mmol) in a mixture of THF (1.0 mL) and HMPA (0.5 mL) at -75 °C. After 30 min the reaction was warmed to -30 °C and a hydrocarbon (0.5–0.8 mmol) of known pK_a was added in THF (1 mL) to the well-stirred solution. After 15 min the reaction mixture was cooled to -75 °C and quenched by slow addition to a rapidly stirred mixture of D_2O, dioxane, and AcOD. Deuterium distribution was measured by mass and ^1H NMR spectra.

In the case of all three dianions virtually no deuterium ($\sim 0.05D$) was incorporated into the triphenylmethane ($pK_a = 31.5$[21]) and the solutions showed little color change. With phenylxanthene (28.5[21]) and fluorene (22.8[21]) distinct color changes were observed with all three diester dianions. The fluorene was found to have incorporated 0.5D after equilibration with any of the three dianions, whereas phenylxanthene had incorporated 0.5, 0.37, and 0.15D when equilibrated with 3, 8, and 11, respectively.[22] When 0.5 equiv of triphenylmethane or phenylxanthene were used, the recovered diesters contained 1.4–1.6D,[10] whereas upon treatment with 0.8 equiv of fluorene the diesters contained $\sim 0.95D$. Although only an estimate of the pK_a values of the three diester dianions can be made, since 10 is unstable under the equilibrium conditions and 8 is only partially soluble at -30 °C, these data do suggest that all three dianions have a pK_a close to that of phenylxanthene (~ 28.5).[23,24]

An increase in stability of the cyclic conjugated system over its acyclic analogue has been proposed as a criterion for determining the aromaticity of a molecule.[27,28] Under such a criterion the dianion 3 is clearly *nonaromatic* since it is formed no more easily than its linear analogue 8. One could consider, however, that 3 should be destabilized compared with 8 because of the greater enforced proximity of the two negative charges. That this does not follow is shown by the similar ease of formation of the dianion 11, in which a similar charge proximity is required.

Does the nonaromaticity of 3 allow any comment to be made about the aromaticity of the parent dianion 1? Cyanocyclopentadiene has a pK_a of 10, whereas cyclopentadiene has a pK_a of 16 and acetonitrile a pK_a of 25.[25,29] Clearly in this case the conjugative and cyclic delocalization effects are supportive. Similarly, the kinetic acidity of 3-cyano-1,2-diphenylcyclopropene is 10^4 less than that of 3-cyano-1,2-diphenylcyclopropane,[28] in this case the effects being opposed because of the antiaromaticity of the cyclopropenyl anion. Since the pK_a for formation of dianion 8 is known, any supportive cyclic delocalization effect in dianion 3 should be reflected in a significant decrease in its pK_a value. The lack of such an effect strongly supports the inference that 1 is nonaromatic.

References and Notes

(1) See P. J. Garratt, "Aromaticity", McGraw-Hill, London, 1971, Chapter 4; P. J. Garratt and M. V. Sargent in "Nonbenzenoid Aromatics", Vol. 2, J. P. Snyder, Ed., Academic Press, New York, 1971, p 208.
(2) W. Adam, *Tetrahedron Lett.*, 1387 (1963).
(3) H. H. Freedman, G. A. Doorakian, and V. R. Sandel, *J. Am. Chem. Soc.*, 87, 3019 (1965).
(4) J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *J. Chem. Soc., Chem. Commun.*, 365 (1972).
(5) E. Vogel, *Justus Liebigs Ann. Chem.*, 615, 14 (1958).
(6) Chemical shifts were measured from benzene as internal standard (C_6H_6, δ 7.33, THF-d_8, Me₄Si). The yield of dianion was quantitative based on comparative integration with the benzene ^1H NMR signal.
(7) ^{13}C NMR, THF-d_8, C_6H_6 internal standard, offset decoupled: 150.4 (singlet), 121.1 (doublet), 93.2 (singlet), 53.6–50.9 (broad multiplet).
(8) For ^{13}C NMR spectra of other dianions of organic systems see J. B. Lambert and S. M. Wharry, *J. Chem. Soc., Chem. Commun.*, 172 (1978).
(9) ^{13}C NMR (CDCl₃, C_6H_6 internal standard): *cis*-2, 170.7 (C═O), 136.3 (C-3,4), 51.5 (OMe), 48.5 (C-1,2); *trans*-2, 171.1 (C═O), 136.9 (C-3,4), 51.6 (OMe), 48.5 (C-1,2); 5, 160.4 (C═O), 141.5 (C-1,2), 50.7 (OMe), 26.2 (C-3,4).

