Absolute Configuration of Sparsomycin. A Chiroptical Study of Sulfoxides[1]

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Abstract: Sparsomycin (**1**) is a naturally occurring compound possessing a wide range of biological activity, including antitumor and antibiotic activity. The R_C enantiomer **1*** and a diastereomer **2** have previously been synthesized. The absolute configuration of **1** was determined by CD spectroscopic studies of precursors of **1***. For several intermediates in the synthesis, the sign of the Cotton effect could be employed in the assignment of the configuration of the sulfoxide sulfur atom by extension of the principles established by Mislow and Snatzke. Sparsomycin was thus assigned the S_C,R_S configuration. The assignment was confirmed by single-crystal X-ray crystallographic studies of a precursor (**5**) of (R_C)-sparsomycin (**1***).

Sparsomycin (**1**), which was originally isolated as a metabolite of *Streptomyces sparsogenes*,[2] has attracted considerable interest because of its biological activity against various tumors,[3,4] bacteria,[4,5] fungi,[6] and viruses[7] and because of its use in studying protein biosynthesis,[8] a process which is inhibited by sparsomycin.[9] The structure (**1**), as first reported in 1970,[10] contains one chiral carbon atom which was shown to possess the *S* configuration and a chiral sulfur atom of the sulfoxide group for which the configuration was not determined. Structure–activity relationship studies have shown[11] that the activity of sparsomycin is dependent upon the configuration of the chiral carbon atom as well as on the presence of the sulfoxide function. However, the influence of the configuration of the sulfoxide sulfur atom has not been determined. Therefore we decided to establish the absolute configuration of sparsomycin's sulfoxide atom so that further work can proceed on studying its structure–activity relationships.

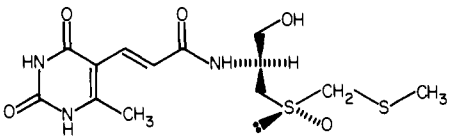
There is a large number of naturally occurring sulfoxides for which the configurations have been determined.[12] Particularly intriguing among these compounds are toxins obtained from poisonous mushrooms of the genus *Amanita*; whereas the compounds of one sulfoxide configuration are very lethal, the compounds of the opposite configuration are inactive up to rather high dose levels.[13]

Recently, we have reported two routes for the total synthesis of the enantiomer (**1***) and diastereomer (**2**) of sparsomycin. One approach is based[14] upon the conversion of the α-chloro sulfoxides **3** and **4** into a diastereomer (**2**) and the enantiomer (**1***), respectively, of sparsomycin. The other route involves[15] sulfenylation of the methyl sulfoxides **6** and **5** to also yield **2** and **1***, respectively. We now wish to report the determination of the absolute configuration of sparsomycin (**1**) by use of *chiroptical studies* and *single-crystal X-ray analysis*. We also wish to report our finding of a possible correlation between the sign of the Cotton effect exhibited by certain chiral sulfoxides involved in this work and the *R,S* designation of their configurations.

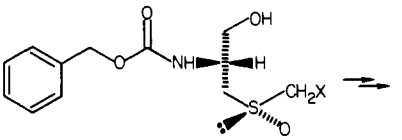
CD Spectra of Sulfoxides. Mislow et al. have shown that a correlation exists between the absolute configuration of methyl alkyl sulfoxides and their optical activity; in the absence of strongly perturbing groups, a negative Cotton effect, centered at the absorption band near 200 mμ in acetonitrile, correlates with the *R* configuration.[16,17] This rule was found to still be applicable when the alkyl group itself is also chiral but not strongly perturbing,[18] as is the case with *S*-methylcysteine *S*-oxide.[19]

We decided to study the Cotton effect of our sulfoxides through the use of CD spectra. In comparison with ORD spectra, CD spectra have the advantage of giving information about individual electronic transitions without background effects.[20] The CD

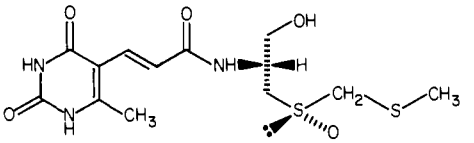
Scheme I



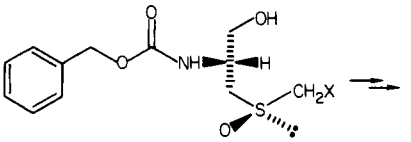
1, sparsomycin (S_C,R_S)



