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A NEW STEROIDAL BIRADICAL

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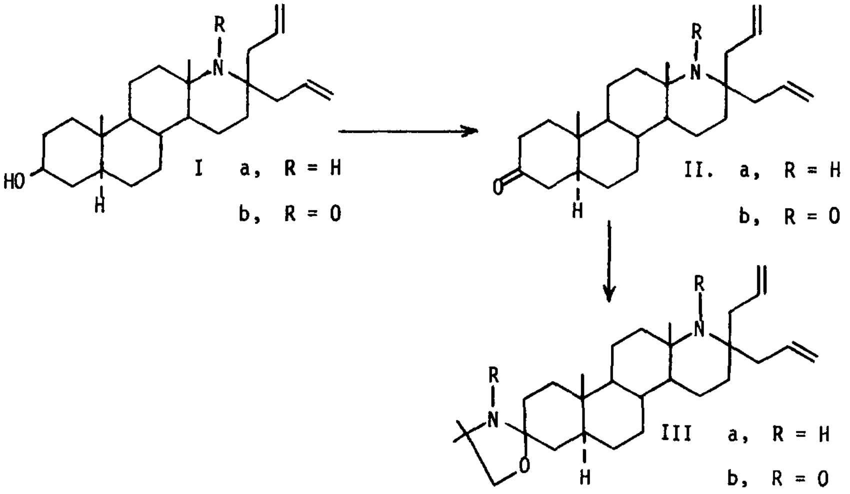
We wish to report the synthesis of a steroidal nitroxyl biradical, IIIb, which in spite of its rather rigid structure was found to have an exchange energy (J) strongly dependent on solvent and temperature


I a, R = H
b, R = O

II. a, R = H
b, R = O

III a, R = H
b, R = O

Ramasseul and Rassat have reported the synthesis and circular dichroism properties of the steroidal nitroxide Ib.[1] Using a modified Sarrett procedure,[2] the amine precursor of this radical (compound Ia) was oxidized to the 3-keto derivative IIa (mp 107-108), ir(KBr)[3300 cm^{-1} (NH), 3050 (CH olefin), 1710 (C=O), 1640 (C=C)], 220 MHz nmr ($CDCl_3$) [δ 1 0 S (19-Me), 1.14 S (18-Me), 4 8-5 1, 5.75-6.0 (6H allylic)]. Compound IIa could be easily oxidized to the mononitroxyl radical IIb with m-chloroperoxybenzoic acid [3] esr ($CHCl_3$) [3 lines, a = 15.4 G]. Refluxing

IIa in xylene with a 20-fold excess of 2-amino-2-methylpropan-1-ol and a trace of p-toluenesulfonic acid for 3 days gave the 3-oxazolidine derivative IIIa: ir (neat) [3300 cm^{-1}(NH) 3050 (CH olefin), 1650 (C=C)], 220 MHz nmr ($CDCl_3$) [δ1 09 S (19-Me), 1.25 (18-Me), 1.25 (oxazolidine Me's), 3 75 S (oxazolidine CH_2), 4.8-5 1, 5.75-6.0 (6H, allylic)], mass spec [440 (M^+), 425 (M^+ - 15), 399 (M^+ - 41)] Compound IIIa was oxidized to the biradical IIIb with a 2-fold excess of m-chloroperoxybenzoic acid in ether.[3] Following purification by column and preparative tlc on silica gel ($CHCl_3$ hexane 19 1) IIIb was obtained as a pale yellow oil (M^+ = 470.350052, for $C_{29}H_{46}N_2O_3$ δ = 1.70 ppm) Michon and Rassat[4] have shown that the nitroxyl group at the 3 position of a 5α-steroid is in the 3β configuration (equatorial nitrogen) For biradical IIIb, assuming the equatorial nitrogen, the distance between the centers of the nitroxyl groups as determined from molecular models is 9.6 A.

Typical esr spectra for biradical IIIb are shown in Fig. 1. S-resonances (not shown) were not found in chloroform but could be observed in hexane.[6] At 20° they consisted of broad, very weak absorptions beginning about ±80 G from the center of the spectrum. They became weaker with increasing temperature and were not detectable at 60°, cooling as low as -60° did not result in any observable sharpening. We have noted sharp S-resonances in rigid biradicals for J up to 170 G[5] and the weak, broad S-resonances in IIIb would indicate that J can have a considerable range of values.

We have made an estimate of the average exchange ($\bar{J}$) by simulation of the T resonance region as shown in Fig. 1. In hexane $\bar{J}$ increased from 140 G at 20° to 200 G at 60°. Above 60° the biradical begins to decompose while $\bar{J}$ appears to increase further. Below 20° a more gradual change in $\bar{J}$ is observed. In chloroform $\bar{J}$ increased from 250 G at 20° to 350 G (±50 G) at 60° This latter value is essentially the limit for measurement of $\bar{J}$ by simulation of the T resonance region.

