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First characterisation of rotational conformers in a chiral nitroxide by EPR spectroscopy†

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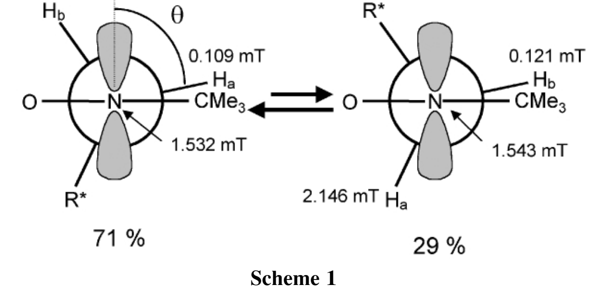
The detection and characterisation in liquid solution by EPR spectroscopy of the rotational conformers of a nitroxide radical containing a chiral centre is reported for the first time.

The EPR spectroscopic observation of free radicals in solution showing unequivalent hyperfine splittings at the methylene protons adjacent to a chiral carbon atom was reported for the first time by Gilbert *et al.* 30 years ago.[1,2] They discovered that racemic mixtures of radicals of formula XYZC–CH$_2$–NO$_2^{\cdot-}$ and XYZC–CH$_2$–N(O$^{\cdot}$)–CMe$_3$ showed magnetically non-equivalent β-hydrogens. Similar behaviour has been found in more recent EPR investigations on related chiral radicals.[3]

The observed non-equivalence of the diastereotopic hydrogens originates from two different contributions: an intrinsic term and a term depending on the conformer populations. In a nitroxide radical of the type XYZC–CH$_2$–N(O$^{\cdot}$)–C(CH$_3$)$_3$ where a prochiral methylene group is bonded to a carbon bearing three different substituents, the lower energy conformations are those where the chiral centre avoids the *tert*-butyl group (see Scheme 1).[4]

Since the nitroxide contains a C$_\beta$ chiral centre the spatial orientation of the two β-hydrogens with respect to both the radical centre and the C$_\beta$ substituents will differ for the two rotamers. Consequently, the methylene protons will be magnetically non-equivalent and the energies associated with the two rotamers will likewise be different. When the interconversion between the two unequivalent conformers is fast on the EPR time scale the observed β-hydrogen splittings will be time averaged over the residence time in each conformation. Since the two conformations have different energies the two splittings will be different, their values being closer to those of the favoured conformer.

It should be pointed out that even in the case that all conformations were equally populated, magnetic nonequivalence would still be observed since in each conformer the two methylene splittings can be coincident only by accident. The residual non-equivalence still present when all conformations are energetically degenerate, is called intrinsic non-equivalence.



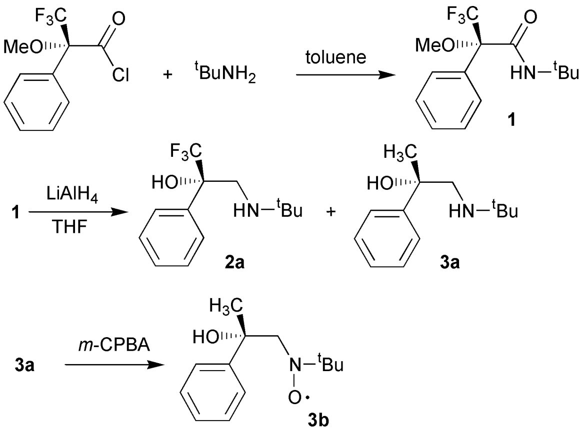
Scheme 1

The evaluation of the relative importance of these two terms is not an easy task since the only reliable method for their estimation would be to record spectra at temperatures low enough to freeze the internal rotation around the N–C$_\alpha$ bond on the EPR time scale. Under these conditions the spectra of each radical rotamer would be observed and these will provide both the methylene hydrogen splittings and the relative populations of each conformation. To the best of our knowledge, no example has yet been reported of chiral free radicals where rotamers have been detected by EPR and therefore the relative importance of these two terms could never be experimentally determined.

We wish to report here an EPR study of an optical pure nitroxide of formula XYZC–CH$_2$–N(O$^{\cdot}$)–CMe$_3$ in which the rotation about the N–C$_\alpha$ bond could be completely frozen at easily accessible temperatures (≤ -76 °C). The nitroxides **2b** and **3b** were generated directly inside the EPR cavity by oxidising the chiral amines **2a** or **3a** (1.0×10^{-3} M), obtained as shown in Scheme 2, with *m*-choloroperbenzoic acid (1.0×10^{-3} M) in toluene. Three groups X, Y, and Z, other than hydrogen, were chosen as substituents at the chiral carbon on the basis of the observation reported by Gilbert and Trenwith[1] that a strong broadening of the two inner lines of the doublet of doublets due to the methylene protons, is observed when substituents bulkier than hydrogen are present.[4]

Disappointingly, in the room temperature EPR spectrum of nitroxide **2b** (X = OH, Y = CF$_3$, Z = Ph) only a weak line broadening was observed, this indicating that the rotation about the N–C$_\alpha$ bond is fast on the EPR time scale (a_{H1} = 1.058, a_{H2} = 1.158 mT, a_{N} = 1.560 mT, a_{F} = 0.090 mT, g = 2.0061).

