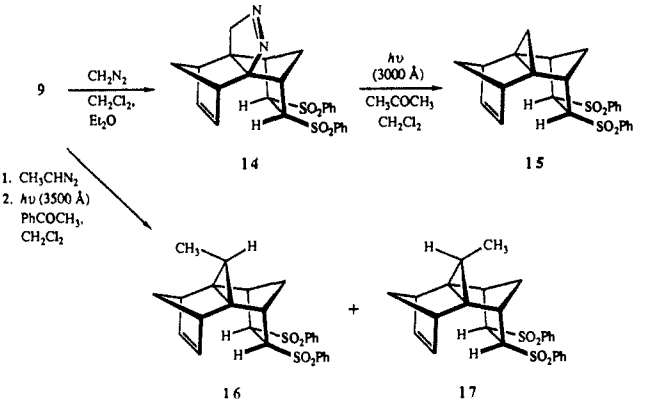
Figure 1. Partial 500 MHz 2D-COSY spectrum (in $CDCl_3$) of the **16**/**17** mixture that has been expanded to cover the δ 3.0–1.0 range.

Selection of the **5** ⇄ **6** isomer pairs was predicated not only on the obvious proximity of the reaction centers that was expected to permit dyotropy to be operational but also the likely prospect for good crystallinity was most certainly an additional consideration. A paramount issue, however, was recognition that the hydrogen atoms never leave the cavity of the *syn*-sesquinorbornene framework. Therefore, their migration should not be accompanied by gross strain energy changes. The product, after all, is simply an isomeric *syn*-sesquinorbornene! The most substantive energy cost that has to be paid is that associated with positioning the two hydrogen atoms into their proper transition-state locations. The reaction rate necessarily depends on how high the price is. As we now show, the relative *k*'s for **5** are linearly dependent upon the intracavity distance.

Synthetic Considerations. In keeping with the established chemistry of *syn*-sesquinorbornadienes,[32,33] the central double bond in disulfone **9**[34] can be engaged in chemical reaction with very high regioselectivity. For example, the action of diimide[33] on **9** resulted in the formation of **10** (Scheme I) without any evidence of overreduction. Similarly, exposure of **9** to a slight excess of *m*-chloroperbenzoic acid[34,35] led cleanly to **11**.

Two-step sequences were required to produce the *N*-phenylaziridine **13** and the cyclopropanes **15**–**17**. Phenyl azide added

Scheme II



smoothly to **9** in dichloromethane solution to give **12**, photolysis of which at 3500 Å in a Rayonet reactor resulted in conversion to **13**.[32] The capture by **9** of diazomethane was also a highly efficient [3 + 2] cycloaddition. Photodenitrogenation of **14** with acetone as sensitizer made possible symmetrical installation of the three-membered ring (Scheme II). For the purpose of placing greater steric bulk on the *syn*-sesquinorbornane exterior, diazoethane was utilized in an identical manner. The result was an inseparable mixture of **16** and **17** in a ratio of ca. 1:2.

The structural assignments to the several disulfones are in excellent agreement with their ^1H NMR spectra.[34] The inherent C_s symmetry of these compounds was clearly apparent from the reduced number of ^{13}C NMR signals. X-ray crystallographic analyses were also performed in order to acquire the requisite detailed structural information (see below). It remained only to determine whether **16** or **17** was formed as the major methylcyclopropane stereoisomer. Resolution of this question was achieved by means of a 2D-COSY experiment recorded in $CDCl_3$ at 500 MHz. As a consequence of the well-separated pattern of signals (see Figure 1), the apical protons of the two norbornyl rings in both isomers could be identified with certainty. Once this was accomplished, an NOE study provided information that was fully diagnostic of stereochemistry. The complete proton assignments

(32) Paquette, L. A.; Carr, R. V. C. *J. Am. Chem. Soc.* **1980**, *102*, 7553.
(33) (a) Paquette, L. A.; Carr, R. V. C.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186. (b) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, *102*, 7218.
(34) Paquette, L. A.; Künzer, H.; Green, K. E.; DeLucchi, O.; Licini, G.; Pasquato, L.; Valle, G. *J. Am. Chem. Soc.* **1986**, *108*, 3453.
(35) Paquette, L. A.; Fischer, J. W.; Browne, A. R.; Doecke, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 686.
(36) Goddard, W. A., III *J. Am. Chem. Soc.* **1972**, *94*, 793.
(37) Sheldrick, G. M. SHELX76, a system of computer programs for X-ray structure determination as locally modified, University of Cambridge, England, 1976.
(38) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. MULTAN 80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, University of York, England and Louvain, Belgium.
(39) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 72, 99, 149. (Present distributor: Kluwer Academic Publishers, Dordrect.)

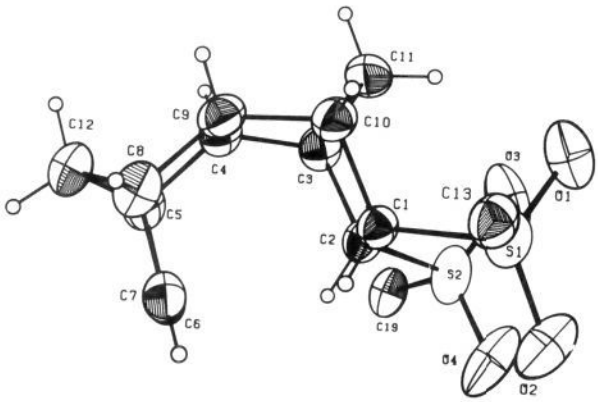
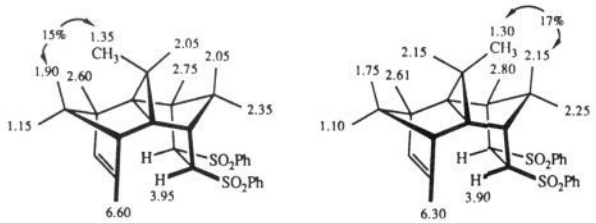


Figure 2. Computer-generated perspective drawing of the final X-ray model of **10** with the phenyl groups omitted for clarity.

