Structure and Conformational Properties of Some Radicals from Thiazolyl Derivatives

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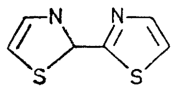
The radical anions of 2,2'-bithiazolyl (I), 2-phenylthiazole (II), 2-(2-thienyl)thiazole (III), dithiazol-2-yl ketone (IV), and 2-nitrothiazole (V) exist as contact ion pairs in ethereal solvents. Whenever the organic anion contains two adjacent binding sites formation of chelate rings occurs, as revealed by examining the temperature and solvent dependence of the alkali hyperfine splitting. As a consequence the conformational stability of these radicals is markedly different from that of the analogous thiophen derivatives.

We have recently been concerned with the e.s.r. study of radicals from substituted thiophens with regard to their stability, electronic distribution, and conformational properties.[1] In a number of cases rotational isomers could be detected and their stereochemistry assigned. For several derivatives the barriers to internal rotation of the thiophen ring were determined by analysing e.s.r. lineshape variations with temperature.[2,3] Also, conformational implications of the formation of alkali metal complexes have been discussed.[4]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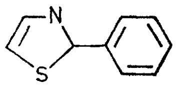
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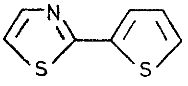
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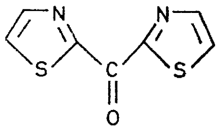
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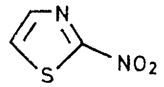
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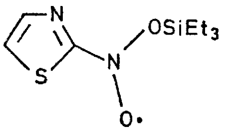
(VI)

In order to compare the properties of the thiophen system with those of similar aromatic rings, we have undertaken an e.s.r. investigation of a series of derivatives (I)—(V) containing the thiazol-2-yl group.

In spite of the close similarity of the thiophen and thiazole nuclei the behaviour of the related radical anions is markedly different, mainly with respect to their conformational stability. Only in the cases of the nitroxide (VI) and the corresponding 2-thienyl derivative was no notable difference observed.

EXPERIMENTAL

2-Phenylthiazole,[5] 2,2'-bithiazolyl,[6] and 2-nitrothiazole,[7] were prepared as described in the literature.

2-(2-*Thienyl*)*thiazole* (III).—A mixture of thiophen-2-thiocarboxamide (3 g), prepared as described [8] for thiobenzamide and used without further purification, and bromoacetaldehyde dimethyl acetal (11 g) was refluxed for 10 h in the presence of a trace of piperidine. The excess of acetal was distilled off and the residue was dissolved in

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[1] L. Lunazzi, A. Mangini, G. F. Pedulli, and M. Tiecco, *Gazzetta*, 1971, **101**, 10.

[2] M. Guerra, G. F. Pedulli, M. Tiecco, and G. Martelli, *J.C.S. Perkin II*, 1974, 562.

[3] C. M. Camaggi, L. Lunazzi, G. F. Pedulli, G. Placucci, and M. Tiecco, *J.C.S. Perkin II*, 1974, 1226.

[4] G. F. Pedulli and A. Alberti, *Chem. Phys. Letters*, 1974, **26**, 392.

[5] G. Vernin, R. Jauffred, J. H. M. Dou, and J. Metzger, *J.C.S. Perkin II*, 1972, 1145.

[6] G. Vernin and J. Metzger, *Bull. Soc. chim. France*, 1963, 2504.

[7] B. Prijs, J. Ostertag, and H. Erlenmeyer, *Helv. Chim. Acta*, 1947, **30**, 1947.

[8] G. Vernin, J. P. Aune, H. J. M. Dou, and J. Metzger, *Bull. Soc. chim. France*, 1967, 4523.

ether. The solution was then washed with sodium carbonate solution and water, dried, and evaporated, and the residue was chromatographed on a silica gel column with light petroleum (b.p. 40—60°)–ether (95 : 5) as eluant. The acetal was eluted first, followed by an oil which was subjected to vacuum distillation. 2-(2-*Thienyl*)*thiazole* (3 g), b.p. 102—103° at 12 mmHg, was obtained as an oil which slowly solidified; m.p. 30—31° (Found: C, 50·1; H, 2·95; N, 8·3. $C_7H_5NS_2$ requires C, 49·95; H, 2·8; N, 8·2%).