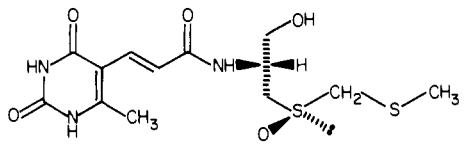
3, X = Cl (R_C,R_S)
6, X = H (R_C,S_S)



2, (R_C,R_S) (diastereomer of sparsomycin)



4, X = Cl (R_C,S_S)
5, X = H (R_C,R_S)



1*, (R_C,S_S) (enantiomer of sparsomycin)

(1) Part of this work was presented at the 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979; American Chemical Society: Washington, D.C., 1979; ORGN 127, and at the meeting of the Netherlands Foundation for Chemical Research (SON), Lunteren, November 5, 1979.

(2) Argoudelis, A. D.; Herr, R. R. *Antimicrob. Agents Chemother.* **1962**, 780–786.

(3) Slechta, L. *Antibiotics (N.Y.)* **1967**, *1*, 410–414.

(4) (a) Brodasky, T. F. *J. Pharm. Sci.* **1963**, *52*, 233–235. (b) Price, K. E.; Buck, R. E.; Lein, J. *Antimicrob. Agents Chemother.* **1964**, 505–517.

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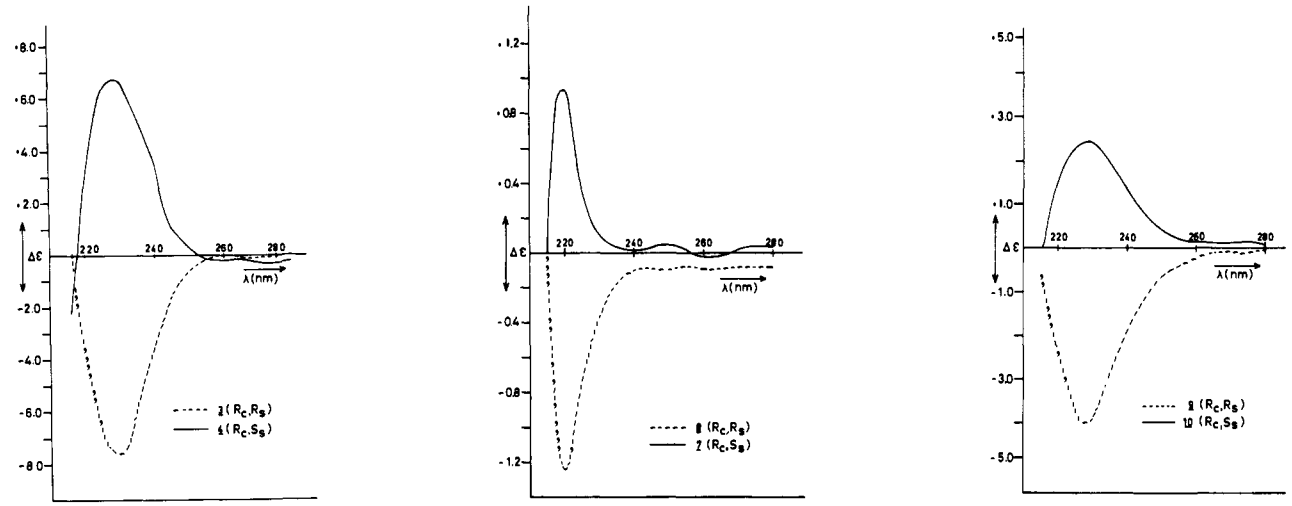
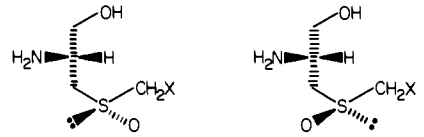


Figure 1. CD spectra of compounds **3**, **4**, and **7–10**.

spectra of the previously mentioned precursors **3** and **4** of the sparsomycin system as well as of the intermediates **7–10** are shown



7, X = H (R_C,S_S) **8**, X = H (R_C,R_S)
9, X = SCH_3 (R_C,R_S) **10**, X = SCH_3 (R_C,S_S)

in Figure 1. The ^1H NMR spectra of the compounds **9** and **10** in the presence of a chiral shift reagent showed that the enantiomeric purity is greater than 95%.