Table II. Relevant Experimentally Determined Structural Parameters (X-ray Methods)

	nonbonded distances, Å			intracavity angles, deg	
compd	C(1)–H··· C(7)	C(2)–H··· C(6)	average distance	C(7)··· H–C(1)	C–(6)··· H–C(2)
	A. Disulfones Carrying a Proximal Double Bond				
10	2.44	2.37	2.41	117.9	122.0
11	2.60	2.46	2.53	117.3	123.1
13	2.40	2.41	2.40	121.0	120.4
15	2.32	2.31	2.32	121.2	122.4
16/17	2.31	2.26	2.28	119.1	119.8
	B. Dyotropisomeric Disulfone				
20	2.38	2.39	2.38	125.9	124.6

(δ values) and key NOE effects are illustrated in formulas A and B.



A B

X-ray Crystallographic Results. In order to facilitate comparison of the molecular geometries of **10**, **11**, **13**, **15**, and **16/17**, we have set **10** as the standard in the expectation that steric compression involving the endo α-sulfonyl protons would be higher when a small ring was located centrally on the *syn*-sesquinorbornene. The X-ray data for **10** (Table I (Supplementary Material), Figure 2) show the molecule to be slightly twisted in the crystalline state such that the C(1)–H···C(7) and C(2)–H···C(6) distances are not identical (Table II). As a result, the intracavity angles defined as those between C(7)···H–C(1) and between C(6)···H–C(2) also are slightly different (Table II). In order to simplify matters to some degree, the two nonbonded distances have been averaged together for the purpose of discussion.

The X-ray crystal structure of **11** has previously been reported,[34] and details of the analysis are consequently not presented here. However, the geometric features within the structure that are of specific relevance to this investigation are compiled alongside the others in Table II. Rather unexpectedly, the intraannular gap in **11** is slightly more extended than it is in **10**.

As concerns the *N*-phenylaziridine **13** (Table I (Supplementary Material), Figure 3), the experimentally determined geometric parameters are seen to change only to a relatively small extent when considered in terms of the standard model. Its nonbonded olefinic carbon/α-sulfonyl proton distances are shortened by only 0.01 Å or so, and the associated intrabridge angles are hardly altered at all.

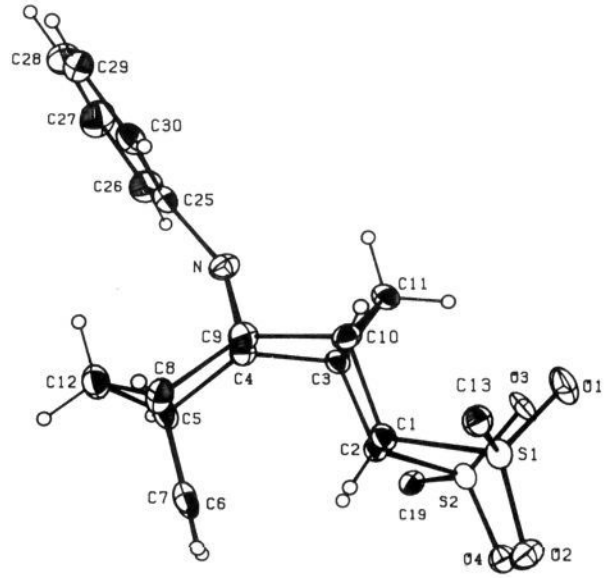


Figure 3. Computer-generated perspective drawing of the final X-ray model of **13** with the phenyl groups bonded to sulfur omitted for clarity.

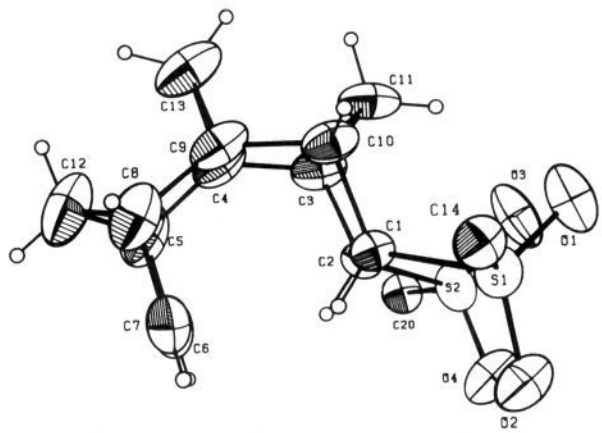


Figure 4. Computer-generated perspective drawing of the final X-ray model of **15** with the phenyl groups omitted for clarity.

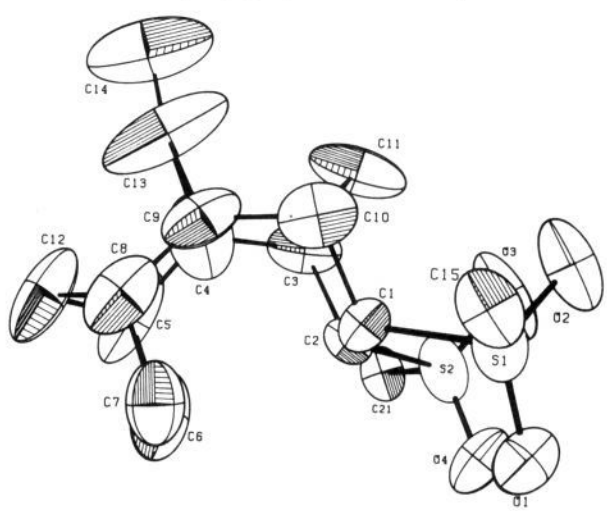


Figure 5. Computer-generated perspective drawing of the final X-ray model of the **16/17** mixture with the hydrogens and phenyl groups omitted for clarity.

The situation differs notably when the central three-membered ring is purely alicyclic. Presumably as a direct result of the need to accommodate the steric demands of the two cyclopropyl hydrogens in **15** (Table I (Supplementary Material), Figure 4), the

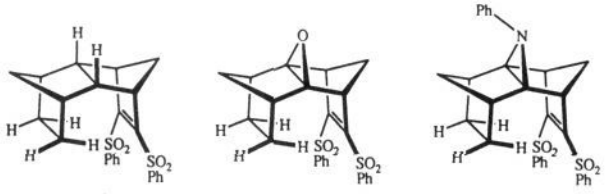
C(1)–H···C(7) and C(2)–H···C(6) distances are shortened to an average value of 2.32 Å. Curiously, the associated angles are not appreciably different from those seen in the other molecules (Table II).