Dithiazol-2-yl Ketone (IV).—To an ethereal solution of diethylamine (15 g), cooled at −30 °C, a solution of thiazol-2-yl chloride[9] (33 g) in ether was added dropwise. The mixture was stirred overnight at room temperature. Dilute hydrochloric acid was added and the two layers were separated; the ethereal solution was washed, dried, and evaporated. The residue was distilled and afforded NN-*diethylthiazole-2-carboxamide* (20 g), b.p. 160° at 12 mmHg (Found: C, 58·9; H, 7·3; N, 7·65. $C_7H_{12}N_2OS$ requires C, 59·0; H, 7·1; N, 7·65%). This compound (2·4 g) was added dropwise, at −70 °C, to a solution of 2-lithiothiazole, prepared from 2-bromothiazole (1·6 g) as described in the literature. The mixture was stirred overnight at room temperature and then hydrolysed with dilute hydrochloric acid. Chloroform was added and the organic layer was separated and dried. The solvent was distilled off and the residue was chromatographed on a silica gel column with light petroleum–ether as eluant. The proportion of the ether was gradually increased to 50%. The first fractions contained the unchanged amide; then the *ketone* (IV) (1·2 g), m.p. 141—142°, was obtained (Found: C, 42·65; H, 2·1; N, 14·2. $C_7H_4N_2OS$ requires C, 42·8; H, 2·05; N, 14·3%).

Hyperfine splitting constants (G) for the radical anions from (I)—(VI)

		Aromatic nucleus									
		Thiazol-2-yl			Phenyl			2-Thienyl			
Compound	Solvent/ counterion	a_{N}	a_4	a_5	a_o	a_m	a_p	a_3	a_4	a_5	$a_{\mathrm{N(NO_2)}}$
(I)	THF/K+	2·91	0·66	4·04							
(II)	THF/Li+	2·26	0·45	3·76	3·10	0·77	5·21				
					3·32	0·81					
(III)	THF/Li+	2·12	0·45	3·42				5·35	1·20	5·35	
(IV)	THF/K+	2·31	0·49	2·75							
		2·41	0·61	2·93							
(IV)	MeOH/MeONa	2·44	0·48	2·89							
		2·60	0·60	3·14							
(V)	DMSO/Bu^{t}OK	3·05	0·70	3·74							8·05
(V)	MeOH/MeONa	2·88	0·58	3·59							9·85
(V)	DME/Na+	3·02	0·70	3·70							7·87
(VI)	Et_3SiH	2·53	0·51	3·41							12·53

Compounds (I)—(V) were reduced to the corresponding radical anions with alkali metals in dimethoxyethane (DME) or tetrahydrofuran (THF). The ketyl from (IV) and the nitro-anion from (V) were also produced by photolysis of deoxygenated solutions containing sodium methoxide, methanol, and DME in the ratio 1 : 3 : 4. The latter radical was also generated by treating (V) with potassium t-butoxide in dimethyl sulphoxide (DMSO). The thiazol-2-yl triethylsilyloxy nitroxide (VI) was produced by photolysing the nitro-derivative (V) in triethylsilane. The reaction sequence leading to this kind of radical and the operating conditions have been already described.[3]

McLachlan[10] spin density calculations were calculated for the radical anion from (I) by using the following parameters: $h_{\mathrm{N}} = 0{\cdot}7$, $k_{\mathrm{CN}} = 1{\cdot}0$, $h_{\mathrm{S}} = 1{\cdot}0$, and $k_{\mathrm{CS}} = 0{\cdot}86$.[1]

RESULTS AND DISCUSSION

The e.s.r. spectrum of the radical anion from 2,2′-bithiazolyl (I) produced in DME with potassium is shown in Figure 1. The radical is very stable, lasting for several days at room temperature, in contrast to the radical anion from 2,2′-bithienyl, which decays rapidly when the temperature is raised above −60 °C. The spectrum of the species from (I) can be straightforwardly interpreted in terms of the coupling of the unpaired electron with two equivalent nitrogen nuclei and two pairs of equivalent protons. The hyperfine splitting constants can be easily assigned by analogy with the corresponding thiophen derivative, as reported in the Table. The assignment has been verified by spin-density MO calculations. When compound (I) is reduced with alkali metals other than potassium, each line is split into four by coupling with the alkali counterion. This indicates that the radical is present in solution as a contact ion pair. The temperature dependence of the Li and Na splittings in DME and THF is shown in Figure 2.