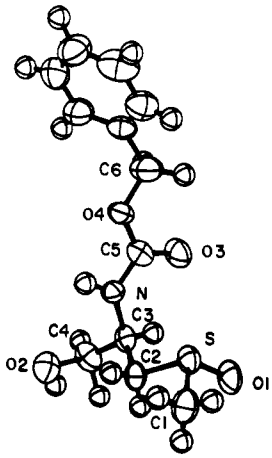


Figure 2. The molecular structure of **5** showing the R_C,R_S configuration.

Of principal importance are the sulfoxides **4** and **5**. First of all, these compounds display ABX patterns for the NC*H*CH_2S(O) segments in their ^1H NMR spectra[21] which are very similar to the corresponding portion of the spectrum of sparsomycin (**1**) but quite different from the corresponding portions of the spectra of compounds **3** and **6**. Furthermore, compounds **4** and **5** can each be converted into the enantiomer (**1***) of sparsomycin[22] by use of our earlier synthetic sequences.[14,15] Therefore, if the absolute configuration of **4** and a derivative of **5**, i.e., **8**, were to be determined, the absolute configuration of **1***, and thus of **1**, would be revealed.

By application of Mislow's rule,[16] the sulfur atom of **8**, a *methyl* alkyl sulfoxide, can be assigned the *R* configuration because of the negative sign of the Cotton effect observed for this compound (see Figure 1). From this measurement, we can conclude that the precursor of **8**, i.e., **5**, also has the *R* configuration, and therefore **1***, derived from **5**, has the *S* configuration at the sulfoxide sulfur atom. This change in nomenclature is due to the reversal in the priority assignments for the sulfur substituents in going from **8** or **5** to **1***. Consequently, the conclusion is reached that **1*** has the R_C,S_S configuration and that *sparsomycin* (***1***) *has the* S_C,R_S *configuration* as depicted in the structural drawing. This assignment was confirmed by a single-crystal X-ray structure