For obvious reasons, the X-ray data for **16**/**17** appear disordered in the region encompassed by C(11) to C(14) (Figure 5). It was fully anticipated that the diffractometer would be incapable of distinguishing between the syn and anti methyl arrangements as well as the positional displacements of C(11) and C(12) that the two stereoisomeric orientations bring into play. Notwithstanding, the molecular subregion demarcated by C(1), C(2), C(6), and C(7) is clearly resolved, and the structural parameters determined for this sector are taken to be a relatively accurate reflection of the state of affairs prevailing in both disulfones. The increase in folding brought on by the methyl group is obviously substantial, such that nonbonded steric compression now reaches a maximum.

Thus, we see that distal structural modifications can affect the extent of downward puckering within a *syn*-sesquinorbornene to more than 0.1 Å. The α-sulfonyl protons move closer to the olefinic carbons as the central ring is made more spatially demanding. The associated angular deformations are comparatively minimal. It is legitimate to inquire how these structural modifications will impact on the relative rates of the dyotropic rearrangements.

Kinetic Measurements and Product Studies. In preparative scale experiments, heating bromobenzene solutions of **10** at the reflux temperature for 2 days was found to result in isomerization to **18**. The dyotropic rearrangement was diagnosed most readily by disappearance of the olefinic (δ 6.08) and α-sulfonyl proton signals (δ 3.69) in **10** in favor of a multiplet absorption in the δ 1.75–1.43 region. The bridgehead protons in the non-sulfur-substituted norbornyl ring were also displaced from δ 2.49 in **10** to 2.23 as a consequence of their loss of allylic character in **18**.

When epoxide **11** was subjected to comparable thermal activation, the conversion to **19** was also incomplete. Chromatographic separation of the isomers was readily accomplished. The somewhat diminished efficiency of the **11** → **19** reaction within the same time frame suggested, however, that intramolecular isomerization within **11** was occurring less readily than in **10**. This reactivity differential was to be subsequently quantified.



18 19 20

In contrast, **13** was observed to undergo more rapid dyotropic shift than either **10** or **11**, the formation of **20** being complete after 30 min in boiling bromobenzene. The spectral changes were entirely similar to those observed earlier. The exceptional crystallinity of **20** prompted its selection for X-ray crystallographic analysis (Table I (Supplementary Material), Figure 6). As detailed in Table II, dyotropic translocation of the pair of hydrogens in this aziridinyl disulfone has the effect of altering the nonbonded C(1)···H–C(7) and C(2)···H–C(6) distances by only 0.01 Å! Although the intracavity angles are 4–5° larger in **20** than they are in **13**, the isomerization is seen not to alter appreciably the overall *syn*-sesquinorbornene topography. We believe this example to be prototypical of all the dyotropisomers prepared in this work. The driving force to reaction can be attributed to the somewhat improved thermodynamic stabilization that accrues to placement of the double bond between the two phenylsulfonyl-substituted carbon atoms.

Qualitatively speaking, the presence of a central cyclopropane ring as in **15**–**17** exerts a notable accelerating effect on the production of **21**–**23**, respectively. In no example was cycloreversion or fragmentation observed as documented for **3**.[31] Consequently, neither the starting materials nor the products **18**–**23** find it energetically feasible to engage in competitive retro [4 + 2] cycloaddition and the like. Stated differently, the dyotropic changes documented herein are exceptionally clean transormations.

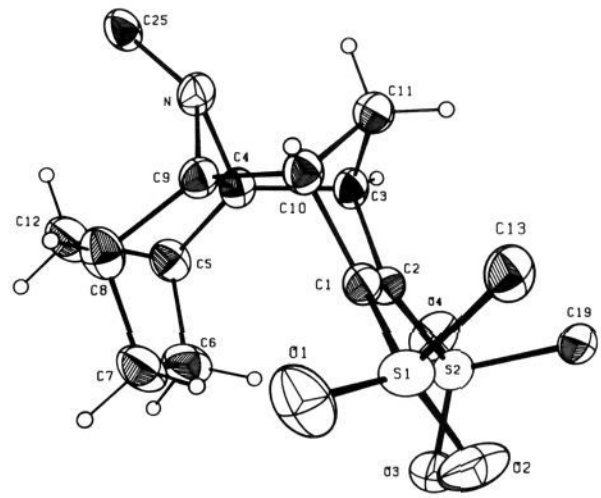


Figure 6. Computer-generated perspective drawing of the final X-ray model of **20** with the phenyl groups omitted for clarity.

Table III. Absolute Rate Data and Equilibrium Constants for the Forward and Reverse Dyotropic Rearrangements[a]

compd	T, °C	k_{for}, s^{-1}	k_{rev}, s^{-1}	k_{eq}
10	130.0 ± 0.1	4.36×10^{-6}	2.57×10^{-6}	1.69
		4.50×10^{-6}	2.61×10^{-6}	1.72
	160.0 ± 0.1	4.13×10^{-4}	2.23×10^{-4}	1.85
		4.37×10^{-4}	2.41×10^{-4}	1.81
11	160.0 ± 0.1	1.71×10^{-5}	3.15×10^{-6}	5.44
		1.88×10^{-5}	3.01×10^{-6}	6.25
13	130.0 ± 0.1	8.36×10^{-5}	1.17×10^{-5}	7.14
		8.17×10^{-5}	1.13×10^{-5}	7.20
15	100.6 ± 0.1	5.42×10^{-5}	2.57×10^{-5}	2.11
		4.70×10^{-5}	2.29×10^{-5}	2.06
	130.0 ± 0.1[b]	7.73×10^{-4}	2.58×10^{-4}	3.00
		7.65×10^{-4}	3.05×10^{-4}	2.51
16	100.0 ± 0.1	5.80×10^{-4}	1.07×10^{-4}	5.43
		6.03×10^{-4}	1.03×10^{-4}	5.87
17	100.0 ± 0.1	3.19×10^{-4}	1.84×10^{-4}	1.74
		3.01×10^{-4}	1.71×10^{-4}	1.76

[a] All reactions performed in bromobenzene-d_5 except where noted. [b] Measurements made in *o*-dichlorobenzene-d_4 solutions. Additional less complete rate studies conducted in *o*-$C_6D_4Cl_2$ solutions denoted a solvent effect to be lacking.

