Tautomerism in a Thioamide-nitroxide: Solvent Effects in Terms of an Electron Spin Resonance Parameter for a 2-Thiocarbonylimidazolidine 1-Oxyl

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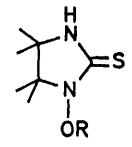
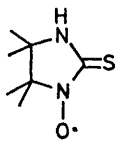
The tautomerism of 4,4,5,5-tetramethyl-2-thiocarbonylimidazolidine 1-oxyl (2) was studied by e.s.r. spectroscopy. In a range of 14 solvents, the proportion of ene-thiol (3a) correlated inversely with the hyperfine coupling constant a_{N-1} of the nitroxide nitrogen atom of the ene-thiol. The coupling constant was low in solvents of low polarity and in hydroxylic solvents, high in electron-pair donating solvents. These effects have been interpreted in terms of hydrogen-bond acceptance by the imino-group of the ene-thiol, hydrogen-bond donation by the thiol group, and resulting changes in the C=N bond order as revealed by a_{N-1}.

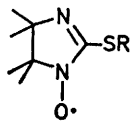
OXIDATION of the *N*-hydroxyimidazolidine (1a) to the thione radical (2) is followed, in certain solvents, by rearrangement of the radical to the ene-thiol tautomer (3a).[1] The rearrangement involves centres of high spin density, and the radicals can be distinguished, and their relative concentrations measured, by e.s.r. This method of studying tautomeric equilibrium is free from interference by solvent and is on a time-scale which is fast even compared with tautomerism involving hetero-atoms. Also, influence of solvents due to polarity or



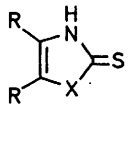
(1)
a; R = H
b; R = Ac



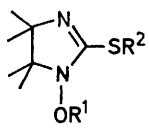
(2)



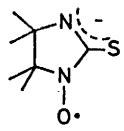
(3)
a; R = H
b; R = Me



(4)
a; X = S
b; X = O



(5)
a; R^1 = Ac, R^2 = Me
b; R^1 = H, R^2 = Me



(6)

hydrogen-bonding may be related to the electronic effects which are revealed by e.s.r. The system (2) ⇌ (3a) was also studied in the context of the use of these or similar radicals as spin-labels [2] which are sensitive both to solvent and to substituent effects. Chemical changes may be carried out at the 2-position or in the immediate side-chain which affect the e.s.r. spectra without decreasing stability. This is in contrast to simple nitroxides, where such reactions cannot take place at positions α to the nitroxide group, since these positions are substituted to prevent decomposition by loss of an α-hydrogen atom.

RESULTS AND DISCUSSION

E.S.R. Spectra of the Tautomers.—The *N*-hydroxyimidazolidine precursor (1a) shows no spectroscopic evidence for the presence of the ene-thiol form (see Experimental section). On oxidation with lead dioxide in certain solvents such as DMSO (see Table), it is converted into a purple solution of the corresponding thione radical (2). In certain other polar solvents such as water and

Hyperfine coupling constants (G)

Solvent	% Ene-thiol (3a)	a_{N-1} (3a) [a]	A_N [b]	a_{N-1} (3a) (norm) $-A_N$	a_{N-1} (3b) [a]
Benzene	>90	9.46	15.40	0	9.56
Chlorobenzene	>90	9.53	15.47	0.04	9.65
Toluene	>90	9.57	15.35	0.23	9.57
Ethanol	>90	9.60	16.03	−0.40	9.70
Water	>90	9.67	17.18	−1.44	10.56
Nitromethane	>90	9.71	15.76	0.05	9.83
t-Butyl alcohol	>90	9.73	15.86	−0.02	9.85
1,4-Dioxan	90	9.73	15.45	0.39	9.63
Pyridine	83	9.75	15.61	0.26	9.73
Formamide	74	9.86	16.33	−0.28	10.12
THF	54	9.89	15.37	0.64	9.61
Acetone	50	9.91	15.53	0.60	9.77
DMF	9	10.13 [c]	15.61	0.88	9.80
DMSO	9	10.16 [c]	15.69	0.85	9.87

[a] ±0.04 G. [b] For di-t-butyl nitroxide (from ref. 5 and P. C. Jost and O. H. Griffith in 'Methods in Enzymology,' eds. C. H. W. Hirs and S. N. Timasheff, Academic Press, New York, 1978, vol. XLIX, p. 369). [c] Obtained by extrapolation from values for solvent mixtures containing water (0—25% v/v).