(10) Quenching 3, prepared in either THF or THF–HMPA, gave 4 containing $\sim 1.5D$ (10% D_0, 30% D_1, 60% D_2) by mass spectrum. The presence of mono- and nondeuterated ester is due to competitive diffusion controlled incorporation of acidic protons already present in the reaction medium. This problem has been previously encountered.[11] No trideuterated ester was obtained when the dianion 8 was quenched in an identical fashion, demonstrating that exchange does not occur under these conditions.
(11) P. L. Creger, *J. Am. Chem. Soc.*, 92, 1396 (1970); M. W. Rathke and A. Lindert, *ibid.*, 93, 2318 (1971).
(12) In HMPA–THF both the ^1H and ^{13}C NMR chemical shifts of the "olefinic" atoms are moved slightly to higher field, presumably owing to coordination of the counterion. Clearly there is no dramatic change in the structure of the dianion as there is for the acetylcyclononatetraenyl anion.[13]
(13) G. Boche and F. Heidenhain, *Angew. Chem., Int. Ed. Engl.*, 17, 283 (1978).
(14) R. N. McDonald and R. R. Reitz, *J. Org. Chem.*, 37, 2418 (1972).
(15) See D. H. O'Brien, A. J. Hart, and C. R. Russell, *J. Am. Chem. Soc.*, 97, 4410 (1975), and reference therein.
(16) H. O. House and B. M. Trost, *J. Org. Chem.*, 30, 2502 (1965).
(17) ^1H NMR (THF-d_8, Me₄Si): *cis*-2, δ 6.21 (s, 2 H), 3.92 (s, 2 H), 3.63 (s, 6 H).
(18) G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Am. Chem. Soc.*, 82, 5846 (1960); C. MacLean and E. L. Mackor, *Mol. Phys.*, 4, 241 (1961); T. Schaefer and W. G. Schneider, *Can. J. Chem.*, 41, 966 (1963).
(19) See A. J. Jones, P. J. Garratt, and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 12, 241 (1973); H. Günther, H. Schmickler, H. Königshofen, K. Recker, and E. Vogel, *ibid.*, 12, 243 (1973).
(20) At high electron density the diatropicity will only cause a relatively small decrease in the chemical shift of the ring protons,[1] and distinguishing between 3a and 3b on this basis would be difficult.
(21) A. Streitwieser, E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, 89, 63 (1967).
(22) Deuteration of fluorene is probably incomplete because of competative protonation from the reaction medium.[10] The deuterated fluorene contained $\leqslant 3\% D_2$; so subsequent exchange has not occurred on quenching.
(23) Reaction of 8 with phenylxanthene at -30 °C, followed by warming to 0 °C and then quenching, gave the same deuterium distribution, indicating that equilibrium had been achieved.
(24) The pK_a of ethyl acetate in water is reported as 24.5,[25] which can be converted to a value of ~ 29.5 in Me₂SO.[26] This suggests that 1,2-diester dianions may be much more readily prepared than is generally assumed.
(25) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 75, 2439 (1953).
(26) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, 97, 7006 (1975).
(27) See R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.*, 85, 431 (1963); M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, 1969; N. C. Baird, *J. Chem. Educ.*, 48, 509 (1971); L. J. Schaad and B. A. Hess, *ibid.*, 51, 640 (1974); W. C. Herndon, *ibid.*, 51, 10 (1974); J.-I. Aihara, *J. Am. Chem. Soc.*, 98, 2750 (1976).
(28) R. Breslow, *Acc. Chem. Res.*, 6, 393 (1973).
(29) O. W. Webster, *J. Am. Chem. Soc.*, 88, 3046 (1966); A. Streitwieser and L. Nebenzahl, *ibid.*, 98, 2188 (1976).

