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INTRINSIC PYRAMIDAL NITROGEN OF N-SULFONYLAMIDES

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Abstract The pyramidalization of the nitrogen in sulfonamides of 7-azabicyclo[2.2.1]heptane is enhanced in the solid state as compared with the corresponding monocyclic sulfonamides of pyrrolidine and 3-pyrroline. We postulate a general structural motif of pyramidal nitrogen in sulfonamides.

We have shown that pyramidalized amide nitrogen is an intrinsic feature of the 7-azabicyclo[2.2.1]heptane motif in the solid state.[1] As regards sulfonamides, examples with planar nitrogen have been reported,[2,4] but most tend to exhibit nitrogen pyramidalization.[3,5,6] The purpose of this paper is to establish the intrinsic structural character of sulfonamides of 7-azabicyclo[2.2.1]heptane by comparing the magnitude of pyramidalization with those of the most pyramidal simple N-sulfonylamides of aziridine and azetidine.

The planarity of sulfonamide nitrogen can be represented in terms of two angle parameters, the summation of the three valence angles around the nitrogen (θ), and the out-of-plane angle (α) of the sulfur atom of the sulfonamides with respect to the plane defined by the nitrogen atom and the two adjacent carbon atoms (Table 1).[7] Deviation from planar nitrogen is represented in terms of a positive value of α and a value of θ smaller than 360 °. The Cambridge Structural Database contains 370 examples of arylsulfonamides of secondary amines, including 19 examples of aziridine derivatives,[5] and 2 examples of azetidine derivatives.[6] The average value of θ of the 349 examples (i.e., except the 21 small ring derivatives) is 352.4 ° (standard deviation 5.7 °), ranging from a minimum of 332.3 ° to a maximum of 360.0 °. The data suggest that planar sulfonamides occur (74 examples of arylsulfonamides in the Cambridge Structural Database take the value of $\theta > 358.0$ °),[2] but that N-sulfonylamides tend to exhibit pyramidal nitrogen more frequently than do amides.[3] In fact, simple monocyclic sulfonamides, N-(p-toluenesulfonyl)pyrrolidine **5** and N-(p-toluenesulfonyl)-3-pyrroline **6**, are pyramidalized (**5**: θ=349.2 °, α=30 °; **6**: θ=353.4 °, α=24 °) in the crystal,[8,9] which is in sharp contrast to the essentially planar nitrogen of the relevant amides of N-benzoylpyrrolidine and N-benzoyl-3-pyrroline.[1] The planar trigonal nitrogen of N-sulfonylamides can be attributed to π bonding between the nitrogen and sulfur atoms, due to p_{π}-d_{π} bonding between the nitrogen lone pair and vacant sulfur orbital,[4] or negative hyperconjugation of the nitrogen lone pair (*vide infra*).[10,11] Thus, the rotational barriers of N-S bonds of sulfonamides are smaller than those of the N-C bonds of amides,[4] leading to potential pyramidalization of the nitrogen of N-sulfonylamides.

The nitrogen atoms of N-(p-toluenesulfonyl)-7-azadibenzobicyclo[2.2.1]heptadiene **1** and N-(p-toluenesulfonyl)-2,3-dimethoxycarbonyl-7-azabicyclo[2.2.1]heptadiene **2** are more pyramidalized (**1**: θ=341.4 °, α=36.0 °; **2**: θ=341.3 °, α=35.9 °) than those of the monocyclic counterparts **5** and **6** (Table 1).[9] The N-S bond (**1**: 1.628 Å; **2**: 1.634 Å) is elongated as compared with those of **5** (1.613 Å) and **6** (1.597 Å) in the crystal