nitromethane however, the purple solution is seen to change within seconds to a yellow solution of the ene-thiol radical (3a). In hydrocarbon solvents a yellow solution is observed instantly. Coupling by the two nitrogen nuclei and labile hydrogen nucleus results in an e.s.r. spectrum of three quartets for radical (2) (Figure 1) since $a_{N-3} \simeq a_H$. For radical (3a) there are three triplets (Figure 2), since the thiol hydrogen does not couple. A more detailed interpretation of the spectra is given elsewhere.[1] The spectrum in DMSO (Figure 1) shows the presence of 9% of the ene-thiol (3a), distinguishable for example as a small peak at higher field than the main spectrum. Various proportions of the tautomers are observed in solvent mixtures such as DMSO–water (Figure 3) where each solvent favours a different tautomer. The spectra may be interpreted by varying the solvent ratios. A similar interpretation was applied in measuring the coupling constants and proportions of

tautomers from the spectra obtained in pure solvents (see Table).

Influence of the Nitroxide Group on Tautomerism.—The thione tautomer predominates in thioamides and thioureas, although the ene-thiol form occurs more often than which show a proportion of ene-thiol form, in contrast to their oxygen analogues (4b) where there is no enol present.[4] The shift in equilibrium has been accounted for in terms of a more basic exocyclic sulphur atom, as a result of greater electron release from a cyclic sulphur atom than from an oxygen. The cyclic sulphur may also be regarded as contributing to resonance in the ring, in which the ene-thiol form may take part by means of the C=N bond. This explanation is supported by HMO calculations. It may therefore be postulated that the effect of the nitroxide group in the present system, in shifting equilibrium towards the ene-thiol, is due to its π-electron donating ability.

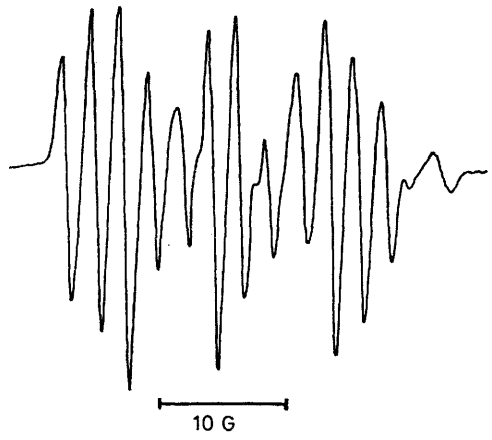


FIGURE 1 E.s.r. spectrum of radical (2), and 9% tautomer (3a), in DMSO

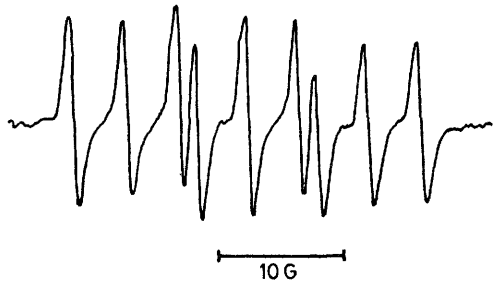


FIGURE 2 E.s.r. spectrum of radical (3a) in benzene

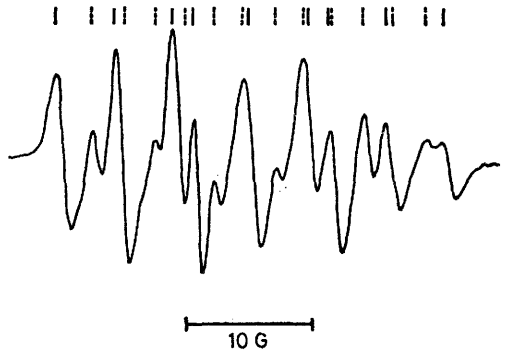
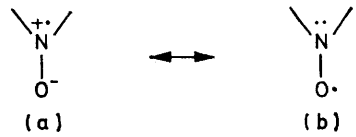


FIGURE 3 E.s.r. spectrum of the tautomeric mixture (2) ⇌ (3a) in DMSO–water (1 : 1 v/v). Full vertical lines indicate absorption peaks for radical (3a); dotted lines indicate peaks for (2)

does the enol form of the corresponding oxygen compounds. Five-membered cyclic systems with 1,3-heteroatoms and 2-carbonyl or 2-thiocarbonyl groups exist almost always as the keto-form, minor amounts of enol occurring in some cases.[3] The influence of the nitroxide group on tautomeric equilibrium in the system (2) ⇌ (3a) is therefore unexpected. A comparable tautomerism is that of the 2-thiocarbonylthiazoles (4a)

If electron release from the nitroxide group favours the ene-thiol form, then it should be possible to relate polarisation of the nitroxide group to the position of tautomeric equilibrium. Polarisation of a nitroxide group may be expressed in terms of the a_N value. The polar resonance form (a) of a nitroxide corresponds to a



high value of a_N. It also corresponds to decreased endocyclic π-electron overlap in system (3a). When there is a high value of a_{N-1} for the nitroxide (3a) therefore, a high proportion of thione tautomer is expected. The Table shows values of a_{N-1} for a range of solvents, and it is seen that the proportion of thione does increase with the coupling constant. A plot (Figure 4) of coupling constant against proportion of thione shows this for solvents in which the radical is not more than 90% ene-thiol.