Peter J. Garratt,* Robert Zahler

Department of Chemistry, University College London
*London WC1H 0AJ, England*

Received June 12, 1978

An N–S Bonded Cation Radical [R₃N–SR₂]⁺· and a Dication [R₃N–SR₂]²⁺ from 5-Methyl-1-thia-5-azacyclooctane

Sir:

We previously reported the formation of a long-lived thioether cation radical which was stabilized by a transannular thioether group.[1] At that time we suggested that other lone-pair donors might be capable of stabilizing a thioether cation radical if no steric or electronic effects prevented a transannular interaction. We now have formed both a long-lived N–S bonded cation radical and a dication of the mesocyclic amino thioether, 5-methyl-1-thia-5-azacyclooctane (I).

Although aliphatic cation radicals and dications having the *same* heteroatoms bonded together are known, i.e., hydrazines,[2] ditertiary amines,[3] dithioethers,[4] diphosphites,[5] and diselenoethers,[6] this is the first example of an aliphatic cation radical and dication in which two *different* heteroatoms are bonded together.

The mesocyclic amino thioether I was prepared by the method of Yethon.[7] When I was oxidized with 2 equiv of NOBF₄ in propionitrile, 2 equiv of NO was evolved. The
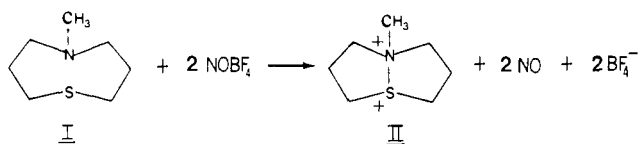
mixture was filtered to give a colorless solid having an elemental analysis and ^{13}C NMR[8] consistent with the tetrafluoroborate salt of the dication II. The structure of the solid dication was substantiated by hydrolysis to the known sulfoxide, 5-methyl-1-thia-5-azacyclooctane 1-oxide[7] (III). A hydrolysis reaction was previously used to confirm the formation of the 1,5-DTCO^{2+} dication.[4]

Treatment of the dication II with I in acetonitrile gives a yellow solution. The solution exhibits a broad ESR signal (g = 2.02) which persists for a few days even at room temperature. This result can be explained by an equilibrium involving the formation of a cation radical, IV. A similar equilibrium exists between the mesocyclic dithioether 1,5-DTCO, its dication, and its cation radical.[4] The ESR signal exhibits some
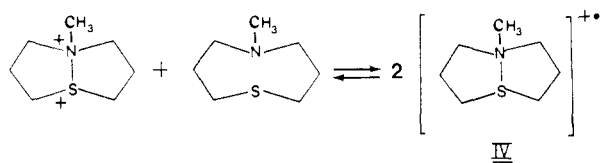
fine structure, but an assignment is difficult because of the nitrogen atom and the large number of nonequivalent protons which may couple with the electron. By comparison with related cation radicals, the unpaired electron is most likely in an N-S σ^* orbital localized primarily on sulfur.

Since we had proposed 1,5-DTCO^{2+} as an intermediate in the rapid reduction of 1,5-dithiacyclooctane 1-oxide with HI,[11] we examined the kinetics of the reduction of III with HI to determine if II forms in this reduction.

The reduction if III with HI to give I proceeds extremely rapidly. In fact, in 5×10^{-3} M HClO$_4$ and 0.3 M NaI, III is reduced as rapidly as 1,5-dithiacyclooctane 1-oxide.[11] III is considerably more reactive than N-(3-methylsulfinylpropyl)-piperidine, a compound in which the amine and sulfoxide are also separated by a chain of three methylene groups, but are not part of a medium ring. The latter compound is reduced at a comparable rate only when the acid concentration is increased a thousandfold to 5.8 M.