(5) Higashide, E.; Hasegawa, T.; Shibata, M.; Mizuno, K.; Akaike, H. *Takeda Kenkyusho Nempo* **1966**, *25*, 1–14; *Chem. Abstr.* **1967**, *66*, 54238*q*.
(6) Owen, S. P.; Dietz, A.; Caminer, G. W. *Antimicrob. Agents Chemother.* **1962**, 772–779.
(7) Thiry, L. *J. Gen. Virol.* **1968**, *2*, 143–153.
(8) (a) Smith, A. E.; Wigle, D. T. *Eur. J. Biochem.* **1973**, *35*, 566–573. (b) Carrasco, L.; Battaner, E.; Vazquez, D. *Methods Enzymol.* **1974**, *30*, 288–289.
(9) (a) Goldberg, I. H. *Cancer Chemoth. Rep. Part 1* **1974**, *58*, 479–489. (b) Vasquez, D. *FEBS Lett.* **1974**, *40* (supplement), S63–S84.
(10) (a) Wiley, P. F.; MacKellar, F. A. *J. Am. Chem. Soc.* **1970**, *92*, 417–418. (b) Wiley, P. F.; MacKellar, F. A. *J. Org. Chem.* **1976**, *41*, 1858–1862.
(11) Dubois, R. J.; Lin, C.-C. L.; Michel, B. L. *J. Pharm. Sci.* **1975**, *64*, 825–829. (b) Vince, R.; Brownell, J.; Lee, C. K. *Biochem. Biophys. Res. Commun.* **1977**, *75*, 563–567. (c) Lin, C.-C. L.; Dubois, R. J. *J. Med. Chem.* **1977**, *20*, 337–341. (d) Lee, C. K.; Vince, R. *Ibid.* **1978**, *21*, 176–179.
(12) (a) Challenger, F. *Endeavour* **1953**, *12*, 173–181. (b) Klyne, W.; Day, J.; Kjaer, A. *Acta Chem. Scand.* **1960**, *14*, 215–217. (c) Hine, R. *Acta Crystallogr.* **1962**, *15*, 635–641. (d) Christensen, B. W.; Kjaer, A. *Acta Chem. Scand.* **1963**, *17*, 846–847. (e) Cheung, K. K.; Kjaer, A.; Sim, G. A. *J. Chem. Soc., Chem. Commun.* **1965**, 100–102. (f) Chistensen, B. W.; Kjaer, A. *Ibid.* **1965**, 225–226. (g) Palmer, K. J.; Lee, K. S. *Acta Crystallogr.* **1966**, *20*, 790–795. (h) Laur, P. H. In "Sulphur in Organic and Inorganic Chemistry", Senning, A., Ed.; Marcel Dekker: New York 1972; Vol. 3, pp 168–210. (i) Klyne, W. "Atlas of Stereochemistry"; Oxford Press: New York, 1978; Vol. 1, pp 235–236; Vol. 2, pp 123–127.
(13) (a) Faulstich, H.; Wieland, T. "Peptides 1971"; Nesvadba, H., Ed.; North Holland Publishing Co.: Amsterdam, 1973; pp 343–350. (b) Faulstich, H.; Bloching, M.; Zobeley, S.; Wieland, T. *Experientia* **1973**, 343–350. (c) Wieland, T.; de Urries, M. P. J.; Indes, H.; Faulstich, H.; Giren, A.; Sturm, M.; Hoppe, W. *Justus Liebigs Ann. Chem.* **1974**, 1570–1579. (d) Buku, A.; Altmann, R.; Wieland, T. *Ibid.* **1974**, 1580–1586.
(14) (a) Ottenheijm, H. C. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1978**, 2347–2438. (b) Ottenheijm, H. C. J.; Liskamp, R. M. J.; Tijhuis, M. W. *Ibid.* **1979**, 387–390.
(15) Helquist, P.; Shekhani, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 1057–1059.
(16) Mislow, K.; Green, M. M.; Laur, P.; McLillo, J. T.; Simmons, T.; Ternay, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 1958–1976.
(17) Snatzke, G.; Snatzke, F. In "Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism"; Ciardelli, F.; Salvadori, P., Eds.; Heyden and Son Ltd.: London, **1973**; p 186.
(18) Axelrod, R.; Bickart, P.; Goldstein, M. L.; Green, M. M.; Kjaer, A.; Mislow, K. *Tetrahedron Lett.* **1968**, 3249–3252.
(19) Barnsley, E. A. *Tetrahedron* **1968**, *24*, 3747. Hermann, P.; Willhardt, I.; Bläha, K.; Fric, I. *J. Prakt. Chem.* **1971**, *313*, 1092–1100.
(20) Velluz, L.; Legrand, M.; Grosjean, M. "Optical Circular Dichroism"; Verlag Chemie: Weinheim, 1965; pp 17–19.
(21) For a discussion of NMR studies of diasteromeric sulfoxides, see: Oae, S. In "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum Press: New York, 1977; pp 399–400.
(22) For the purpose of developing our initial routes to sparsomycin, we chose to prepare the R_C enantiomer which is derivable from commonly available L-cysteine. Recently completed is the synthesis of **1**, having the natural configuration from D-cysteine and from L-serine.

determination of **5** (vide infra).

Intriguing is that the sign of the Cotton effect of the α-chloro sulfoxide **4** is the opposite of that of **8**. Whereas the sulfur atoms of these two compounds have *geometrically analogous arrangements* of their substituents, they have *opposite R,S designations*, merely because of *reversed priority assignments* of their substituents. So that this point could be pursued further, the CD spectra of compounds **3**, **7**, **9**, and **10** were also examined; note that in the compounds **7–10** the possibly perturbing benzyloxycarbonyl group is absent.[23] From studying all of the spectra shown in Figure 1, the following conclusions may be reached.

(i) For the sulfoxides **3**, **4**, and **7–10** the sign of the Cotton effect centered at the absorption band in the region 220–230 mμ is not influenced by the configuration of the α-carbon atom.[24]

(ii) The sign of the Cotton effect changes by introduction of a chloro or alkylmercapto group on the methyl group which leads to a change in the *R,S* assignment of the sulfoxide.

The phenomenon of the correlation of the sign of the Cotton effect with configuration has been explained by Snatzke, at least for several other chromophores, through use of qualitative MO theory.[25]

Without further examples of the effect of heteroatomic substituents in addition to the two types studied here, we would certainly be premature in stating that the effect that we have observed to date in a few limited cases will ultimately be found to be a general phenomenon for substituted sulfoxides. Clearly, more complete investigations are necessary to determine whether simple correlations exist between configurations and Cotton effect of nonmethyl sulfoxides. Further studies of this nature are continuing in our laboratories.