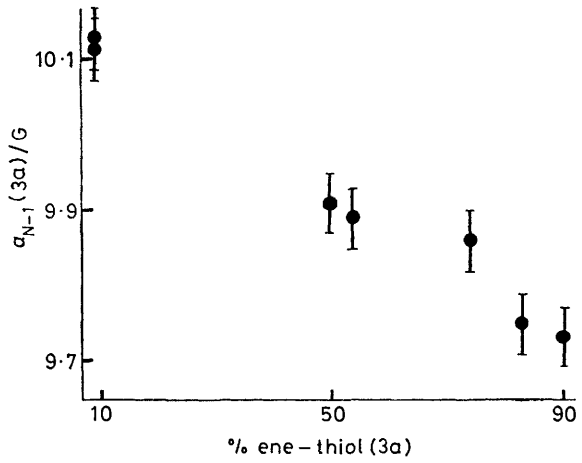


FIGURE 4 Plot of percentage of ene-thiol (3a) against hyperfine coupling constant a_{N-1} in 1,4-dioxan, pyridine, formamide, THF, acetone, DMF, and DMSO

Effects of Hydrogen-bonded Donor Solvents.—The solvent polarity parameter [5] A_N is included in the Table for comparison. This is based on polarisation of a simple

nitroxide, di-t-butyl nitroxide. There is not a direct relationship between A_N and proportion of ene-thiol, however. For example, the radical exists mainly as the ene-thiol both in hydrocarbon and in hydroxylic solvents, although the latter produce higher A_N values than DMSO, in which the radical is mainly thione. A high solvent polarity, as measured by A_N, therefore does not always correspond to a higher proportion of thione.

It is not unexpected that the variation in tautomeric equilibrium over a range of diverse solvents should not show a simple relationship to a solvent polarity parameter, since the hydrogen-bonding capability of the solvent, for example, has to be taken into account. When the a_{N-1} values are normalised to A_N for benzene, and compared with their corresponding values of A_N (see Table), the hydroxylic solvents show negative deviations in a_{N-1} (normalised). The low nitroxide nitrogen coupling constants in hydroxylic solvents for imino-nitroxides have been noted previously and attributed to hydrogen-bonding by the imino-group.[6] Similarly, protonation, or complexation of the imino-nitrogen atom with metal cations, lowers a_{N-1}.[1,6] These effects can be explained by considering the relation between a_{N-1} and a_{N-3}. The coupling constant for N-1 is given by equation (1).[7,8] Since Q^N_{N-1} is greater than

$$a_{N-1} = Q^N_{N-1}\rho_{N-1} + Q^N_{ON}(1 - \rho_{N-1} - \rho_{N-3}) \quad (1)$$

Q^N_{ON} by a factor of 10—20,[9] approximation (2) is obtained. Similarly,[8,9] relationship (3) holds.

$$a_{N-1} \simeq Q^N_{N-1}\rho_{N-1} \quad (2)$$

$$a_{N-3} \simeq Q^N_{N-3}\rho_{N-3} \quad (3)$$

Assuming [6] $Q^N_{N-1} \simeq Q^N_{N-3}$ then $a_{N-1}/(a_{N-1} + a_{N-3})$ is the fraction of unpaired spin at N-1. The spin density at N-1 will vary inversely as the C=N bond order: resonance involving this bond will reduce the bond order, increase a_{N-3}, and decrease a_{N-1}.

Protonation of imino-nitroxides occurs on the imino-nitrogen atom,[6] and the increased resonance delocalisation of spin to N-3, with decrease in a_{N-1}, is in contrast to simple nitroxides, where protonation on oxygen increases the nitroxide nitrogen coupling.[10] In hydroxylic solvents the nitroxide nitrogen coupling of the ene-thiol (3a) is low in comparison with A_N, and the accompanying increase in C=N bond order means a shift of tautomeric equilibrium towards ene-thiol.