A more interesting behaviour was instead observed with nitroxide **3b** (X = OH, Y = CH$_3$, Z = Ph) produced by oxidation of the amine **3a** that represents a minor product of the reduction of the amide **1** with LiAlH$_4$ whose yield, however, can be increased by increasing the reaction time and the moles of LiAlH$_4$ added (see ESI†). Actually, the EPR spectrum of **3b** was strongly dependent on temperature and, at 95 °C, consisted of twelve lines (Fig. 1a) due to the coupling of the unpaired electron with the nitrogen nucleus (a_{N} = 1.540 mT) and with



Scheme 2

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† Electronic supplementary data (ESI) available: preparation and spectroscopic characterization of **3a**, Arrhenius plot for the rotation of the N–C$_\alpha$ bond in **3b**. See http://www.rsc.org/suppdata/cc/b2/b200323f/

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two unequivalent protons (a_{H1} = 1.016, a_{H2} = 1.243 mT). At this temperature the observed β-proton splittings are averaged over the residence times in each conformation indicating that the rotation about the N–C$_\alpha$ bond is fast on the EPR time scale, although the broadening of the $M_I(2H) = 0$ lines suggests that the rate of conformational interconversion is not fast enough to reach the motional narrowing limit. By lowering the temperature to 20 °C, the latter lines became too broad to be detected (Fig. 1b) and only the sum of the β-H splittings could be measured. (a_N = 1.539, $a_{H1}+a_{H2}$ = 2.251 mT, $g = 2.0060$). At −76 °C new lines, corresponding to two distinct paramagnetic rotamers, appeared in the spectrum (Fig. 1c), this indicating that the rotation about the N–C$_\alpha$ bond is slow on the EPR time scale at this temperature. Simulation of the latter spectrum (Fig. 1d) provided the values of both the hyperfine splitting constants and relative amounts of the frozen rotamers (see Scheme 1).[5]

The measured data, reported in Scheme 1 show that in both rotamers the β-proton splittings are almost identical, one being large and the other close to zero. On the basis of the β-proton splitting dependence on the dihedral angle θ between the symmetry axes of the 2p$_z$ orbital containing the unpaired electron and the N–C–H plane, predicted by the well-known Heller-McConnell equation,[6] it can be inferred that the minimum energy conformations of the radical are those where one of the methylene C–H bond makes an angle of *ca.* 30° with the 2p$_z$ orbital on nitrogen and the other is almost eclipsed by the *tert*-butyl group (see Scheme 1).

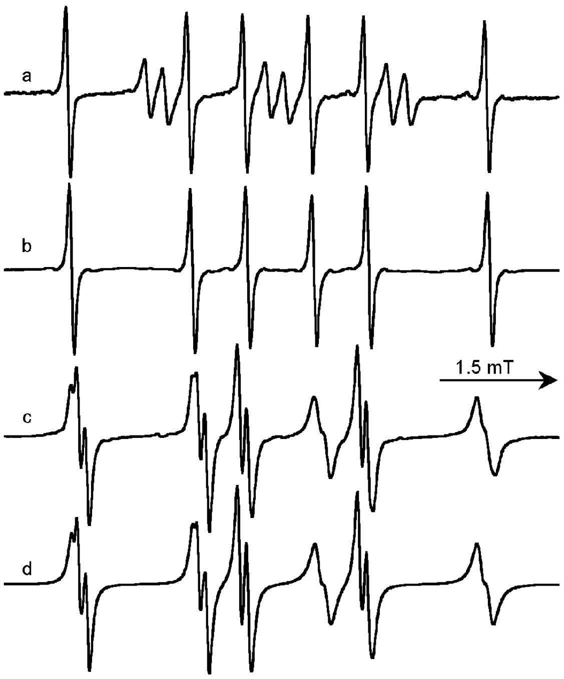

Fig. 1 EPR spectra of (*R*)-**3b** recorded in toluene at 95 °C (a), 20 °C (b), −76 °C (c) and computer simulation of the latter one (d).

By simulating the experimental EPR spectra at different temperatures by using well-established procedures[7] based on the density matrix theory,[8] we could determine the activaction parameters for the N–C$_\alpha$ bond rotation as $\Delta S^\ddagger$ = 0.60 ± 0.25 e.u. $\Delta H^\ddagger$ = 5.97 ± 0.08 kcal mol^{-1} and $\Delta S^\ddagger$ = 0.41 ± 0.20 e.u. $\Delta H^\#$ = 6.11 ± 0.07 kcal mol^{-1} (see ESI†). These values give a free energy difference of 0.2 kcal mol^{-1} and a population ratio of 1.41 for the two rotamers at 20 °C.

Given the similarity of the β-proton splittings of the two rotamers, the main factor determining the magnetic non-equivalence of these splitting is the free energy difference of the two conformations with the intrinsic term being responsible for only 18% of the observed value of $\Delta a_{H\beta}$.[9]

In conclusion, it has been demonstrated, for the first time, that the observed magnetic non-equivalence of diastereomeric protons in the EPR spectra of chiral radicals mainly arise from the population difference of the various conformations. It should be pointed out that the optical pure nitroxide **3b** represents a suitable probe to investigate the effect of chiral perturbations on the conformational equilibrium of a radical containing a chiral centre. This can be important in determining the factors giving rise to preferential stabilisation of a given conformation and, consequently, to stereoselective reactions of acyclic radicals.[10]

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4 Actually, only the two rotamers with the chiral substituent avoiding the *tert*-butyl group have been detected in radical **3b** (*vide infra*).

5 The same EPR spectra were observed by using the (*R*) or the (*S*) enantiomer of **3b**, as expected.

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9 If the energies of the two rotamers were identical, the values of a_{H1} and a_{H2} would be 1.086 and 1.127 mT ($\Delta a_{H\beta}$ = 0.041 mT) in the averaged spectrum.

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