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ESR study of stereochemistry in chiral nitroxide radical crystals

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The distinct differences in ESR spectra were revealed for the polycrystalline samples of the enantiomer and racemate of nitroxide 1, as well as of their diastereomeric salts with optically active amine 2.

Chiral nitroxides were synthesised for the first time by Rozantsev and Krinitzkaya.[1] These were (±)-3-carboxy-2,2,5,5-tetramethylpyrrolidine-1-oxyl (3-carboxyproxyl) **1** and derivatives of this acid, in particular, amide(3-carbamoylproxyl) (±)-**1a**. The ESR spectra of (±)-**1** and formation of its H-bonded dimers in non-polar solvents at different temperatures have been studied in detail,[2(a)] and no dimerization was observed in dilute aqueous water solutions.[2(b)] Nitroxide (±)-**1a** has been resolved into enantiomers;[3] the absolute configuration of (*R*)-(±)-**1a** was determined,[2(b),4(a)] its CD and UV spectra[2(b)] and the crystal structures of (*R*)-(+)-**1** (space group $P2_12_12_1$, $Z = 4$)[4(a)] and (±)-**1** (space group $Pna2_1$ or $Pnma$, $Z = 4$, $Z' = 0.5$)[4(b)] were examined.

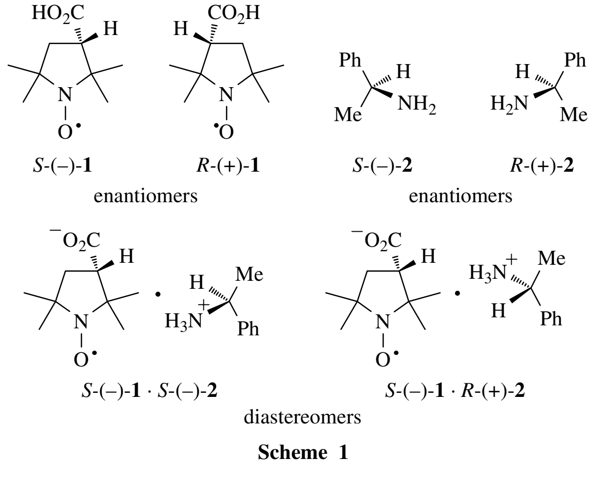
A number of optically active nitroxides are known.[5] They were used in various fields.[5,6] The spontaneous resolution of chiral nitroxides was described.[7]

Since 1972, ESR and ENDOR studies on the stereochemistry of radicals are in progress.[8] There are reliable data on differences in spectral parameters between diastereomeric radicals including nitroxides.[8(e)] However, chiral nitroxide crystals were not studied. It may be thought of the distinctions in ESR parameters of crystals between enantiomer and racemate each of **1** and **1a** because their structures are substantially different.[4,9] In fact, the anticipated distinctions in ESR were recently found in the crystals of both enantiomer and racemate of **1a**.[9]

In this work, with the aim of studying the ESR spectra, commercially available (±)-**1** was resolved into enantiomers using a known method[3] *via* diastereomeric salts with optically active α-phenylethylamines (Scheme 1).†

Typical ESR spectra‡ of the powder samples of enantiomeric (–)-**1** and racemic (±)-**1** are shown in Figure 1. There were no significant differences in the spectra recorded for the same samples oriented with relative angles equal to 0°, 45° and 90° in the resonator. This fact meant that the test powders were really polycrystalline, and ESR spectra of various forms could be compared without any precise orientation in a resonator. Nitroxides (–)-**1** and (+)-**1** had practically identical ESR spectra. Figure 1 shows that there is a noticeable difference in the positions of ESR lines in a magnetic field for racemic and enantiomeric forms of radicals in a solid state. This difference can be caused by variation of local polarity in the nearest surrounding of N–O groups in both crystal forms (it can be connected with various space groups and packing of the racemic and enantiomeric crystals,[4] *i.e.*, with a difference in local magnetic fields). Unfortunately, we could not prepare good single crystals of both forms for an ESR study.