21 22 23

The absolute rate constants given in Table III were determined in C_6D_5Br or *o*-$C_6D_4Cl_2$ solution by monitoring suitable ^1H NMR spectral changes at 300 MHz. No sensitivity of k to concentration was noted. As a consequence of the widely differing reactivity of certain of the disulfones, it proved most convenient to group two or three *syn*-sesquinorbornenes together for steric analysis at a given temperature. By measuring the rate of dyotropisomerization for selected compounds at two temperatures, we found it possible to expedite arrival at the desired rate profile (Table IV).

The k_{for} data in Table IV reveal a distinct trend wherein epoxide **11** is seen to be less mobile in hydrogen group-transfer isomerization than the other compounds examined. Replacement of the oxirane unit by a pair of hydrogen substituents gives rise to a 24-fold rate acceleration. The *N*-phenylaziridine **13** and cyclopropane derivative **15** undergo the rearrangement more than 400

and 4000 times faster than **11**, respectively. In **16** and **17**, there are kinetic repercussions to the stereochemistry of the pendant methyl. When CH_3 is syn to the phenylsulfonyl groups as in **17**, dyotropic migration occurs with 25000-fold greater ease than in the epoxide. Anti CH_3 orientation as in **16** causes the rate differential to increase to approximately 50000!

The kinetic techniques that were employed permitted concurrent determination of the rate constants for the reverse reactions (k_{rev}), and these are listed in Table III. It is noteworthy that the relative ordering is the same. Measurement of the equilibrium constants (Table III), made possible by the reversibility of these rearrangements, was accomplished in each example by calculating the first half-life and allowing the thermolysis to proceed for at least 10 half-lives.

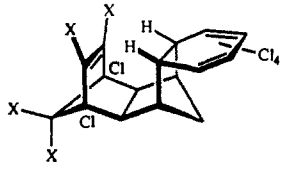
A plot of log k_{for} versus the average nonbonded distance from the α-sulfonyl protons to the center of the proximal trigonal carbons (Table II) defines a remarkably good straight line (Figure 7). No such correlation is obtained when the intracavity angles are given comparable treatment. Consequently, *distance is critically important to reactivity in these systems. Modulation on the order of 0.1 Å in the size of the intracavity gap is reflected in a rate spread greater than 10^4.*

Discussion

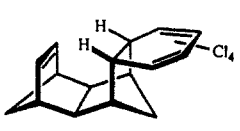
The notion that hydrogen atoms positioned geminal to a sulfone group should be capable of dyotropic translocation has proven to be a utilitarian one, especially in the present setting where proximity is structurally enforced. The suprafacial transfer of these hydrogens need not occur via a fully symmetric transition state. However, the process must be minimally synchronous. The alternative option of a stepwise mechanism involving the migration of one hydrogen at a time is far less likely since the involvement of diradical intermediates can be estimated to have enthalpic demands in excess of 50 kcal/mol.[31] However, the $\Delta H^{\ddagger}$ for **13** was determined to be 27 kcal/mol, a value similar in magnitude to that found in **3** (35–39 kcal/mol).[31]

The present kinetic analysis reveals marked effects on rearrangement as the structural characteristics of the X component across C(4) and C(9) is varied (see **5**). It is seen that such modifications of the *syn*-sesquinorbornene framework impact significantly on the intracavity space available to the α-sulfonyl protons. However, inductive effects do not remain constant throughout the series, and it is relevant to ask whether the dramatic increase in kinetic reactivity does not stem largely from electronic perturbations.

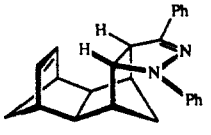
Although insufficient data are presently available to discuss the possible impact of acceptor/donor substituent effects in a meaningful way at the theoretical level,[21,22,36] several pertinent facts can be documented in this connection. Mackenzie has observed that chlorine and methoxyl substituents bonded directly to the receptor π-bond as in **24a** and **24b** retard rearrangement.[27,29] By suitable extrapolation, **25** was shown to be 2×10^5 more reactive than **24a** at 36 °C. The 2-pyrazoline **26**, which has heteroatoms linked directly to the donor carbons, also experiences dyotropic isomerization less readily than **25**. The possible involvement of radical or dipolar intermediates is further discounted



24a, X = Cl
b, X = OCH_3



25



26

Table IV. Relative Rates within and across Temperature Zones[a]

compd	100 °C k_{for}	100 °C k_{rev}	130 °C k_{for}	130 °C k_{rev}	160 °C k_{for}	160 °C k_{rev}	overall relative k_{for}
16	11.70	4.32					48000
17	6.13	7.33					25200
15	1.0	1.0	174	109			4100
13			18.7	4.44			440
10			1.0	1.0	23.6	75.2	24
11					1.0	1.0	1

[a] The values used here are the averaged data pairs given in Table III.

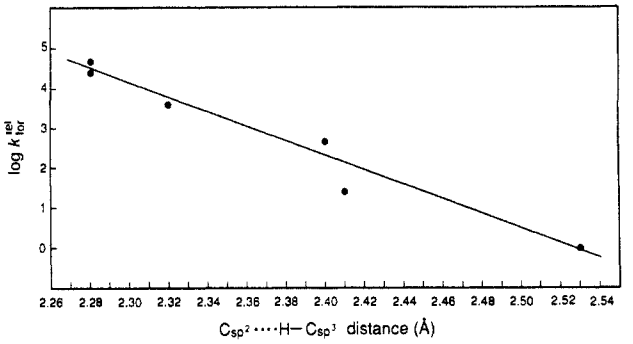


Figure 7. Plot of log k_{for}^{rel} versus the average $PhSO_2C$–H···sp^2C distance.

by these results, since all three types of substituents would be expected to be stabilizing and rate-enhancing under these circumstances. The data do disclose, however, that a balance of effects exists when the proximity of the flanking π-bond is altered and when different heteroatoms are bonded to any of the four carbon atoms involved directly in the pericyclic process.