The rate of reduction of III is first order in III, first order in acid (Table I, runs a–d), and second order in iodide (Table I, runs e–h). A proposed reaction mechanism for the reduction of III (Scheme I) is similar to that for simple sulfoxides[12] and for 1,5-dithiacyclooctane 1-oxide.[11]

The first-order acid dependence is explainable in terms of the quantitative initial conversion of III to V, a compound known to have a stable hydrogen bond between the nitrogen and oxygen atoms as determined by an X-ray analysis of its perchlorate salt.[7]

In step 1, the sulfoxide oxygen is protonated to give a dicationic intermediate, IV. In step 2 the iodosulfonium salt VII is formed.[13] Step 3 is the rate-determining step and leads to the sulfide and iodine. That step 3 is rate determining is in contrast to simple sulfoxides where the rate-determining step is the formation of an iodosulfonium salt[12] and to 1,5-dithiacyclooctane 1-oxide where the rate-determining step is the formation of the dication.[11] Thus, in this reduction, steps leading to the formation of VII have been accelerated.

The question of whether dication II is involved in the reduction cannot be answered from the form of the rate law but can be inferred by analyzing the possible alternatives which lead to an accelerated formation of VII. Step 2, the usual rate-determining step in sulfoxide reductions, proceeds by a

Table I. The Pseudo-First-order Rate Constant k_1 for the Reaction between $\sim 10^{-4}$ M III and I$^-$ in HClO$_4$ at 25.6 °C[a]

run	HClO$_4$, M	NaI, M	NaClO$_4$, M	$10^3 k_1$, s^{-1}
a	0.0049	0.30		1.97 ± 0.02[b]
b	0.0097	0.30		3.81 ± 0.04[b]
c	0.0193	0.30		9.76 ± 0.16[b]
d	0.049	0.30		43 ± 1[c]
e	0.0193	0.25		9.1 ± 0.1[c]
f	0.0193	0.20	0.05	6.0 ± 0.5[c]
g	0.0193	0.15	0.10	3.2 ± 0.1[c]
h	0.0193	0.10	0.15	1.46 ± 0.01[c]

[a] Spectrophotometric rates at 353 nm on a Cary 17 spectrophotometer in a thermostated cell. [b] Error indicates scatter in least-square plots of ln $(A - A_t)$ vs. t. [c] Error indicates an average of values of separate runs.

Scheme I
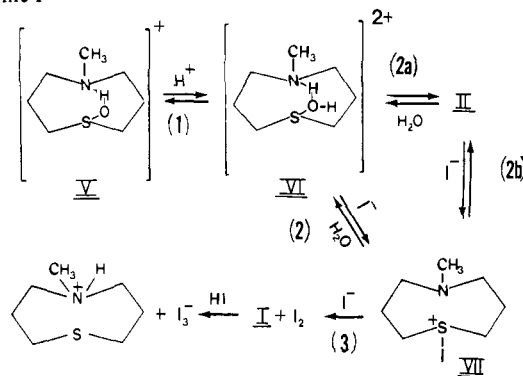
concerted iodide attack and loss of water. However, there is no strong argument for proposing that VI would undergo a more rapid reaction with iodide than any other sulfoxide. Although the S–O bond is quasi-axial and could contribute to some acceleration,[14] hydrogen bonding would decrease the vulnerability of sulfur to attack by iodide and lead to a decreased rate.

Alternatively, if II forms by loss of water from VI (step 2a), a rapid reaction with iodide would be expected since there are fewer steric or electronic constraints. It may be recalled that the reverse reaction of II with water is known to give V. Thus, the simplest mechanism which is consistent with both the rate law and the accelerated reduction of III proceeds via the dication II.

The observation that a tertiary amine accelerates the reduction of sulfoxides in acid aqueous solution and stabilizes a thioether cation radical and dication in nonaqueous media indicates the diversity of intramolecular effects on the reactivity of thioethers and sulfoxides. Similar intramolecular interactions involving the thioether sulfur may be extremely important pathways for electron transfer reactions in proteins.