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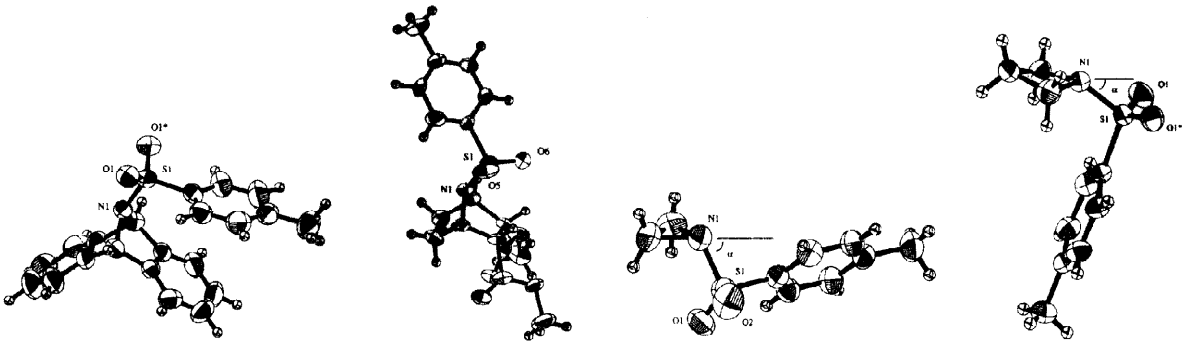
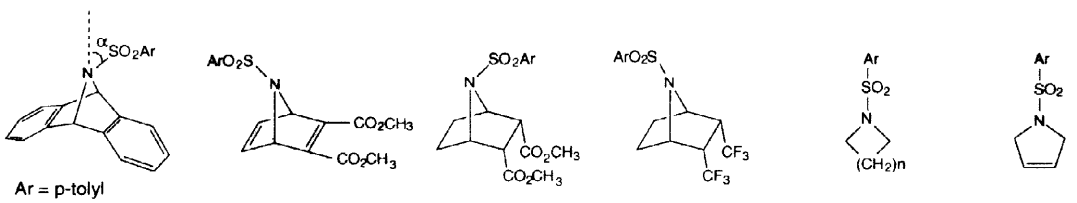
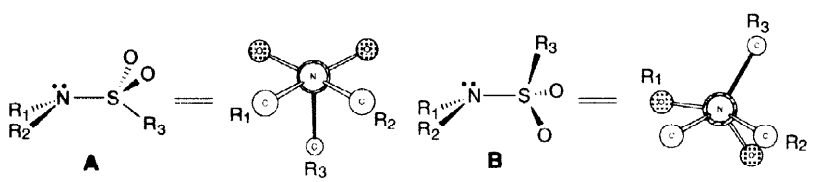


1 3 7 8

Figure 1 ORTEP Diagrams Showing 50 % Probability Displacement Ellipsoids



state. The crystal structure of a nitrogen-pyramidal N-methylsulfonyl amide of 7-azabicyclo[2.2.1]heptadiene, i.e., N-(methylsulfonyl)-2,3-dimethoxycarbonyl-7-azabicyclo[2.2.1]heptadiene, complexed with tricarbonyl iron was also reported.[12] The observed pyramidalization can be regarded as a fixation of the inherent pyramidal nitrogen atom by iron complexation.



Greater nitrogen pyramidalization (α=41 °) is observed in the saturated sulfonamide, (*p*-toluenesulfonyl)-2,3-dimethoxycarbonyl-7-azabicyclo[2.2.1]heptane **3**. The N-S bond is also elongated significantly. (*p*-Toluenesulfonyl)-2,3-ditrifluoromethyl-7-azabicyclo[2.2.1]heptane **4** is also pyramidalized, the out-of-plane angle (α) of **4** being comparable with that of the monocyclic saturated counterpart **5**; nevertheless, the N-S bond of **4** is elongated as compared with that of **5**. Our single crystal structural determinations of the simplest sulfonamides of a small ring system,[9,13] i.e., *p*-toluenesulfonylaziridine (**7**) and *p*-toluenesulfonylazetidine (**8**) provide a reference of maximum pyramidalization of the sulfonamides, α (and θ) being 59.5 ° (291.2 ° (2))/59.1 ° (291.3 °(2)), and 37.25 ° (338.8 °(1)), respectively. Thus, the degree of pyramidalization inherent in 7-azabicyclo[2.2.1]heptane seems to be comparable to that of azetidine N-sulfonylamides.[5,6]

In the case of unsymmetrical substrates, the tilt direction of the sulfonyl group with respect to the nitrogen trigonal plane is an issue. With **2**, *anti*-tilting of the sulfonyl group with respect to the diester group is observed, the direction being the same as in the case of the relevant benzoyl compound, N-benzoyl-7-azadibenzobicyclo [2.2.1]heptadiene.[1] The *syn*-tilting of the sulfonamide group of **3** is observed, while the tilt direction of the sulfonyl substituent is changed to *anti* in the case of **4**.