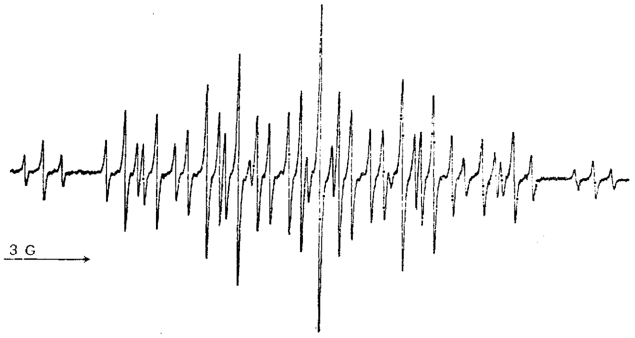

FIGURE 1 Room temperature e.s.r. spectrum of the radical anion from (I) in DME (counterion K+)

Since 2,2′-bithiazolyl can exist in two different conformations, we expected to be able, as in the case of the radical anion from 2,2′-bithienyl, to detect the *cis*- and *trans*-rotamers. However at room temperature no trace of a second species was revealed even at high

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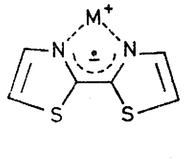
[9] A. L. Lec, D. Mackay, E. L. Manerey, *Canad. J. Chem.*, 1970, **48**, 3554.

[10] A. D. McLachlan, *Mol. Phys.*, 1960, **3**, 233.

amplification. This might be because we are observing the averaged spectrum; however this explanation seems most unlikely in view of the large energy barriers to rotation expected for this kind of radical. When the temperature was lowered the only effect observed was an increase in the asymmetric broadening of the high-field lines due to incomplete averaging of the nitrogen hyperfine and g tensors. No lines from a second species were detected even in the low-field part of the spectrum, which was still well resolved. It therefore seems safe to conclude that the radical anion from (I) exists entirely in one of the two possible conformations. Knowledge of the preferred conformation in the neutral molecule could be of some help in deciding which is the more stable in the radical anion. Unfortunately no X-ray studies of the structure of this compound have yet been reported. However similar derivatives such as 3,3′-bisisoxazole [11] and 2,2′-bithienyl [12] are known to crystallize in the *trans*-conformation. This form remains the more stable in solution, although it is not always the only one present.[13] By analogy we may postulate the *trans*-structure for the only observed isomer of the radical anion from (I).

We should not forget, however, that the radical is present in solution not as a free ion but as an ion pair. Usually when alkali metal complexes of bidentate molecules are formed, chelation of the counterion by the two binding sites of the anion occurs. This effect has been observed both in aliphatic and in aromatic semidiones [14] and in the radical anion of 2,2′-bipyridyl.[15] In these cases the ion pair may exist entirely in the *cis*-conformation even though the *trans*-form is favoured in the corresponding free ion or neutral molecule. Therefore we cannot exclude the possibility that in the 2,2′-bithiazolyl radical anion the interaction between metal and nitrogen lone pairs may lead to a stabilization of the *cis*-conformation through the formation of a chelate structure such as (A). This hypothesis could be confirmed if we knew the sign of the hyperfine splitting constant at the alkali metal, which is usually negative for chelate complexes.[14-16] In fact when the counterion is on the molecular plane of the organic anion the most important mechanism of spin transfer from the anion to the cation involves indirect spin polarization due to σ–π exchange.[17] This mechanism, which is similar to that invoked to explain the way spin density is acquired by protons in π-radicals, gives negative splittings at the alkali metal if the spin density at the adjacent atoms is positive, as in the present case ($\rho^{\pi}_{N} = 0{\cdot}140$). For instance in the radical ion pairs of 2,2′-bipyridyl the signs of the Li and Na splittings, determined by measuring the Knight shift in the alkali metal n.m.r. spectrum, have been found to be negative.[15] One other way of determining the sign of the coupling at the cation is to measure its temperature dependence, since it seems to be generally accepted that the temperature coefficient, $\mathrm{d}a_{\mathrm{M}}/\mathrm{d}T$, is always positive.[18] Therefore a_{M} will be positive or negative depending on whether its absolute value, $|a_{\mathrm{M}}|$, increases or decreases with increasing temperature. The latter trend has always been found in the radical ion pairs of *cis*-semidiones with small counterions.[14,16,19]