X-ray Analysis. So that the assignment of configuration based upon CD spectra could be confirmed, a single-crystal X-ray structure determination of **5** was performed.[26] This compound crystallizes from water as long, thin, orthorhombic needles in the form of a monohydrate with 2 molecules/asymmetric unit. A crystal was mounted in a sealed capillary filled with the supernatant liquid from the recrystallization. Mounting by more conventional techniques resulted in the rapid deterioration of the crystal, apparently due to loss of the water of hydration. The structure of one of the two unique molecules is shown in Figure 2. By reference to the chiral carbon atom of the *R* configuration, the chiral sulfur atom can readily be seen to possess the *R* configuration also.[28]

Conclusion

We have determined the absolute configuration of sparsomycin (**1**) by a combination of chiroptical, X-ray crystallographic, and chemical techniques. Further work may now be directed toward determining the relationship between the sulfoxide configuration and the biological activity of sparsomycin. Also, the principles delineated in this paper may be applied to the structural investigation of other compounds such as γ-glutamyl-marasmine[29] that are related to sparsomycin.

Experimental Section

Circular dichroism spectra were measured with a Dichrograph II apparatus (Roussel-Jouan, France). The concentrations varied between 7.0×10^{-4} mol L^{-1} and 5.9×10^{-3} mol L^{-1}; acetonitrile was used as solvent.[30] For the ^1H NMR spectra a Bruker WH-90 was used with Me_4Si as an internal standard. Thin-layer chromatography (TLC) was carried out with the use of Merck plates which were precoated with silica gel F-254 or silica gel 60 F-254 silanised, thickness 0.25 mm. Spots were visualized with a UV hand lamp, iodine vapor, and, in the case of amines and amides, with ninhydrin TDM,[31] respectively.

***N*-((Benzyloxy)carbonyl)-*S*-(chloromethyl)cysteinol *S*-Oxides 3 and 4 and *N*-((Benzyloxy)carbonyl)-*S*-methylcysteinol *S*-Oxides 5 and 6.** The syntheses of compounds **3–6** have been described before;[14a,15] detailed experimental descriptions are presented elsewhere.[32,33]

***S*-Methylcysteinol *S*-Oxides 7 and 8 and *S*-((Methylthio)methyl)-cysteinol *S*-Oxides 9 and 10.** Protection of the alcohol function of **3** or **4** with the THP group and subsequent treatment with sodium methylmercaptide gave the N,O-protected derivatives of **9** and **10**, respectively; these conversions have been described previously.[14a]

Removal of the N-Protecting Group. Ammonia was condensed until complete dissolution of the compound occurred. After removal of the external cooling bath, sodium was added carefully to the refluxing ammonia solution[34] until the blue color persisted for a few minutes. The solvent was evaporated subsequent to the addition of a few crystals of ammonium chloride. The residue thus obtained was extracted twice with chloroform. Evaporation of the solvent gave a yellow oil, which was chromatographed under slightly increased pressure (10 cmHg) on silica gel (Merck 60-H). When CH_2Cl_2/CH_3OH (v/v) was used as eluent in a ratio of 9:1 the O-protected derivatives of **9** or **10** were isolated in 10–38% yield. Subsequent elution with CH_2Cl_2/CH_3OH (85:15, v/v) gave the O-protected derivatives of **7** or **8** in 20–30% yield. The product ratios **7**:**9** and **8**:**10** varied from experiment to experiment. All compounds were homogeneous on TLC (CH_2Cl_2/MeOH, 75:25, v/v. ^1H NMR ($CDCl_3$): **7**-OTHP δ 1.62 (m, 6 H, $OCH_2(CH_2)_3$, 2.66 (s, 3 H, S (O)CH_3), 2.83 (d, 2 H, $CH_2S(O)$), 3.52 (m, 3 H, $CHCH_2O$), 3.78 (m, 2 H, OCH_2CH_2), 4.59 (br s, 1 H, OC(H)O); **8**-OTHP δ 1.62 (m, 6 H, $OCH_2(CH_2)_3$), 2.63 (s, 3 H, S(O)CH_3), 2.80 (m, 2 H, $CH_2S(O)$), 3.53, (m, 3 H, $CHCH_2O$), 3.74 (m, 2 H, OCH_2CH_2), 4.60 (br s, 1 H, OC(*H*)O); **9**-OTHP δ 1.60 (m, 6 H, $OCH_2(CH_2)_3$), 2.33 (s, 3 H, SCH_3), 2.60–3.27 (m, 2 H, $CH_2S(O)$), 3.47 (m, 3 H, $CHCH_2O$), 3.71 (m, 2 H, OCH_2CH_2), 3.67 and 3.89 (AB spectrum, 2 H, J = 13.5 Hz, S(O)-CH_2S), 4.58 (br s, 1 H, OC(*H*)O); **10**-OTHP δ 1.60 (m, 6 H, OCH_2-$(CH_2)_3$), 2.33 (s, 3 H, SCH_3), 2.85–2.89 (AB part of ABX spectrum, 2 H, $CH_2S(O)$), 3.55 (m, 5 H, CCH_2O, H_2NCH, OCH_2CH_2), 3.67 and 3.84 (AB spectrum, 2 H, J = 13.5 Hz, S(O)CH_2S), 4.60 (br s, 1 H, OC(*H*)O).