The dependence of $\bar{J}$ on temperature and solvent is similar to that observed by Glarum and Marshall[6] for flexible dinitroxides, and combined with the absence of clearly defined S-resonances, indicates a considerable flexibility in IIIb. This

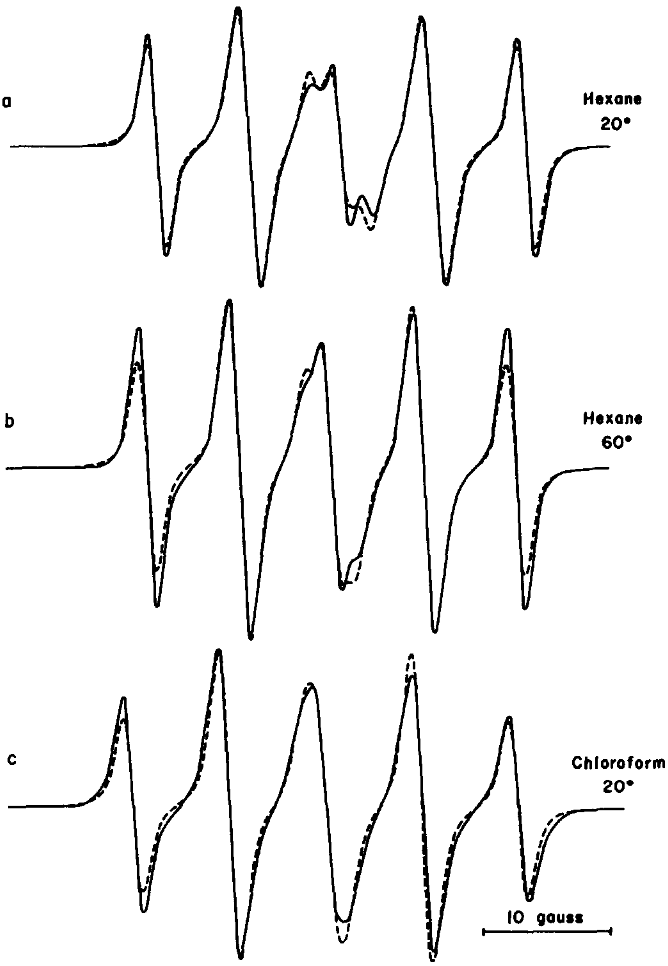


Fig. 1. Typical esr spectra of IIIb. The solid lines are experimental spectra and dotted lines are computer simulations. The simulation program was based on the theoretical work of Lemaire.[8] A first derivative lineshape consisting of 80% Lorentzian and 20% Gaussian character was used. Other parameters were (a) $\underline{a}_1$ = 14.0 G, $\underline{g}_1$ = 2.0058, $\underline{a}_2$ = 15.0 G, $\underline{g}_2$ = 2.0061, $\underline{J}$ = 140 G; (b) $\underline{a}_1$ = 14.0 G, $\underline{g}_1$ = 2.0058, $\underline{a}_2$ = 15.0 G, $\underline{g}_2$ = 2.0061, $\underline{J}$ = 200 G; (c) $\underline{a}_1$ = 14.8 G, $\underline{g}_1$ = 2.0058, $\underline{a}_2$ = 15.5 G, $\underline{g}_2$ = 2.0060, $\underline{J}$ = 250 G. The $\underline{a}$ and $\underline{g}$ values used were those determined experimentally for the mononitroxyl analongs (3-doxyl-5α-cholestane[3] and Ib) under the same conditions of solvent and temperature. The simulations are visual "best fits" to within ±20 G for $\underline{J}$ The samples were prepared at concentrations sufficiently dilute ($\sim 10^{-5}$ molar) to avoid the possibility of intermolecular exchange.

flexibility most likely involves neither the doxyl group at the 3 position nor the A, B or C rings of the steroid nucleus Allinger et al[7] have studied D-ring flexibility in molecules similar to biradical IIIb. By measurement of the dipole moments of several derivatives of D-homoandrostane-3,17a-dione they were able to conclude that the D-ring in the unsubstituted D-homosteroid was essentially rigid. However, introduction of two methyl groups at the 17 position resulted in a flexible D-ring, probably due to a destabilization of the chair conformation by steric interaction of the axial methyls at positions 17 and 18 A similar interaction in biradical IIIb should render the D-ring flexible and account for our observations.

The distance between centers of the N-O bonds in IIIb shows little variation with changes in the conformation of the D-ring. The considerable dependence of $\bar{J}$ on temperature would therefore indicate a much stronger dependence of $\bar{J}$ on molecular conformation than has been supposed in studies of flexible nitroxyl biradicals.[8] This suggests that interpretations of changes in $\bar{J}$ with temperature for flexible biradicals in terms of intramolecular motions should be approached with caution

We are presently studying rigid biradicals in an effort to determine if the major contribution to the exchange in biradicals such as IIIb occurs through space (via direct orbital overlap) or through the multi-sigma bond pathway between the radical subunits.

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