(A)

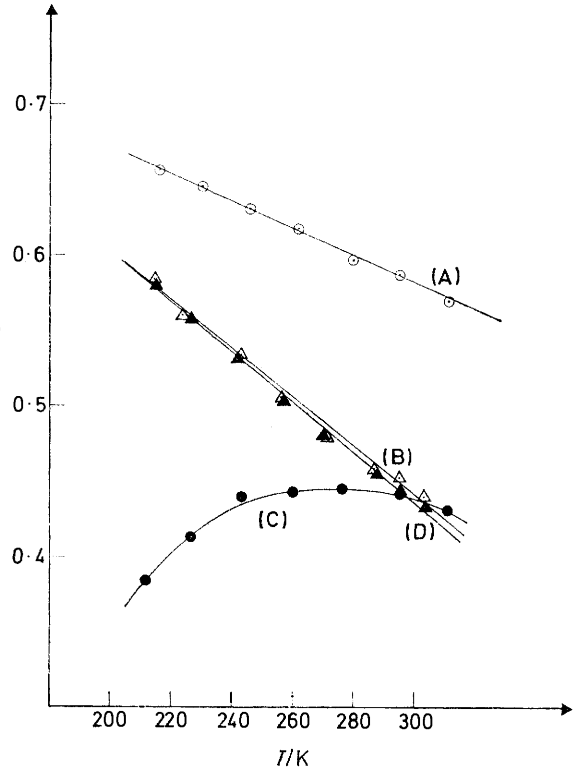


FIGURE 2 Temperature dependence of the alkali metal splittings in the radical anion from (I): (A) Li–THF; (B) Li–DME; (C) Na–THF; (D) Na–DME

In the complexes of 2,2′-bithiazolyl (I) with lithium both in DME and in THF and with sodium in DME the alkali coupling constant increases when the temperature is lowered (Figure 2); its sign should then be negative in agreement with the proposed chelate structure (A).

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[11] M. Cannas and G. Marongiu, *Z. Krist.*, 1968, **127**, 388.

[12] G. J. Visser, G. J. Heeres, J. Walters, and A. Vos, *Acta Cryst.*, 1968, **24B**, 427.

[13] P. Bucci, P. F. Franchini, A. M. Serra, and C. A. Veracini, *Chem. Phys. Letters*, 1971, **8**, 421; C. A. Veracini, D. Macciantelli, and L. Lunazzi, *J.C.S. Perkin II*, 1973, 751.

[14] G. A. Russel and D. F. Lawson, *J. Amer. Chem. Soc.*, 1971, **94**, 1699; M. Brustolon, C. Corvaja, and L. Pasimeni, *J.C.S. Faraday II*, 1973, 403.

[15] T. Takeshita and N. Hirota, *Chem. Phys. Letters*, 1969, **4**, 369.

[16] G. F. Pedulli, A. Alberti, L. Testaferri, and M. Tiecco, *J.C.S. Perkin II*, 1974, 1701.

[17] M. C. R. Symons, *Nature*, 1969, **224**, 685.

[18] E. de Boer, *Rec. Trav. chim.*, 1965, **84**, 609; S. A. Al-Badawi, and T. E. Gough, *Canad. J. Chem.*, 1970, **48**, 2798.

[19] E. Warhurst and A. M. Wilde, *Trans. Faraday Soc.*, 1969, **65**, 1413.