Effects of Hydrogen-bonded Acceptor Solvents.—The hydrogen-bonded acceptor solvents, the ethers, pyridine, acetone, and DMSO show positive deviations in a_{N-1} (normalised) from the A_N values (see Table). Hydrogen bonding by a thiol group is expected to be weak, but was investigated. The *S*-methyl derivative (3b) was prepared for comparison, by the route (1a) ⟶ (1b) ⟶ (5a) ⟶ (5b) ⟶ (3b), in which the *N*-hydroxy-group was protected by acetylation. In this derivative there is no possibility of hydrogen-bond donation by the sulphur group, and comparison of a_{N-1} values for the radicals (3a and b) should reveal higher values than average for the former in hydrogen-bonded acceptor solvents. From the graph (Figure 5) this is seen to be so for solvents which are expected to form the strongest bonds.[11,*]

Solvation of the thiol group of radical (3a) by electron-pair donors compares with formation of the radical anion (6),[1] where there is also release of charge into the ring. For 2-substituents it has been shown [6] that $a_{N-3}/(a_{N-1} + a_{N-3})$, the fraction of unpaired spin on the imino-nitrogen atom, is proportional to σ_p^+. The decrease

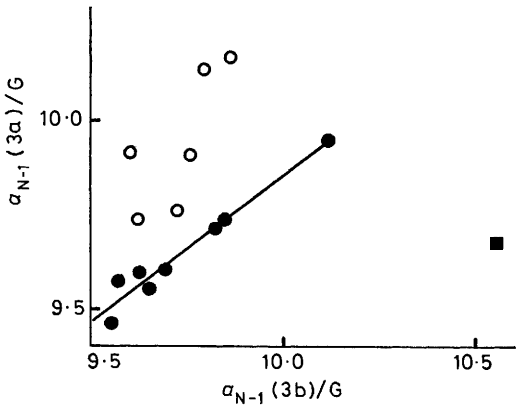


FIGURE 5 Plot of hyperfine coupling constant a_{N-1} for methyl derivative (3b) against a_{N-1} (3a): ●, electron-pair non-donating solvents; ○, electron-pair donating solvents; ■, water

in a_{N-3} with charge donation is because of resonance involving the C=N bond. In the present system, reduction in the C=N bond order by the hydrogen-bonded acceptor solvents means a shift in tautomeric equilibrium towards thione.

The System (2) ⇌ (3a) *as a Spin-labelled Thioamide.*—The electronic effects caused by hydrogen-bonding of solvent molecules with the thioamide groups apparently over-ride those caused by hydrogen-bonding with the nitroxide group. Although both the nitroxide and imino-groups are electron-pair donors, the latter is the more basic. Also, simple nitroxides such as di-t-butyl nitroxide do not appear to hydrogen-bond so strongly with hydroxylic solvents that these solvents become exceptions to the general correlation of A_N values with other cybotactic solvent polarity parameters.[5] The effects of solvents on electronic structure and tautomeric equilibrium in the radicals (2) ⇌ (3a) may therefore be considered as due primarily to solvation of the thioamide group. The system may be regarded as a spin-labelled thioamide.

A_N and other cybotactic parameters are based essentially on systems involving polarisation of a single bond.

* The high a_{N-1} value for the *S*-methyl derivative in water is possibly due to competition by the sulphide group for hydrogen-bond donation by the solvent cages which water is known to form about large spherical hydrocarbon groups, in this case the *gem*-dimethyl groups. This increase in a_{N-1} compares with the decrease in A_N for di-t-butyl nitroxide when water cages are dispersed by the addition of an aprotic solvent. For a discussion, see M. C. R. Symons, 'Chemical and Biochemical Aspects of Electron Spin Resonance Spectroscopy,' Van Nostrand-Reinhold, New York, 1978, p. 90.

These solvation models are very different from a tautomeric system containing both a hydrogen-bonded donating and a hydrogen-bonded accepting group. The nitroxide (3a) provides a solvent classification based on a single spectroscopic parameter for a tautomer and this classification may be relevant to other such systems. The radical or a similar spin-labelled molecule may find application as a cybotactic probe for an environment affecting tautomerism.

EXPERIMENTAL

AnalaR or purified reagent-grade solvents were used for e.s.r. spectroscopy. E.s.r. spectra were recorded on a Decca X-1 spectrometer with 100-kHz modulation, amplitude 1.3 G. The coupling constants were measured by using Mn^{II} in magnesium oxide as standard (separation of lines 3 and 4 = 86.8 G).