In **11** and **13**, the oxygen and nitrogen atoms are well-separated from the seat of rearrangement. Accordingly, a substantial dropoff in their inductive contributions can be expected. For this reason, the rate spread of 10^4 cannot be attributed in a wholesale way to such electronic contributions. Furthermore, it is emphasized that the heteroatoms in **11** and **13** are situated in three-membered rings and that suitable cyclopropane analogues were also studied.

The impressive differences in reactivity within the disulfone series are most convincingly correlated with proximity effects (Figure 7). By constraining the reacting units into a relatively small, conveniently alterable volume, their reactivity can be controlled in a tunable way. It is interesting to conjecture whether compression beyond the present 2.28 Å limit (Table II) would lead to further enhancement in reactivity. This would be the case, of course, unless the critical distance point has been exceeded.

While our results are supportive of Menger's spatiotemporal hypothesis,[16] they do not contraindicate Houk's contentions.[17] When reacting groups are placed in a specific arrangement with respect to each other, energetic as well as entropic effects are brought into play. Since the $\Delta S^{\ddagger}$ values for type II dyotropic reactions[26] range from modestly negative[27,29] to slightly positive,[31] the changes in freedom of motion that occur between the ground and transition states do not give evidence of making dominant contribution to the observed rates. Rather, the observed kinetic profile originates from the progressive stabilization of the transition states involved by bringing the α-sulfonyl hydrogens incrementally closer to the olefinic carbons to which they migrate. Thus, the reactivity determinant is the energy required to stretch these C–H bonds into the proper transition-state geometry. For *syn*-sesquinorbornenes, this process becomes less costly as greater proximity is enforced.

Experimental Section

Diimide Reduction of 9. To a magnetically stirred solution of **9**[34] (1.00 g, 2.3 mmol) in dichloromethane (20 mL) was added 0.29 mL of 30% hydrogen peroxide followed dropwise by anhydrous hydrazine (220 mg, 6.9 mmol). The reaction mixture was not allowed to heat up. Nitrogen evolution began almost immediately and continued for 3 h. After an additional 4 h of stirring, the solvent was removed in vacuo. The residual white solid was purified by MPLC on silica gel (elution with ethyl ace-

tate/petroleum ether/tetrahydrofuran 48:48:4). There was isolated 690 mg (69%) of **10** alongside 300 mg of unreacted starting material.

For **10**: colorless solid, mp 215 °C; IR (KBr, cm^{-1}) 3055, 3030, 2960, 1575, 1438, 1315, 1140, 1078, 994, 760, 700, 635; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94–7.51 (m, 10 H), 6.08 (s, 2 H), 3.69 (d, J = 2.1 Hz, 2 H), 2.67–2.48 (m, 7 H), 1.69 (d, J = 8.1 Hz, 1 H), 1.60 (d, J = 10.5 Hz, 1 H), 1.42 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.17, 133.29, 132.92, 128.87 (2C), 128.26 (2C), 66.60, 59.59, 48.08, 44.67, 43.87, 43.26; MS m/z (M^+) calcd 440.1120, obsd 440.1108. Anal. Calcd for $C_{24}H_{24}O_4S_2$: C, 65.44; H, 5.55. Found: C, 65.05; H, 5.50.

Phenyl Azide Addition to 9. To a magnetically stirred solution of **9** (750 mg, 1.7 mmol) in dry dichloromethane (20 mL) was added phenyl azide (204 mg, 1.7 mmol). The flask was capped, sealed, and stirred for 24 h before the solvent was evaporated in vacuo. Flash chromatography of the remaining light brown solid (silica gel, elution with 60% ethyl acetate in petroleum ether) gave 580 mg (61%) of **12** as a white solid.

Without further purification, the adduct was dissolved in acetone (10 mL), deoxygenated by bubbling nitrogen through this solution, and irradiated with a bank of 3500 Å lamps in a Rayonet reactor for 15 min. Solvent removal and chromatographic purification on silica gel (elution with 40% ethyl acetate in petroleum ether) provided pure **13** (39 mg, 85%) as a white solid that turns brown on standing at room temperature; mp 125 °C; IR (KBr, cm^{-1}) 3030, 2940, 1561, 1455, 1437, 1305, 1250, 1210, 1135, 1060, 760, 690, 635; ^{13}C NMR (300 MHz, $CDCl_3$) δ 7.98–6.40 (series of m, 17 H), 3.95 (d, J = 2.8 Hz, 2 H), 3.06 (s, 2 H), 2.88 (s, 2 H), 2.17 (d, J = 12.0 Hz, 1 H), 1.89 (d, J = 8.5 Hz, 1 H), 1.78 (d, J = 12.2 Hz, 1 H), 1.37 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 148.32, 140.86, 138.74 (2C), 133.65 (2C), 129.88 (2C), 129.40 (4C), 128.36 (4C), 118.81 (2C), 113.02 (2C); MS m/z (M^+) calcd 529.1380, obsd 529.1382. Anal. Calcd for $C_{30}H_{27}NO_4S_2$: C, 68.04; H, 5.14. Found: C, 68.09; H, 5.09.