In THF the sodium coupling at first slightly increases, reaches a maximum, and finally decreases. This behaviour may reflect the formation at low temperature of ion pair aggregates having a large positive alkali splitting.

A similar explanation has been given to justify the concentration dependence of the splitting of the cation in the sodium–2,2′-bipyridyl system.[15]

Another factor supporting the chelate structure (A) is the decrease in absolute magnitude of the metal coupling along the series Li, Na, K, being undetectable for the last; this has always been observed whenever metal chelates are formed.[16]

We expected that the caesium complex of 2,2′-bithiazolyl (I) would be of particular interest, since the large dimensions of the caesium atom should prevent the formation of a very stable chelate complex; hence it might be possible to detect both isomers. Unfortunately the e.s.r. spectrum is complicated and could not be completely interpreted. It seems however that this complexity arises from the presence of more than one radical species, which would agree with our hypothesis.

In the radical ion pairs of 2-phenylthiazole (II) which cannot exist in chelated forms, no metal coupling was detected with lithium above −66 °C, and the sodium and potassium splittings were 1·40 and 0·26 G, respectively in THF at −40 °C, both having a positive temperature dependence. The e.s.r. spectrum of the latter radical can be interpreted in terms of the coupling of the unpaired electron with a nitrogen atom and seven nonequivalent protons. This means that the rate constant for internal rotation of the two rings is much less than 10^5 s^{-1} even at room temperature, as indicated by the absence of selective line broadening. This situation is similar to that encountered with the radical anion of 2-phenylthiophen [20] and further supports the hypothesis that, in the case of (I), we were observing a single isomer and not an averaged spectrum. The assignment of the hyperfine splitting constants in the radical from (II) reported in the Table has been made by analogy with the symmetric derivatives.

The e.s.r. spectra of the 2-(2-thienyl)thiazole (III) metal complexes show no coupling with the lithium atom, and moderately large sodium and potassium couplings, similar to those of the radical from (II), thus suggesting that formation of a nitrogen–sulphur–metal chelate does not occur. This is not surprising since the ‘ aromatic ’ sulphur atom is known to be a poor ligand for alkali cations.[4] Also in this case the e.s.r. spectrum of the lithium ion pair, which is very well resolved, shows no traces of a second species in the temperature range −60 to 0 °C. This is evidence for the presence of only one isomer, which, in the present case, should be that having the sulphur atoms *trans* as in analogous derivatives.[13,20]

Information on the relative electron-withdrawing capacities of the aromatic rings involved may be obtained from the relative values of the hyperfine splitting constants of each group in the symmetric and asymmetric derivatives. The coupling constants reported in the Table for the radical anions of (I), (II), and (III), and those already known for the 2,2′-bithienyl and biphenyl radical anions,[1] suggest that the electron-withdrawing power is greater for 2-thienyl than for phenyl, which in turn can delocalize the unpaired electron much better than thiazol-2-yl.

Unexpected results have been obtained when examining dithiazol-2-ylketyl. The room temperature e.s.r. spectrum of this radical produced by potassium reduction in THF (see Figure 3) shows that all the six interacting nuclei are not equivalent.

The ketyl (IV) may exist in any of three possible conformations, two of which are symmetric (*cis,cis* and *trans,trans*) and one asymmetric (*cis,trans*). Since in the two former conformations the nuclei of the two thiazolyl rings are equivalent, the observed e.s.r. spectrum could be explained by assuming that the only isomer present is the *cis,trans*. Further, the interconversion between the two equivalent *trans,cis*- and *cis,trans*-forms should be much smaller than the difference, in frequency units, between the splitting constants of the two thiazolyl groups. These results are surprising, as in the corresponding ketyls of thiophen and thienothiophens at least two isomers were detected at low temperature, the *cis,trans* and the *trans,trans*, while the averaged spectrum was always observed at room temperature.[2]

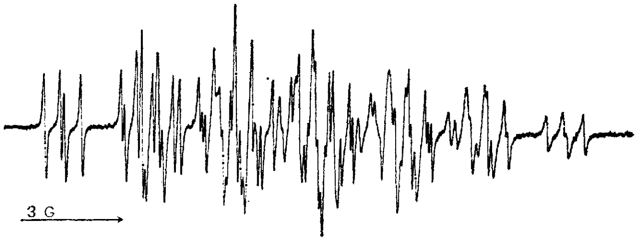

FIGURE 3 Room temperature e.s.r. spectrum of the radical anion from (IV) in THF (counterion K^+)

Since there is no apparent reason why the rotation of the thiazolyl group should be much slower than that of 2-thienyl and 2-thienothienyl rings, an alternative explanation is required to justify the anomalous behaviour of the radical from (IV).