Removal of the O-Protecting Group. A solution of the O-protected dithioacetal-*S*-oxides **7**, **8**, **9**, or **10** in ethanol, the pH of which was adjusted at 3 with 0.1 N aqueous HCl, was refluxed. The reaction, which took about 1.5 h, was monitored by TLC (silanised silica gel; eluent $CHCl_3$/MeOH saturated with NH_3, 9:1, v/v). When the reaction was complete, solid carbonate was added, and the resulting suspension was stirred overnight at room temperature. Filtration and subsequent concentration to dryness gave a colorless oil which was extracted twice with acetonitrile. Evaporation of the solvent gave the unprotected amino alcohol in quantitative yield. All four compounds thus prepared were homogeneous on TLC (silanised silica gel, eluent as used for monitoring the reaction). The enantiomeric purity of **9** and **10** was determined by ^1H NMR spectroscopy in $CDCl_3$. A racemic mixture[22] of **9** showed in the presence of tris[3-((trifluoromethyl)hydroxymethylene)-D-campho-

(23) Amide and urethane bonds have an n,π* transition at 220–250 m, so that the Cotton effects observed for **3** and **4** must be the result of two chromophores, one inherently chiral, the other inherently symmetric but chiral perturbed.

(24) This conclusion is in accordance with the observations made with *S*-methylcysteine-*S*-oxide; see ref 19.

(25) Snatzke, G. *Angew. Chem.* **1979**, *91*, 380–393.

(26) Crystals of **5** belong to the orthorhombic space group $P2_12_12_1$ with a = 13.4448 (3) Å, b = 41.950 (6) Å, c = 5.102 (2) Å, and Z = 8. There are two $C_{12}H_{17}SNO_4 \cdot H_2O$ formula units per asymmetric unit. Data were collected on an Enraf-Nonius CAD4A diffractometer with use of Cu Kα X-radiation in the range $0 < 2\theta \leq 90°$. The structure was solved by using the MULTAN direct method programs and refined to values of 0.029 and 0.036 for the 343 variables and 1237 observations with $F_o > 3\sigma(F_o)$. The computing was carried out on a PDP 1145 computer with use of the Enraf-Nonius Structure Determination Package developed by Okaya and Frenz.[27]

(27) Okaya, Y. In "Computing in Crystallography"; Schenk, H., Olthof-Hazekamp, R., van Koningsveld, H., Bassi, G. C., Eds.; Delft University Press: The Netherlands, 1978; pp 153–165. Frenz, B. A. *Ibid*, pp 64–71.

(28) Supplementary material.

(29) Gmelin, R.; Luxa, H.-H.; Roth, K.; Höfle, G. *Phytochem.* **1976**, *15*, 1717–1721.

(30) Although CD Spectra of amino-containing compounds are commonly obtained from solutions to which acid has been added, we were precluded from following this procedure because of the acid-sensitivity of our compounds, especially the alkylmercapto sulfoxides which, as a general class, are very well-known to undergo facile acid-catalyzed hydrolysis: (a) Ogura, K.; Tsuchihashi, G.; *Tetrahedron Lett.* **1971**, 3151–3154. (b) Richman, J. E.; Herrmann, J. L.; Schlessinger, R. H. *Ibid.* **1973**, 3267–3270. (c) Schill, G.; Jones, P. R. *Synthesis* **1974**, 117–118. If we had been able to use acidic conditions, a complication may have been the quite different basicities of the amines **7–10** compared to those of the carbamates **3** and **4**. Furthermore, we have already commented on the apparent absence of effects arising from the configuration of the α-carbon atom and, to a limited extent, changes in the nature of substituents about this position.