Diazomethane Addition to 9. A solution of **9** (420 mg, 0.96 mmol) in dichloromethane was treated with 10 equiv of diazomethane dissolved in ether. The flask was swirled and placed in a freezer for 8 h. At this point, the reaction mixture was washed with dilute acetic acid (2 × 20 mL), 10% sodium bicarbonate solution, water, and brine prior to drying. Solvent evaporation in vacuo left a yellow foam that was taken up in 2 mL of acetone and placed in a freezer. Filtration afforded 420 mg (91%) of **14** as a white crystalline solid: mp 215 °C; IR (KBr, cm^{-1}) 3050, 2965, 1475, 1467, 1442, 1340, 1330, 1166, 1150, 1083, 1055, 908; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.54 (m, 10 H), 6.19 (br s, 2 H), 4.36 (d, J = 18.9 Hz, 1 H), 4.27 (d, J = 18.9 Hz, 1 H), 3.98 (dd, J = 8.8, 2.4 Hz, 1 H), 3.93 (dd, J = 8.8, 2.4 Hz, 1 H), 3.00 (d, J = 1.1 Hz, 1 H), 2.92 (br s, 1 H), 2.67 (br s, 1 H), 2.54 (dd, J = 12.2, 1.2 Hz, 1 H), 2.43 (br s, 1 H), 1.62 (dd, J = 9.9, 1.1 Hz, 1 H), 1.12 (d, J = 12.2 Hz, 1 H), 0.99 (d, J = 9.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 140.81, 140.50, 135.57, 133.81, 133.66, 132.57, 129.30, 129.03, 128.33, 114.40, 93.11, 66.76, 65.58, 56.39, 55.91, 48.55, 47.94, 45.72, 45.11, 40.41, 30.81. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 62.48; H, 5.04. Found: C, 62.50; H, 5.52.

Photodenitrogenation of 14. In a dry quartz vessel was placed a solution of **14** (285 mg, 0.63 mmol) in dichloromethane (50 mL). To this was added 4.0 mL of acetone as sensitizer. After deoxygenation of this solution with nitrogen for 10 min, the vessel was capped and irradiated for 30 min with a full bank of 3000 Å lamps in a Rayonet reactor. The solvent was evaporated, and the residue was taken up in dichloromethane before filtration through a plug of silica gel to remove a yellow polymer. The eluate was freed of solvent, and the resulting solid was recrystallized from acetone to give **15** (200 mg, 75%) as white crystals: mp 246 °C; IR (KBr, cm^{-1}) 3010, 2960, 1580, 1530, 1495, 1442, 1330, 1307, 1278, 1260, 1145, 1080, 908, 685, 665, 620; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99–7.50 (m, 10 H), 6.34 (t, J = 1.7 Hz, 2 H), 3.95 (d, J = 2.8 Hz, 2 H), 2.80 (br s, 2 H), 2.64 (br s, 2 H), 2.30 (d, J = 12.6 Hz, 1 H), 1.85 (d, J = 12.5 Hz, 1 H), 1.65 (d, J = 9.8 Hz, 1 H), 1.25 (d, J = 8.7 Hz, 1 H), 1.12 (d, J = 9.7 Hz, 1 H), 1.00 (d, J = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 141.29 (2C), 138.30 (2C), 133.38 (2C), 128.97 (4C), 128.34 (4C), 67.89 (2C), 54.97, 43.89 (2C), 43.83 (2C), 39.40, 33.13 (2C), 13.08; MS m/z (M^+) calcd 452.1116, obsd 452.1144. Anal. Calcd for $C_{25}H_{24}O_4S_2$: C, 66.36; H, 5.35. Found: C, 66.56; H, 5.57.

Diazoethane Addition to 9. A solution of **9** (200 mg, 0.56 mmol) in dichloromethane at 0 °C was treated with 1.5 equiv of diazoethane as a solution in ether. After stirring 3 h at 0 °C the solution was warmed to room temperature. The reaction mixture was washed with dilute acetic acid (2 × 20 mL), water, and brine prior to drying. Filtration and removal of the solvent gave a pale yellow foam. Purification by MPLC (50% ethyl acetate in petroleum ether as eluant) afforded 140 mg (65%) of a mixture of isomers as a white solid.

Without further purification, the adduct was dissolved in dichloromethane (75 mL) and was placed in a quartz vessel. To this was added acetophenone (20 mg) as sensitizer. After saturation of this solution with nitrogen, the tube was capped and irradiated with one-half of a full bank of 3500 Å bulbs in a Rayonet reactor for 35 min. The solvent was removed leaving a yellow foam. Purification by MPLC (50% ethyl acetate in petroleum ether as eluant) gave 59 mg (45%) of the cyclopropane disulfone as a mixture of isomers (**16**/**17**: mp 200–203 °C dec; IR (KBr, cm^{-1}) 3090, 3050, 2950, 1575, 1440, 1330, 1305, 1150, 1080, 770, 715, 690; ^1H NMR (300 MHz, $CDCl_3$) δ isomer A 7.80–7.40 (m, 10 H), 6.54 (br m, 2 H), 3.95 (d, J = 2.9 Hz, 2 H), 2.73 (s, 2 H), 2.60 (s, 2 H), 2.36 (ABq, J = 13.5 Hz, 1 H), 2.10–2.00 (m, 2 H), 1.91 (ABq, J = 9.2 Hz, 1 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.20–1.00 (m, 1 H); isomer B 8.00–7.40 (m, 10 H), 6.28 (br m, 2 H), 3.92 (d, J = 2.9 Hz, 2 H), 2.79 (s, 2 H), 2.60 (s, 2 H), 2.26 (ABq, J = 13.1 Hz, 1 H), 2.20–2.10 (m, 2 H), 1.72 (ABq, J = 10.3 Hz, 1 H), 1.30 (d, J = 6.3 Hz, 3 H), 1.20–1.00 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (both isomers) 141.36, 141.25, 140.64, 137.50, 133.37, 128.99, 128.23, 68.73, 67.87, 56.03, 45.13, 44.86, 43.72, 43.16, 40.92, 40.23, 37.92, 36.90, 20.55, 16.60, 16.06; MS m/z (M^+) calcd 466.1273, obsd 466.1280. Anal. Calcd for $C_{26}H_{26}O_4S_2$: C, 66.93; H, 5.62. Found: C, 67.02; H, 5.78.