References and Notes

(1) W. K. Musker and T. L. Wolford, *J. Am. Chem. Soc.*, **98**, 3055 (1976).
(2) S. F. Nelson and C. R. Kessel, *J. Am. Chem. Soc.*, **99**, 2392 (1977).
(3) R. W. Alder, R. Gill, and N. C. Goode, *J. Chem. Soc. D*, 973 (1976).
(4) W. K. Musker and P. B. Roush, *J. Am. Chem. Soc.*, **98**, 6745 (1976).
(5) T. Gillbro, C. M. L. Kerr, and F. Williams, *Mol. Phys.*, **28**, 1325 (1974).
(6) K. Nishikida and F. Williams, *Chem. Phys. Lett.*, **34**, 302 (1975).
(7) I. C. Paul and K. T. Go, *J. Chem. Soc. B*, 33 (1969); A. Yethon, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1968.
(8) Data for II: ^{13}C NMR (CD$_3$CN) C$_4$, C$_6$ at 71.5 (double intensity), C$_3$, C$_7$ at 29.2 (double intensity), C$_2$, C$_8$ at 53.5 (double intensity), CH$_3$ at 54.2. The position of the ^{13}C NMR peaks in II is consistent with the ^{13}C NMR of both quaternary ammonium salts[9] and dithioether dications.[10] Anal. Calcd for C$_7$H$_{15}$NSB$_2$F$_8$ (II): C, 26.37; H, 4.74; Found: C, 25.90; H, 4.90.
(9) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.
(10) W. K. Musker, T. L. Wolford, and P. B. Roush, *J. Am. Chem. Soc.*, **100**, 6416 (1978).
(11) J. T. Doi and W. K. Musker, *J. Am. Chem. Soc.*, **100**, 3533 (1978).
(12) J. G. Tillett, *Chem. Rev.*, **76**, 747 (1976).

(13) VII may also exhibit a transannular interaction between the nitrogen and sulfur atoms.
(14) R. Curci, F. DiFuria, A. Levi, and G. Scorrano, *J. Chem. Soc., Perkin Trans.* 2, 408 (1975).

W. Kenneth Musker,* Albert S. Hirschon, Joyce Takahashi Doi

Department of Chemistry, University of California
*Davis, California 95616*
Received June 5, 1978

Synthesis of Nucleoside [18O]Pyrophosphorothioates with Chiral [18O]Phosphorothioate Groups of Known Configuration. Stereochemical Orientations of Enzymatic Phosphorylations of Chiral [18O]Phosphorothioates

Sir:

The study of enzymatic transformations of chiral phosphorothioates is recognized as a means for delineating the stereochemical courses of reactions catalyzed by phosphotransferases and nucleotidyltransferases.[2] The capability to synthesize chiral [18O]phosphorothioates of known configuration will facilitate these investigations. We report here syntheses of **4** and **5**, the diastereomers of ADPβS,β18O[3] which are epimeric at P$_\beta$.