(31) Arx, E. von; Faupel, M.; Brugger, M. *J. Chromatogr.* **1976**, *120*, 224–228.

(32) Ottenheijm, H. C. J.; van Nispen, S. P. J. M.; Tijhuis, M. W.; Liskamp, R. M. J., submitted for publication.

(33) Helquist, P.; Hwang, D.-R.; Shekhani, M. S., manuscript in preparation.

(34) The procedure of Nesvadba and Roth was applied, using a simplified apparatus: Nesvadba, H.; Roth, H. *Monatsh. Chem.* **1967**, *98*, 1432–1436.

rato]ytterbium(III) two well-separated signals for the SCH_3 group. The more downfield shifted signal could be assigned to the R_C,S_S enantiomer, the other one to the S_C,S_S compound. The same phenomenon was observed with a racemic mixture of **10**. According to this method, compounds **9** and **10** were found to be optically pure. With the methyl sulfoxides **7** and **8**, no chemical shift difference could be observed in the presence of the shift reagent used or with the Pr or Eu analogues. ^{1}H NMR ($CDCl_3/CD_2Cl_2$): **7** δ 2.64 (s, 3 H, S(O)CH_3), 2.84 (d, 2 H, CH_2S(O)), 3.30-3.71 (m, 3 H, $CHCH_2O$); **8** δ 2.63 (s, 3 H, S(O)CH_3) 2.55-3.02 (m, 2 H, CH_2S(O)), 3.30-3.80 (m, 3 H, $CHCH_2O$); **9** δ 2.33 (s, 3 H, SCH_3), 2.87 and 3.05 (8 lines, AB part of ABX spectrum, 2 H, J_{AB} = 13 Hz, J_{AX} = 5 Hz, J_{BX} = 6 Hz, $CHCH_2$S(O)), 3.33-3.71 (m, 3 H, $CHCH_2O$), 3.72 and 3.86 (AB spectrum, 2 H, J = 13.5 Hz, S(O)CH_2S); **10** δ 2.34 (s, 3H, SCH_3), 2.80-3.00 (AB part of ABX spectrum, 2H, $CHCH_2$S(O)), 3.33-3.71 (m, 3H, $CHCH_2O$), 3.73 and 3.81 (AB spectrum, 2H, J = 13.8 Hz, S(O)CH_2S).

Compounds 7 and 8 from 6 and 5, Respectively. The N-protected alcohol **5** or **6**[15,33] were treated with sodium in liquid ammonia as described for the preparation of the O-protected derivatives of **7-10**. When the reaction was complete and no sodium consumed anymore, slightly more than 1 equiv of ammonium chloride was added, after which the solvent was evaporated. The residue was extracted twice with acetonitrile, and subsequently the solvent was evaporated. The amino alcohols **8** and **7**, both obtained in 80% yield, were identical (TLC, ^{1}H NMR) with those obtained above.

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Supplementary Material Available: Tables of crystal data, scattering factors, bond distances and bond angles, positional and thermal parameters, and calculated and observed structure factor amplitudes (17 pages). Ordering information is given on any current masthead page.