General Dyotropic Rearrangement Procedure. A. Disulfone 10. A solution of **10** (31.2 mg, 0.071 mmol) in 2 mL of bromobenzene was heated at the reflux temperature for 2 days. The bromobenzene was removed in vacuo, and the residue was submitted to MPLC purification (silica gel, elution with 40% ethyl acetate in petroleum ether). There was obtained 20 mg (65%) of **18** as a white solid: mp 198–199 °C dec; IR (KBr, cm^{-1}) 3065, 3000, 2950, 2920, 2870, 1557, 1473, 1443, 1320, 1248, 1155, 1027, 736, 688, 610; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81–7.47 (m, 10 H), 3.07 (d, J = 1.5 Hz, 2 H), 2.68 (br s, 2 H), 2.23 (br s, 2 H), 1.75–1.43 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 154.06 (2C), 140.28 (2C), 133.86 (2C), 129.08 (4C), 128.58 (4C), 62.99 (2C), 50.72 (2C), 49.91 (2C), 48.06 (2C), 28.91 (2C), 25.21 (2C); MS m/z (M^+) calcd 440.1116, obsd 440.1108. Anal. Calcd for $C_{24}H_{24}O_4S_2$: C, 65.44; H, 5.50. Found: C, 65.50; H, 5.57.

B. Epoxy disulfone 11: 34 mg (0.075 mmol) of **11** in 3 mL of bromobenzene; reflux for 21 h; MPLC gave 25 mg (75%) of **19** and returned 9 mg (25%) of **11**.

For **19**: IR (KBr, cm^{-1}) 3060, 3000, 2970, 2950, 1575, 1470, 1445, 1320, 1220, 1150, 1085, 1020, 760, 730, 690, 650; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–7.51 (m, 10 H), 3.44 (s, 2 H), 2.68 (s, 2 H), 2.08 (dt, J = 8.5, 1.5 Hz, 1 H), 1.93 (d, J = 9.3 Hz, 1 H), 1.61–1.38 (m, 5 H), 0.95 (d, J = 9.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.91, 139.50, 134.35, 129.36, 128.71, 65.06, 57.70, 51.77, 39.98, 39.47, 25.21; MS m/z (M^+) calcd 454.0909, obsd 454.0933. Anal. Calcd for $C_{24}H_{22}O_5S_2$: C, 63.42; H, 4.88. Found: C, 63.20; H, 4.95.

C. Aziridino disulfone 13: 32 mg (0.061 mmol) of **13** in 3 mL of bromobenzene; reflux for 30 min; MPLC gave 26 mg (81%) of **20** as a pale yellow solid, mp 231–231.5 °C; IR (CH_2Cl_2, cm^{-1}) 3060, 2980, 1588, 1492, 1441, 1400, 1322, 1156, 1083, 645, 635; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–6.52 (series of m, 15 H), 3.47 (s, 2 H), 2.75 (s, 2 H), 2.07 (dt, J = 8.6, 1.5 Hz, 1 H), 1.72–1.52 (m, 5 H), 1.31 (d, J = 8.5 Hz, 1 H), 0.85 (d, J = 11.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.33 (2C), 149.01, 139.7, 134.12 (2C), 129.74 (2C), 129.23 (4C), 118.59 (2C), 113.58 (2C); MS m/z (M^+) calcd 529.1380, obsd 529.1389. Anal. Calcd for $C_{30}H_{27}NO_4S_2$: C, 68.04; H, 5.14. Found: C, 67.84; H, 5.49.

D. Cyclopropa disulfone 15: 30 mg (0.066 mmol) of **15** in 2 mL of bromobenzene; reflux for 20 min; MPLC gave 20.1 mg (67%) of **21** and returned 9.9 mg of **15**.

For **21**: colorless solid, mp 246–247 °C; IR (KBr, cm^{-1}) 3020, 2940, 1580, 1442, 1322, 1155, 1084, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.48 (m, 10 H), 3.23 (br s, 2 H), 2.43 (br s, 2 H), 1.77–1.69 (m, 2 H), 1.57 (br s, 4 H), 1.05–0.95 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 158.83 (2C), 140.15 (2C), 133.92 (2C), 129.14 (2C), 128.73 (2C), 58.05, 51.54 (2C), 43.37, 38.91 (2C), 33.42 (2C), 27.66 (2C), 11.95; MS m/z (M^+) calcd 452.1116, obsd 452.1124. Anal. Calcd for $C_{25}H_{24}O_4S_2$: C, 66.36; H, 5.35. Found: C, 66.56; H, 5.57.

E. Methylcyclopropa disulfones 22/23: 20 mg (0.043 mmol) in *o*-dichlorobenzene (3.0 mL); reflux for 30 min; MPLC gave 12 mg (66%) of **22**/**23** as a white solid, mp 199–200 °C; IR ($CDCl_3$, cm^{-1}) 3100, 2990, 2950, 1580, 1465, 1440, 1320, 1305, 1150, 1080, 905; ^1H NMR (300 MHz, $CDCl_3$) δ isomer A 7.90–7.40 (m, 10 H), 3.19 (s, 2 H), 2.40 (s, 2 H), 2.20–1.40 (series of m, 6 H), 1.30 (d, J = 6.2 Hz, 3 H), 1.10–0.80 (m, 2 H); isomer B 7.90–7.40 (m, 10 H), 3.19 (s, 2 H), 2.37 (s, 2 H), 2.20–1.40 (series of m, 6 H), 1.22 (d, J = 6.2 Hz, 3 H), 1.10–0.80 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (both isomers) 161.04, 157.91, 140.13, 140.05, 133.87, 129.10, 128.71, 59.35, 59.24, 52.72, 51.51, 44.82, 40.05, 39.11, 38.06, 37.00, 29.00, 28.43, 20.01, 18.51, 16.59, 16.17; MS m/z (M^+) calcd 466.1273, obsd 466.1283. Anal. Calcd for $C_{26}H_{26}O_4S_2$: C, 66.93; H, 5.62. Found: C, 66.57; H, 5.70.

Kinetic Measurements. The thermolyses were performed in a thermostatted oil bath. Rates were determined by repeated integration of

select ^1H NMR signals at 300 MHz. The integrals were normalized to that of the starting material before heating was initiated. Generally, five data points run in duplicate were obtained for each substrate at each temperature.

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Supplementary Material Available: X-ray experimental data and tables of crystal data, bond distances and angles, least-squares planes, final fractional coordinates, and thermal parameters for **10**, **13**, **15**, **16/17**, and **20** (43 pages). Ordering information is given on any current masthead page.