From the XRD data[4] for radicals (+)-**1**, and (±)-**1**, we could calculate the average distances d among any ten neighbouring paramagnetic centres in the crystal lattice (centres of N–O bonds). Values of $d_{\text{en}} = 7.32$ Å for enantiomeric and $d_{\text{rac}} = 7.27$ Å for racemic crystal were estimated. They are so close that one cannot assume any difference in the magnitude of the dipole–dipole interaction between radicals in powders of both types.



Scheme 1

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† (±)-**1**, mp 200 °C; (*S*)-(–)-**1**, mp 206 °C, $[\alpha]_D^{20}$ –93.7° (*c* 0.32, EtOH); (*R*)-(+)-**1**, mp 205 °C, $[\alpha]_D^{20}$ +84.8° (*c* 0.33, EtOH) [lit.,[3(b)] $[\alpha]_D^{23}$ –85° (*c* 0.37, EtOH)] and $[\alpha]_D^{23}$ +83° (*c* 0.38, EtOH).

(–)-**1**·(–)-**2**, mp 166–167 °C (acetone); (–)-**1**·(+)-**2**, mp 197–200 °C (acetone); in the sealed capillary (both compounds are sublimated at 120 and 170 °C, respectively). (–)-**1**·(–)-**2**, $[\alpha]_D^{20}$ –105.9° (*c* 0.34, EtOH), (–)-**1**·(+)-**2**, $[\alpha]_D^{20}$ –78.8° (*c* 0.33, EtOH).

‡ ESR spectra were recorded with a Bruker 200D-SRC X-band spectrometer (microwave frequency of 9.74 G) in a 50 or 100 μl capillary containing 0.2 mg of powder at 298 and 77 K with a modulation amplitude equal to 0.2 G and with a 0.2 mW microwave power (or 5 mW in some measurements). At these parameters, the spectra of niroxides are not saturated.[10] For precise measurements of the g values, a standard (paramagnetic centres in LiCl with $g = 2.0023$) was used.

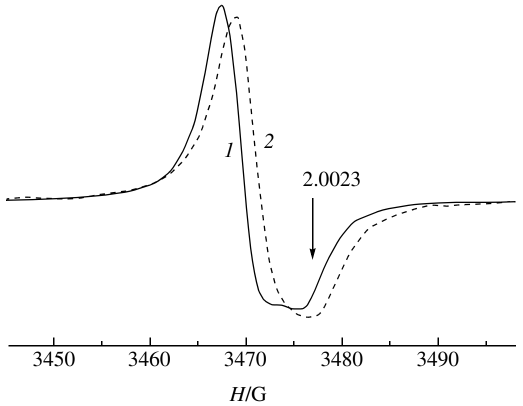

Figure 1 ESR spectra of polycrystalline samples (powders) of (*1*) enantiomeric (*S*)-(–)-**1** and (*2*) racemic (±)-**1** radicals at 298 K. A vertical arrow depicts the position of the standard signal in LiCl ($g = 2.0023$).[‡]

To confirm differences in the ESR spectroscopic behaviour of optically active isomers and a racemate, diastereomeric salts (–)-**1**·(–)-**2**, (–)-**1**·(+)-**2**, (+)-**1**·(+)-**2** and (+)-**1**·(–)-**2** were studied. Room-temperature spectra of diastereomeric salts such as (–)-**1**·(–)-**2** and (–)-**1**·(+)-**2** (or *vise versa*) in toluene did not demonstrate any significant difference. This fact probably meant that radical and amine molecules at a 4×10^{-4} M concentration were not associated in solution at ambient temperature.

The ESR spectra of the same diastereomeric salts in powders showed noticeably different situation (Figure 2). Indeed, one can see that the spectrum shape of (–)-**1**·(–)-**2** and (–)-**1**·(+)-**2** samples at 298 K are different, although their resonance positions in a magnetic field are identical. This fact is also confirmed by the second derivative ESR spectra of the same samples (Figure 3). At the same time, the spectra of (–)-**1**·(–)-**2** and (–)-**1**·(+)-**2** powders are superimposable with the spectra of (+)-**1**·(+)-**2** and (+)-**1**·(–)-**2** salts, respectively (Figures 2 and 3). From these results, one may conclude that the formation of two various aggregates of optically active radicals with optically active amine **2** molecules occurred.