In addition, the sulfonamides (**1**, **2**,**4** and **8**) take the conformation in which the S-C bond is *anti*-periplanar with respect to the N lone pair (**A**). The sulfonamide group of **3** and **7** takes a *syn*-periplanar conformation (**B**). These conformational preferences of *syn*- or *anti*-periplanar structures have been generally observed even in planar sulfonamides,[2,3] and have been rationalized in terms of negative hyperconjugation between the nitrogen lone-pair and the electron-deficient C-S bond ($\sigma^*_{C\text{-}S}$).[10,11,14-16] The relevant negative hyperconjugation is suggested theoretically to be strongly enhanced in α-sulfonyl carboanions,[17] which are

Table 1 Nitrogen Pyramidalization of Sulfonamides [a]

	angles around N θ (deg.)	out-of-plane angle α (deg.)	N-S bond length (Å)
1	341.4 (2)	36.0	1.628 (3)
2	341.3 (2)	35.9	1.633 (3)
3 [b]	336.4 (6)	41.1	1.635 (7)
	336.7 (6)	40.6	1.636 (7)
4	347.8 (2)	29.1	1.627 (3)
5	349.2 (3)	30.4	1.613 (3)
6	353.4 (3)	23.7	1.597 (4)
7 [b]	291.2 (2)	59.5	1.649 (3)
	291.3 (3)	59.1	1.647 (3)
8	338.8 (1)	37.3	1.620 (2)

a) Standard deviations are shown in parentheses. b) Two kinds of molecule are involved in a unit cell.

isoelectronic to pyramidal sulfonamides. Localization of the nitrogen lone pair in the pyramidal sulfonamides, i.e., increase of electron-donating ability of the nitrogen non-bonding orbital, is postulated to counterbalance the attenuation of the negative hyperconjugation due to the elongation of the N-S bond.

In summary, the 7-azabicyclo[2.2.1]heptane motif also favors nitrogen pyramidalization of N-sulfonylamides. In the case of sulfonamides with enhanced pyramidalization, negative hyperconjugation between the nitrogen lone-pair and the electron-deficient C-S bond can participate to fix the preferred *syn*- and *anti*-conformations. Pyramidal nitrogen sulfonamides may provide a new platform to design peptide mimics[18] or a new motif[19,20] bearing an unnatural three-dimensional extension in drug design and molecular assemblies. The findings in this paper provide a fundamental basis for such future applications.

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References and Notes

(1) Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K. *Tetrahedron Lett.* **1998**, *39*, 865.

(2) Selected references on structures of planar sulfonamides in the crystalline state. The sulfonamides cited below take the value of θ >358.0 in the Cambridge Structural Database: Sugio, S.; Kitamura, K.; Mizuno, H.; Wakahara, A.; Ikehara, M.; Tomita, K.-I. *Acta Crystallogr., Sect.C (Cr. Str.Comm.)*, **1984**, *40*, 1608. Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, O. S.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 787 (pyramidal sulfonamides are also reported herein). Derewenda, U.; Stepien, A.; Olszak, T. A.; Kraakowiak, K.; Perrin, M., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1987**, *43*, 2167. Taira, Z.; Uchi, J., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1988**, *44*, 2002. Stepien, A.; Grabowski, M. J.; Glinka, R.;