1-*Hydroxy*-4,4,5,5-*tetramethyl*-2-*thiocarbonylimidazolidine* (1a).—A suspension of 2,3-bis(hydroxyamino)-2,3-dimethylbutane sulphate (Eastman) (1.2 g) and anhydrous potassium carbonate (1 g) in dry THF (10 ml) and carbon disulphide (20 ml) was stirred for 4 days. After filtration and evaporation, the main impurity was sulphur. This was removed by chromatography on silica (70 g), with ether–methanol (3 : 1) as eluant. Recrystallisation from ethyl acetate–hexane yielded the N-*hydroxy*-2-*thioketone* (0.5 g), m.p. 178—179° (decomp.) with rapid heating (Found: C, 48.25; H, 8.2; N, 16.0; S, 18.25. $C_7H_{14}N_2OS$ requires C, 48.25; H, 8.1; N, 16.1; S, 18.4%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), 3 230br (H-bonded NH and OH), and 1 430 (C=S) cm^{-1}; $\delta(CDCl_3)$ 1.23 (6 H, s, $2CH_3$), 1.26 (6 H, s, $2CH_3$), 7.32 (1 H, OH), and 8.12 (1 H, NH).

The O-*acetate* (1b) was prepared with acetyl chloride in benzene, and crystallised from chloroform–hexane, m.p. 172—175° (Found: C, 50.4; H, 7.65; N, 13.25; S, 14.85. $C_9H_{16}N_2O_2S$ requires C, 50.0; H, 7.4; N, 12.95; S, 14.8%); $\nu_{max.}$ (KBr) 3 450 (NH), 3 220br (H-bonded NH), 1 800 (C=O), and 1 432 (C=S) cm^{-1}; $\delta(CDCl_3)$ 1.24 (6 H, s, $2CH_3$), 1.34 (6 H, s, $2CH_3$), 2.30 (3 H, s, CH_3CO_2), and 7.94 (1 H, NH).

1-*Acetoxy*-4,4,5,5-*tetramethyl*-2-*methylthioimidazoline* (5a).—To a solution of the O-acetate (1b) (500 mg) in acetone (10 ml) was added potassium carbonate (300 mg) and methyl iodide (0.7 ml) in acetone (10 ml). The mixture was stirred overnight under nitrogen, then filtered. The solvent was evaporated, the residue extracted with light petroleum (b.p. 60—80°), and the extract filtered. Light petroleum was evaporated and the residual oil crystallised from ethyl acetate–hexane to afford the *methylthio-compound* (360 mg), m.p. 58—59° (Found: C, 52.25; H, 8.25; N, 12.15; S, 13.85. $C_{10}H_{18}N_2O_2S$ requires C, 52.15; H, 7.8; N, 12.15; S, 13.9%); $\nu_{max.}$ (KBr) 1 795 (C=O) cm^{-1}; $\delta(CDCl_3)$ 1.14 (6 H, s, $2CH_3$), 1.23 (6 H, s, $2CH_3$), 2.22 (3 H, s, CH_3CO_2), and 2.47 (3 H, s, CH_3S).

1-*Hydroxy*-4,4,5,5-*tetramethyl*-2-*methylthioimidazoline* (5b).—1-Acetoxy-4,4,5,5-tetramethyl-2-methylthioimidazoline (5a) (100 mg) in aqueous NaOH (10%; 10 ml) was warmed on a steam-bath (10 min). The mixture was cooled and extracted with ethyl acetate. The solution in ethyl acetate was dried ($MgSO_4$) and the solvent was evaporated. The residual oil (65 mg) crystallised from ethyl acetate–hexane, m.p. 157—158° (Found: C, 50.85; H, 8.8; N, 14.6; S, 16.7. $C_8H_{16}N_2OS$ requires C, 51.05; H, 8.5; N, 14.9; S, 17.0%); $\delta(CDCl_3)$ 1.16 (12 H, s, $4CH_3$), 2.48 (3 H, s, CH_3S), and 7.33 (1 H, s, OH).

4,4,5,5-*Tetramethyl*-2-*thiocarbonylimidazolidine* 1-*Oxyl* (2) *and Tautomer* (3a).—To a solution (1 ml) of the *N*-hydroxy-precursor (1a) (10^{-3}M in the appropriate solvent) was added lead dioxide (20 mg). The mixture was shaken (10 s), centrifuged, and the supernatant solution removed with a dropper. The solution was deoxygenated with a stream of nitrogen before obtaining the spectrum. In water there was considerable decomposition of the radical in the time required to run a spectrum. Measurements in water were therefore confirmed with D_2O, in which there was no noticeable decomposition.

4,4,5,5-Tetramethyl-2-methylthioimidazolidine 1-oxyl (3b) was similarly prepared.

I am grateful to Mrs G. Fitzpatrick for her assistance in obtaining the spectra.

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