Rather symmetric single line spectra ($g = 2.0062\pm0.0004$) of the diastereomeric salt samples reflect a situation of strong spin exchange between unpaired electrons of nitroxide radicals in the matrix. In accordance with ref. 11, the local concentration $[R]_{loc}$ of the interacting spins can be estimated from the exchange line narrowing of the ESR spectrum using the correlation[12]

$$\nu_e = K_e[R]_{loc}^2 \approx 3.0\times10^{11}\,(\Delta H)^{-1}, \qquad (1)$$

where ν_e is the frequency, K_e is the rate constant of spin exchange in the solid state, ΔH is the line width (in G) and [R] is the radical concentration. It was measured that $K_e \approx 3\times10^9$ s^{-1} (mol dm^{-3})$^{-2}$ for the pyrrolidine, pyrroline and imidazoline nitroxide radicals in liquid and frozen (at 77 K) solutions.[11,13]

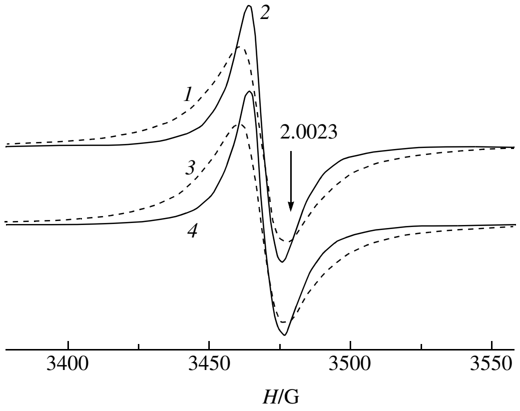

Figure 2 ESR spectra of radical amine salts (–)-**1**·(–)-**2** (*1*) and (–)-**1**·(+)-**2** (*2*), (+)-**1**·(+)-**2** (*3*) and (+)-**1**·(–)-**2** (*4*) in polycrystalline powders at 298 K. A vertical arrow depicts the position of the standard signal in LiCl ($g = 2.0023$).[‡]

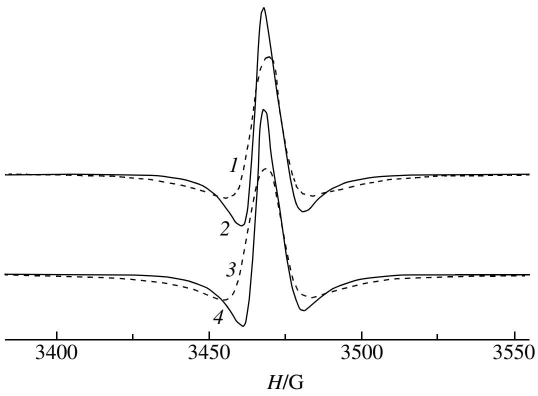

Figure 3 ESR spectra (second derivative) of distereomeric salts (see Figure 2).[‡]

Therefore, knowing the value of K_e, one can estimate $[R]_{loc}$ from the ESR line narrowing. Substituting the experimental ΔH values, which are equal to 16.2±0.4 and 12.2±0.3 G for (–)-**1**·(–)-**2**, (+)-**1**·(+)-**2** and (–)-**1**·(+)-**2**, (+)-**1**·(–)-**2** salts, respectively, we obtained $[R]_{loc} \approx 2.5$ and 2.85 dm^3 mol^{-1} for these two pairs. Hence, the mean distance <*d*> between the unpaired electrons of the radicals in both types of diastereomeric salts is approximately 8.7 and 8.4 Å, according to the equation $<d> = [R]^{-1/3}$. These values are considerably larger in comparison with 7.3 Å calculated for the radical but are absolutely reasonable taking into consideration that diastereomeric radicals are diluted with diamagnetic amine molecules in a solid.

Note that solid-phase ESR spectroscopy is sensitive to the stereochemistry of compounds and can be used for the discovery and study of chiral radicals in a solid state.

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