Sabatino, P.; Sanseverino, L. R. di, *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1989**, *45*, 485. Stepien, A.; Derewenda, U.; Grabowski, M. J.; Glinka, R.; Thozet, A. *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1989**, *45*, 97. Yamaguchi, K.; Hayakawa, H.; Ashizawa, H.; Tanaka, H.; Miyasaka, T., *Acta Crystallogr. Sect. C (Cr. Str. Comm.)*, **1990**, *46*, 1065. Stepien, A.; Grabowski, M. J.; Krakowiak, K.; Bavoux, C., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1991**, *47*, 2735. Stepien, A., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1991**, *47*, 2733. Erickson, M. S.; Fronczek, F. R.; McLaughlin, M. L., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1992**, *48*,202. Clive, D. L. J.; Etkin, N. *J. Org. Chem.*, **1993**, *58*, 2442. Hokelek, T.; Patir, S.; Gulce, A.; Okay, G., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1994**, *50*, 450. Beddoes, R. L.; Kettle, J. G.; Joule, J. A., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1994**, *50*, 1989. Theobald, F.; Rodier, N.; Aubry, C.; Ciamala, K.; Dinh An, N., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1994**, *50*, 791. Love, B. E.; Raje, P. S., *J. Org. Chem.*, **1994**, *59*, 3219. Urtiaga, M. K.; Arriortua, M. I.; Badia, D.; Dominguez, E.; Cameno, A. M. G., Solans, X., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1994**, *50*, 1604. Mohialdin-Khaffaf, S.; Persaud, K. C.; Pritchard, R. G., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1996**, *52*, 2607. Helliwell, M.; Zhao, Y.; Joule, J. A., *Acta Crystallogr., Sect. C (Cr. Str. Comm.)*, **1997**, *53*, 884.

(3) Selected references on structures of pyramidal sulfonamides in the crystalline state: Crich, D.; Bruncko, M.; Natarajan, S.; Teo, B. K.; Tocher, D. A. *Tetrahedron* **1995**, *51*, 2215. Pearson, W. H.; Fang, W.; Kampf, J. W., *J. Org. Chem.*, **1994**, *59*, 2682. Gallagher, T.; Davies, I. W.; Jones, S. W.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Shaw, R. W.; Vernon, P., *J. Chem. Soc., Perkin Trans 1*, **1992**, 433. Andrews, J. F. P.; Regan, A. C.; Wallis, J. D.; Povey, D. C. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1992**, *C48*, 2196. Häkkinen, A.-M.; Ruostesuo, P.; Kivetäs, R. *J. Chem. Soc., Perkin Trans. 2*, **1988**, 815. Sim, G. A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *C43*, 778. Jordan, T.; Smith, H. W.; Lohr, L. L.; Lipscomb, W. N., *J. Am. Chem. Soc.*, **1963**, *85*, 846.

(4) Solution structures of sulfonamides: Moriarty, R. M., *Tetrahedron Lett.*, **1964**, 509. Moriarty, R. M. *J. Org. Chem.*, **1965**, *30*, 600. Speckamp, W. N.; Pandit, U. K.; Korver, P. K.; van der Haak, P. J.; Huisman, H. O. *Tetrahedron*, **1966**, *22*, 2413. Jennings, W. B.; Spratt, R. *J. Chem.Soc., Chem. Commun.* **1970**, 1418.

(5) N-Sulfonylamides of aziridine: a) Cauletti, C.: Vona, M. L. Di; Gargano, P.; Grandinetti, F.; Galli, C.; Lillocci, C., *J. Chem. Soc., Perkin Trans. 2*, **1986**, 667. b) Martino, A. Di; Galli, C.; Gargano, P.; Mandolini, L., *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1345. c) Anet, F. A. L.; Trepka, R. D.; Cram, D. J., *J. Am. Chem. Soc.*, **1967**, *89*, 357. Selected references on crystal structural data of N-sulfonylamides of substituted aziridines: d) Werry, J.; Stamm, H.; Lin, P.-Y.; Falkenstein, R.; Gries, S.; Irngartinger, H., *Tetrahedron*, **1989**, *45*, 5015. e) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y.; Taga, T.; Miwa, Y., *Tetrahedron Letters*, **1990**, *31*, 6663.

(6) Structural determinations of sulfonamides of azetidine derivatives are shown in Marchand, A. P.; Rajagopal, D.; Bott, S. G.; Archibald, T. G. *J. Org. Chem.*, **1994**, *59*, 5499. Becker, D. P.; Flynn, D. L., *Tetrahedron*, **1993**, *49*, 5047. See also references 5 a) and b).

(7) The out-of-plane angle (α) defined here is exactly twice the magnitude of the tilt angle of an amide bond as defined in a)Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.*, **1971**, *59*, 169. b) Dunitz, J. D.; Winkler, F. K., *Acta. Cryst.* **1975**, *B31*, 251.