Additional information was gained by reducing the ketone (IV) with alkali metals other than potassium. Intense and well resolved e.s.r. spectra were obtained with Na and Cs, but no spectrum could be detected with Li. In both cases the presence of only one isomer and nonequivalence of the hyperfine splittings of the two rings was observed. This indicates that no conformational changes depending on the nature of the counterion occur. The spectra also show coupling of the unpaired electron with the alkali metal which changes with temperature as shown in Figure 4. The results concerning both the absolute values and the tem-

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[20] P. Cavalieri d'Oro, A. Mangini, G. F. Pedulli, P. Spagnolo, and M. Tiecco, *Tetrahedron Letters*, 1969, 4179.

perature dependence of the alkali splittings are similar to those obtained for the ion pairs of 2,2′-bithiazolyl and of semidiones, thus suggesting that dithiazol-2-ylketyl also gives, with alkali metals, chelated complexes.

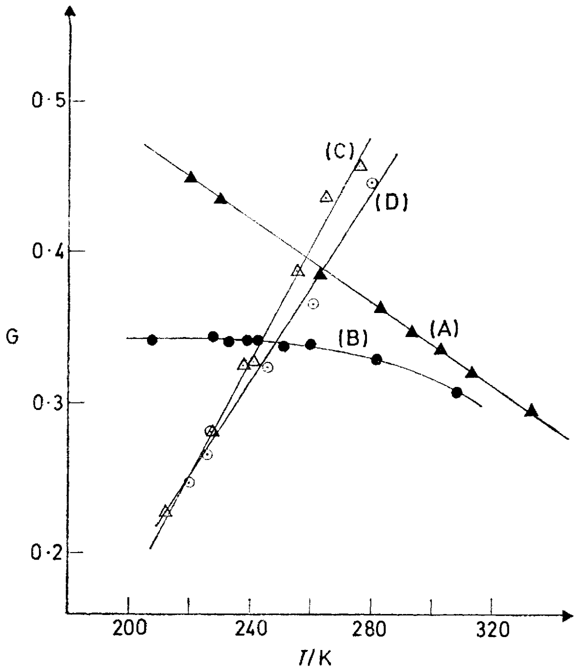
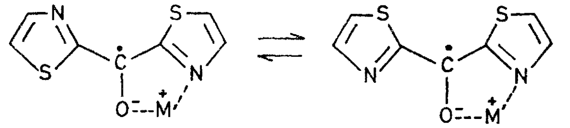


FIGURE 4 Temperature dependence of the alkali metal splittings in the radical anion from (IV): (A) Na–DME; (B) Na–THF; (C) Cs–DME; (D) Cs–THF

Their most reasonable structure is (B), where the counterion is chelated by the lone pairs of the carbonyl oxygen and one thiazole nitrogen atom.

It is thus clear that the nonequivalence of all hyperfine splitting constants observed, even at room temperature, is not related to the conformational stability of the radical from (IV) but to the formation of the chelate ring. In fact, in the *trans,trans* symmetric isomer too, the partial bond of the alkali cation with one thiazole nitrogen atom causes the nonequivalence of the two aromatic groups. They may become equivalent only if the rate of transfer of the cation between the two nitrogen atoms is greater than 10^6 s^{-1}. On the other hand the energy to destroy the chelate ring is probably too large for it to be possible to observe this process at high temperature. Although the assumed structure (B) implies that one ring is fixed in the *trans*-conformation, the other one, which is not involved in the formation of the metal bridge, may exchange between the *cis*- and *trans*-positions with a rate constant comparable to that found for other diarylketyls. When the temperature is lowered the high-field lines broaden, as has been observed in the e.s.r. spectrum of di-2-thienylketyl.[2] However at still lower temperature, instead of a sharpening of the lines, with resolution of peaks due to the presence of distinct rotational isomers, an increase in asymmetric line broadening is observed. The latter effect is caused by the large anisotropy of the nitrogen hyperfine tensor and may obscure the separation of the peaks originating from the two isomers.