(±)-Benzoabikoviromycin, a Potential Antiviral Agent Synthesized by the Palladium-Catalyzed Ring Expansion of 2-Alkynyl-2-hydroxybenzocyclobutenones

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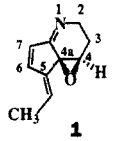
Abstract: Abikoviromycin [(4*R*,4a*S*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyridine 4,4a-oxide] is an antiviral and antifungal antibiotic isolated from culture broths of *Streptomyces abikoensis* and *Streptomyces rubescens* and more recently from *Streptomyces* sp. NA-337. It was shown to be identical with latumcidin, isolated in 1958 from the culture broth of *Streptomyces reticular liatumcidicus*. Given its interesting biological acitivity and novel structure, abikoviromycin should have attracted the attention of both synthesis and medicinal chemists interested in probing further the chemical and biological properties of this highly functionalized molecule, as well as its analogues. However, abikoviromycin is highly unstable and polymerizes rapidly upon isolation even at −50 °C. It is readily decomposed by heat, by acid, or on standing in the dry state. This extreme reactivity has probably precluded in-depth studies of the molecule, and therefore, it is not surprising that there have been no synthetic efforts in the area published to date. Starting from the premise that the chemical reactivity of abikoviromycin is associated with polymerization of the diene–imine portion of the molecule, masking of the 6,7-double bond as part of a benzene ring might lead to increased stability of the resulting molecule while still retaining aspects of the biological activity. A brief and concise synthesis of racemic benzoabikoviromycin is described on the basis of the previously developed facile and stereoselective palladium(2+)-catalyzed ring expansion of 2-alkynyl-2-hydroxybenzocyclobutenone monoketals to alkylideneindandione monoketals.

Abikoviromycin is an antiviral and antifungal antibiotic isolated from culture broths of *Streptomyces abikoensis* and *Streptomyces rubescens* and more recently from *Streptomyces* sp. NA-337.[2] It was shown to be identical with latumcidin, isolated in 1958 from the culture broth of *Streptomyces reticular liatumcidicus*.[3] Abikoviromycin was studied by Gurevich and co-workers using chemical and spectroscopic methods, and they assigned the structure (4*S*,4a*R*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyrindine 4,4a-oxide to the antibiotic.[4] In a later X-ray crystallographic study of the selenate salt, the molecule was assigned the opposite configuration at C-3 and C-4.[5] Therefore, abikoviromycin has the structure shown in **1** [(4*R*,4a*S*)-5-(1′*E*)-ethylidene-2,3-dihydro-1,5-pyrindine 4,4a-oxide or 7-ethylidene-1a,2,3,7-tetrahydrocyclopent[*b*]oxireno[*c*]pyridine].



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Abikoviromycin is highly unstable and polymerizes rapidly upon isolation even at −50 °C. It is readily decomposed by heat, by acid, or on standing in the dry state; however, it can be handled in dilute solutions and in the form of its salts (sulfate, picrate, selenate). It is effective against eastern and western but not Venezuelan equine encephalomyelitis viruses at dilutions of 1:8 000 000 when mixed with virus suspensions and injected intracerebrally into mice. It was shown to inhibit infection of cell cultures by influenza A and B viruses, Newcastle disease virus, and Chikungunya virus.[6] It is weakly antibacterial and antifungal, and it does not appear to have been tested in antitumor assays. Reduction of abikoviromycin with $NaBH_4$ was shown to produce dihydroabikoviromycin, the product of imine reduction. Dihydroabikoviromycin was subsequently isolated directly from a culture broth that also produced an enzyme capable of oxidizing dihydroabikoviromycin to abikoviromycin.[7] Most recently a related antibiotic, *N*-hydroxydihydroabikoviromycin, with antimicrobial activity against *Klebsiella pneumoniae* was isolated from a *Streptomyces* species.[8]

Given its interesting biological activity and novel structure, abikoviromycin should have attracted the attention of both synthesis and medicinal chemists interested in probing further the chemical and biological properties of this highly functionalized

(1) Camille and Henry Dreyfus Teacher Scholar, 1985–1990.
(2) (a) Umezawa, H.; Tazaki, T.; Fukuyama, S. *Jpn. Med. J.* **1951**, *4*, 331; *Chem. Abstr.* **1952**, *46*, 7167c. (b) Onda, M.; Konda, Y.; Narimatsu, Y.; Tanaka, H.; Awaya, J.; Omura, S. *Chem. Pharm. Bull.* **1974**, *22*, 2916.
(3) (a) Sakagami, Y.; Yamaguchi, I.; Yonehara, H.; Okimoto, Y.; Yamanouchi, S.; Takiguchi, K.; Sakai, H. *J. Antibiot.* **1958**, *11A*, 231. (b) Sakagami, Y.; Utahara, R.; Yagishita, K.; Umezawa, H. *J. Antibiot.* **1958**, *11A*, 231.
(4) (a) Gurevich, A. I.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V. *Tetrahedron Lett.* **1968**, 2209. (b) Gurevich, A. I.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V. *Khim. Prir. Soedin.* **1971**, *7*, 104; *Chem. Abstr.* **1971**, *75*, 5752e.
(5) Kono, Y.; Takeuchi, S.; Yonehara, H.; Marumo, F.; Saito, Y. *Acta Crystallogr.* **1971**, *B27*, 2341.
(6) Roikhel, V. M.; Krauzova, V. I.; Zeitlenok, N. A. *Tr. Inst. Polio. Virusn. Entsefalitov Akad. Med. Nauk SSSR* **1971**, *16*, 247; *Chem. Abstr.* **1973**, *78*, 80181h.
(7) (a) Tsuruoka, T.; Shomura, T.; Ogawa, Y.; Ezaki, N.; Watanabe, H.; Amano, S.; Inouye, S.; Niida, T. *J. Antibiot.* **1973**, *26*, 168. (b) Ogawa, T.; Tsuruoka, T.; Shomura, T.; Watanabe, H.; Inouye, S.; Niida, T. *J. Antibiot.* **1973**, *26*, 186.
(8) Takahashi, S.; Serita, K.; Enokita, R.; Takao, O.; Haneishi, T. *Sankyo Kenkyusho Nempo* **1986**, *38*, 105; *Chem. Abstr.* **1987**, *107*, 55392n.

0002-7863/90/1512-291$02.50/0