The synthesis is outlined in Scheme I. $H_2$18O (0.5 g, 99% enriched) is introduced in aqueous workup after reacting adenosine with thiophosphoryl chloride.[4] The yield is 50% relative to adenosine, and the enrichment of 18O at each thiophosphoryl oxygen is 80–90%. Activation with diphenyl phosphorochloridate[5] followed by coupling to methoxymethylidene-AMP[6] yields **2** and **3** in 50–60% total yields. These are separated in 80–90% isomeric purity[7] by column chromatography on DEAE-Sephadex A-25. Cleavage of unblocked ribosyl rings in **2** and **3** with $NaIO_4$, deblocking in acid, and alkaline elimination of the cleaved nucleoside fragments yield **4** and **5** in ~75% yield.[8]
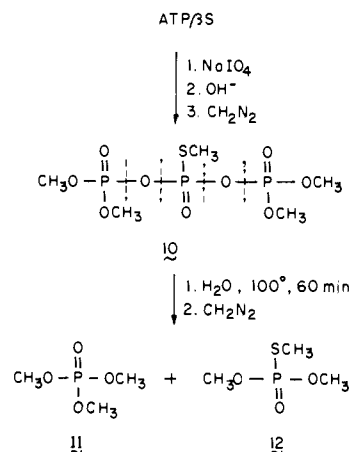
Scheme I
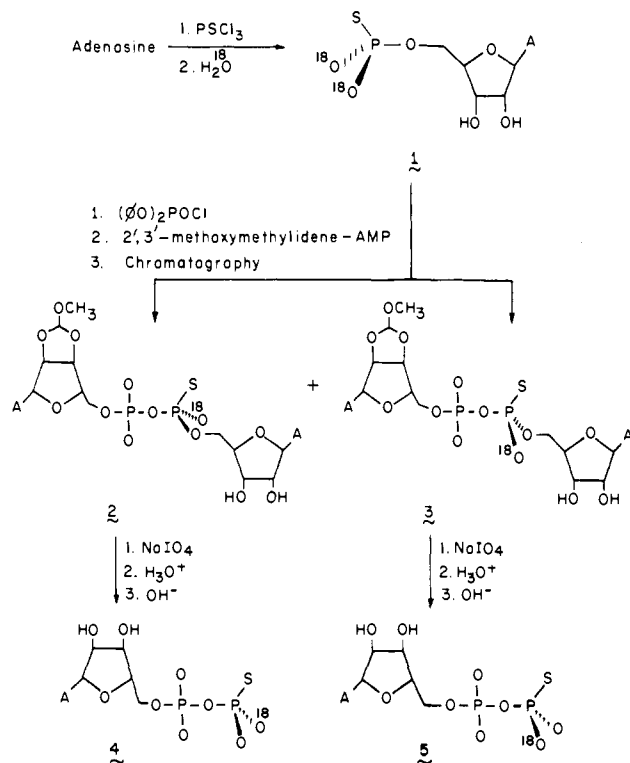
Scheme II
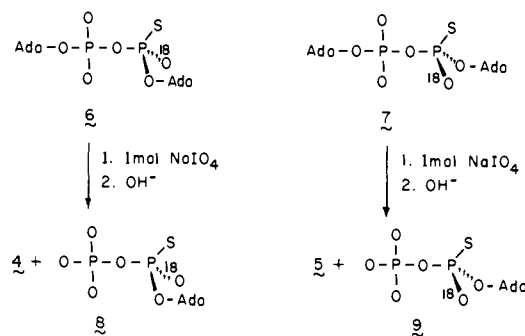
Scheme III

Table I. Enzymatic and Mass Spectral Analyses of [18O]-Thiophosphoryl Groups in **4** and **5**

compd phosphorylated	phosphorylating[a] system	mass % 18O[b]	
		trimethyl phosphate	trimethyl phosphorothioate
4	acetate kinase	20.7 ± 1.1	40.5 ± 1.8
	pyruvate kinase	7.4 ± 2.0	71.6 ± 0.1
5	acetate kinase	1.4 ± 0.5	78.6 ± 4.2
	pyruvate kinase	17.4 ± 1.0	46.6 ± 1.8

[a] The phosphorylating systems acting on **4** or **5** were either acetyl phosphate and *E. coli* acetate kinase (Sigma Chemical Co.) or phosphoenol pyruvate and rabbit muscle pyruvate kinase (Sigma Chemical Co.). [b] Trimethyl phosphate and trimethyl phosphorothioate obtained in the degradation outlined in Scheme III were subjected to gas chromatographic–mass spectral analysis using a Du Pont 21-490 spectrometer coupled to a Perkin-Elmer 990 gas chromatograph. Oxygen-18 enrichments were calculated from the relative parent ion and m + 2 intensities after correcting for the natural abundances of 18O and 34S.

Since compounds **3, 5,** and **7** (or **2, 4,** and **6**)[9] are identical in configuration at the chiral phosphorus, determination of this configuration in one defines it in the other two. Scheme II shows how **6** or **7**[9] derived from **2** or **3** may be converted to mixtures of ADPαS,α18O and ADPβS,β18O. Treatment of **6** (containing no 18O) led to **8** which, by 31P NMR,[10] was shown to have the *S* configuration at P$_\alpha$.[11] Similar treatment of **7** led to **9** with the *R* configuration. Inasmuch as maximum yields of ADPβS from **6** or **7** are low, **2** and **3** were the compounds actually used as precursors for chiral ADPβS,β18O. Therefore, the configurations at P$_\alpha$ of **2** and **3** had to be correlated with those of **6** and **7**. This was done by deblocking **2** and **3** in dilute acid[8] and comparing 31P NMR spectra of the products with those of **6** and **7**, whose configurations had been determined. The spectrum of the compound obtained from **2** was super-