(8) The mean values of the summation of the three valence angles around the nitrogen (θ), and the S-N bond length of 19 examples of N-tosylpyrrolidine fragments (without pyrroles) in the Cambridge Structural Database are 351.2 ° (standard deviation 0.86°) and 1.620 Å (standard deviation 0.003 Å), respectively.

(9) Crystal data for **1** ($C_{21}H_{17}NO_2S$): a=20.278(3), b=11.181(4), c=8.080(2)Å, β=106.08(2)°, SG=C2/m, R=0.046. Crystal data for **2** ($C_{17}H_{17}NO_6S$): a=10.599(1), b=8.223(1), c=20.386(3)Å. β=101.58(1)°, SG=$P2_1/n$, R=0.055. Crystal data for **3** ($C_{17}H_{21}NO_6S$): a=15.338(3), b=6.933(2), c=33.357(5)Å, β=96.41(1)°, SG=$P2_1/n$, R=0.069. Crystal data for **4** ($C_{15}H_{15}NO_2SF_6$): a=7.345(1), b=20.937(2), c=10.774(1)Å, β=93.13(1)°, SG=$P2_1/n$, R=0.049. Crystal data for **5** ($C_{11}H_{15}NSO_2$): a=8.671(4), b=9.240(6), c=8.241(3)Å, α=116.20(3), β=92.12(4), γ=76.55(4)°, SG=$P\bar{1}$, R=0.052. Crystal data for **6** ($C_{11}H_{13}NSO_2$): a=8.2540(7), b=21.9348(6), c=6.2099(7)Å, SG=$P2_12_12_1$, R=0.060. Crystal data for **7** ($C_9H_{11}O_2NS$): a=7.168(1), b=21.9853(8), c=12.373(1)Å, β=92.55(1), SG=$P2_1/c$ R=0.046. Crystal data for **8** ($C_{10}H_{13}NSO_2$): a=7.514(1), b=9.910(1), c=13.6635(9)Å, SG=Pnma, R=0.034. Crystallographic details will be published in a full paper. See also Yamaguchi, K. *Chem. Pharm. Bull.*, **1993**, *41*, 424-429. teXsan: Crystal Structural Analysis Package, Molecular Structure Corporation, **1985 & 1992**.

(10) Elguero, J.; Goya, P.; Rozas, I.; Cataleán, J.; De Paz, J. L.G. *J. Mol. Struct. (Theochem)*, **1989**, *184*, 115-129.

(11) Lambert, J. B.; Takeuchi, Y. "*Cyclic Organonitrogen Stereodynamics*", VCH, New York, **1992**

(12) Sun, C.-H.; Chow, T. J.; Liu, L.-K. *Organometallics*, **1990**, *9*, 560. Liu, L.-K.; Sun, C.-H.; Yang, C.-Z.; Wen, Y.-S.; Wu, C.-F.; Shih, S.-Y.; Lin, K.-S. *Organometallics*, **1992**, *11*, 972.

(13) The crystallographic data of the simplest sulfonamides of aziridine (**7**) and azetidine (**8**), which can exclude contributions of substituents and an additional ring structure on the pyramidality of these relevant sulfonamides, are not available in the literature.

(14) Laube, T.; Ha, T.-K. *J. Am. Chem. Soc.*, **1988**, *110*, 5511-5517.

(15) Rahman, M. M.; Lemal, D. M. *J. Am. Chem. Soc.*, **1988**, *110*, 1964-1966.

(16) Blanca, M. B. -D.; Maimon, E.; Kost, D., *Angew. Chem. Int., Ed. Engl.*, **1997**, *36*, 2216-2218.

(17) Raabe, G.; Gais, H-J.; Fleischhauser, J. *J. Am. Chem. Soc.*, **1996**, *118*, 4622-4630.

(18) Calcagni, A.; Gavuzzo, E.; Lucente, G.; Mazza, F.; Pinnen, F.; Pochetti, G.; Rossi, D. *Int. J. Pept. Protein Res.* **1991**, *37*, 167-73.

(19) Bindal, R. D.; Golab, J. T.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1990**, 112, 7861-7868.

(20) Horwitz, J. P.; Massova, I.; Wiese, T. E.; Besler, B. H.; Corbett, T. H. *J. Med. Chem.* **1994**, *37*, 781-6.