Reactivity and Mechanism of Hydrolysis of Phosphonamides

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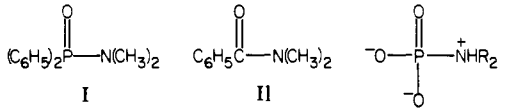
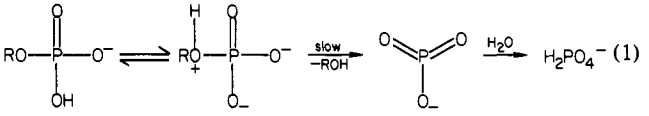
Abstract: The rates of hydrolysis of three phosphonamides, *N,N*-dimethylphenylphosphonamide (XII), *N*-(phenylphosphonyl)pyrrolidine (XIII), and *N*-(phenylphosphonyl)morpholine (XIV), have been investigated. There is first-order dependence on acidity in the pH range 4-7 with a pH independent region at low pHs, consistent with saturation due to complete formation of the neutral amide. The specific rate constant (k_2) and the acidity constant (K_a) were obtained from the dependence of pseudo-first-order rate constants on [H^+]; k_2 is 1.27×10^{-2} s^{-1} and 1.42×10^{-3} s^{-1} and pK_a is 4.8 and 5.3 for XII and XIII, respectively. The small value of the acidity constants is consistent with predominant N-protonation. The activation parameters for XII are $\Delta H^{\ddagger}$ = 11.1 kcal/mol, $\Delta G^{\ddagger}$ = 20.35 kcal/mol, and $\Delta S^{\ddagger}$ = -31 eu. Solvent and salt effects on the rate of hydrolysis of XII are insignificant. The solvent isotope effect, $k_2(H_2O)/k_2(D_2O)$, is 1.2 and $K_a(H_2O)/K_a(D_2O)$ is 3.2. Fluoride ion catalyzed the rate of reaction of XII. The Brönsted β value is about -1, implying rate-determining breakage of the P-N bond. The results appear to be most consistent with an $S_N2(P)$ mechanism. The reactivity of phosphorus amides is discussed in terms of their structure.

Phosphorus amides display interesting reactivity. Diphenylphosphinamide (I) hydrolysis 10^5 times faster than its carbon analogue, benzamide (II), under acidic conditions.[1] Yet their alkaline hydrolysis rates are almost identical, which indicates that they are equally susceptible to nucleophilic reaction. We have suggested[1] that the acid lability of phosphinamides is due to the position of protonation: N-protonation in contrast to O-protonation in carboxylic amides[2] would result in a substantial difference in hydrolytic reactivity.



I II III

The structural similarity between phosphoramidate monoanions (III) and phosphate monoester monoanions ($^-HO_3POR$) (IV) prompted several investigators to look into the amide hydrolytic mechanisms in the hope of clarifying the dynamics of metaphosphate-generating systems.[3-11] A zwitterionic intermediate (V) is throught to be involved in the hydrolysis of monoesters; and there is evidence for a mechanism[12,13] (eq 1) involving the



IV V VI

highly reactive metaphosphate ion (VI) as an intermediate. The

(1) (a) Koizumi, T.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8073. (b) Tyssee, D. A.; Bausher, L. P.; Haake, P. *Ibid.* **1973**, *95*, 8066.
(2) (a) Sundberg, R. J.; Martin, R. B. *Chem. Rev.* **1974**, *74*, 471. (b) Martin, R. B.; Hutton, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 4752. (c) Homer, R. B.; Johnson, C. D. In "The Chemistry of Amides"; Zabicky, J., Ed.; Wiley: New York, 1970; Chapter 3, p 187. (d) Benedetti, E.; DiBlasio, B.; Baine, P. *J. Chem. Soc., Perkin Trans. 2* **1980**, 500.
(3) Chanley, J. D.; Feageson, E. *J. Am. Chem. Soc.* **1963**, *85*, 1181.
(4) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1964**, *86*, 1410.
(5) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1965**, *87*, 3199.
(6) Oney, I.; Caplow, M. *J. Am. Chem. Soc.* **1967**, *89*, 6972.
(7) Benkovic, S. J.; Benkovic, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 4714.
(8) Benkovic, S. J.; Sampson, E. J. *J. Am. Chem. Soc.* **1971**, *93*, 4009.
(9) Jameson, G. W.; Lawlor, J. M. *J. chem. Soc. B* **1970**, 53.
(10) Baker, J. R.; Lawlor, J. M. *Aust. J. Chem.* **1976**, *29*, 949.
(11) (a) Allen, G. W.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8080. (b) Haake, P.; Allen, G. W. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 2691. (c) Haake, P.; Allen, G. W. *Bioorg. Chem.* **1980**, *9*, 325.
(12) (a) Bruice, T. C.; Benkovic, S. J. "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1976; Vol. II. (b) Emsley, J.; Hall, D. "The Chemistry of Phosphorus"; Wiley: New York, 1976. (c) Hudson, R. F. "Structure and Mechanism in Organophosphorus Chemistry"; Academic Press: New York, 1965. (d) Kirby, A. J.; Warren, S. G. "The Organic Chemistry of Phosphorus"; Elsevier: Amsterdam, 1967.
(13) Kirby, A. J.; Varvoglis, A. G. *J. Am. Chem. Soc.* **1967**, *89*, 415.

0002-7863/81/1503-1723$01.25/0