(B) *cis,trans* (B) *trans,trans*

We have also generated the ketyl from (IV) by photolysis in alkaline alcoholic solution, expecting that a strongly solvating agent as methanol would prevent the formation of chelated complexes. However in this case too the e.s.r. spectra show nonequivalence of the six splitting constants. This result may be interpreted in two ways: either the chelate ring is so stable that it cannot be destroyed even by methanol (in this respect it is worth mentioning that coupling at the alkali metal has been detected with lithium methoxide but not with sodium or potassium methoxide), or the hydroxylic proton of methanol is involved in bifurcate hydrogen bonding to oxygen and nitrogen (this assumes that the alcoholic hydrogen is involved in the formation of a five-membered ring). The later hypothesis seems not unreasonable since ketyls are known to show strong hydrogen bonding with an alcoholic group through the carbonyl oxygen,[21] and n.m.r. and i.r. evidence for the existence of intramolecular bifurcate hydrogen bonding has been presented recently.[22]

Two kinds of radicals were obtained from 2-nitrothiazole (V): the corresponding radical anion and thiazol-2-yl triethylsilyloxy nitroxide (VI). The former was produced by treatment with potassium t-butoxide in DMSO and by photolysis in methanol in presence of methoxide ions. The measured hyperfine splitting constants are reported in the Table. Since this radical, like the previous ones, could give ion pairs, where the counterion is chelated by the aromatic nitrogen atoms and one of the two oxygen atoms of the nitro-group, compound (V) was also reduced with alkali metals in DME to discover whether this is the case. The Li and Na splittings showed negative temperature dependences, and no coupling was detected with potassium. This behaviour is typical of chelate ion pairs and differs from that observed with the alkali complexes of nitrobenzene.[23] We also examined the ion pairs of 2-nitrothiophen and found that the alkali splittings run parallel to those of nitrobenzene although their values are smaller, as expected on the basis of the greater electron-withdrawing power of 2-thienyl with respect to phenyl, which, reducing the spin density at the nitro-group, is reflected in the smaller alkali splittings. The coupling of the Cs atom is positive, as inferred from its temperature dependence, but much smaller than in nitrobenzene and 2-nitrothiophen. There is thus little

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[21] K. Nakamura, B. F. Wong, and N. Hirota, *J. Amer. Chem. Soc.*, 1973, **95**, 6919.

[22] J. Dabrowski and Z. Switsun, *Tetrahedron*, 1973, **29**, 2261.

[23] C. Y. Ling and J. Gendell, *J. Chem. Phys.*, 1967, **47**, 3475; J. M. Gross and J. D. Barnes, *J. Chem. Soc.* (*A*), 1969, 2437.

doubt that the 2-nitrothiazole ion pairs also have chelated structures.

Thiazol-2-yl triethylsilyloxy nitroxide (VI), where there is no possibility of chelation through alkali metal or hydrogen bridges because of the experimental conditions employed for its observation, behaves quite similarly to the 2-thienyl triethylsilyloxy nitroxides. In fact at low temperature the overall e.s.r. spectrum consists of a superimposition of distinct spectra arising from the two *cis*- and *trans*-rotamers, while at room temperature the hyperfine splitting constants are completely averaged. From the analysis of the lineshape variations with temperature, which will be reported elsewhere,[24] the activation energy for rotation of the 2-thiazolyl group has been found to be intermediate between those of the 2-thienyl and 3-thienyl rings in the corresponding nitroxides.

[4/1574 *Received*, 29*th July*, 1974]

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[24] A. Alberti, M. Guerra, G. F. Pedulli, and M. Tiecco, *Gazzetta*, in the press.