Interaction of the Radical Ion of Chlorpromazine with Deoxyribonucleic Acid

Sir:

Piette, Bulow, and Yamazaki[1] have recently proposed that the positive ion radical of chlorpromazine (cpz^+) may be responsible for the psychotropic activity of this tranquilizer. It occurred to us that because of the chemical and structural similarity of cpz^+ to the mutagenic acridine dye ions (*e.g.*, acridine, proflavine, and acridine orange), cpz^+ might *intercalate* in DNA in the same manner as that described by Lerman[2] for the acridine dyes. In this case, the aromatic molecular plane of cpz^+ would be perpendicular to the DNA helix axis. In this communication, we present strong evidence for this perpendicularity based on paramagnetic resonance. A direct casual relationship between intercalation in DNA (or RNA) and the psychotropic activity of cpz^+ is thus an interesting possibility.

The radical cpz^+ was prepared by persulfate oxidation[3] and added to solutions of calf thymus DNA so that the resultant concentration of nucleotide base pairs was 3×10^{-3} *M*; there was approximately one cpz^+ ion for five base pairs. The solution pH was 5.0. The radical was found to be markedly stabilized by the presence of DNA. Figure 1 gives three spectra obtained with a Varian 35-kMc. spectrometer. Figure 1a gives the "no flow" magnetic resonance of cpz^+ bound to DNA; the line shape is typical of a "polycrystalline" sample and of course bears no resemblance to the known spectrum of cpz^+ in aqueous solution.[3,4,4a] Figure 1b shows the "perpendicular flow" resonance of DNA-bound cpz^+ when the DNA helix axes are oriented perpendicularly to the applied field by flowing the solution through a capillary tube in the resonance cavity (shear rate $\sim$ 3000 sec.$^{-1}$). Figure 1c gives the corresponding "parallel" resonance spectrum.

The observed spectra are readily interpreted in terms of Lerman's intercalation model[2] where the helix axis is perpendicular to the aromatic molecular plane of cpz^+. Consider first the N^{14} hyperfine splitting. The *isotropic* N^{14} hyperfine splitting, *a*, measured from the solution spectrum is *ca.* 6 gauss.[3,4] By analogy with known C^{13} anisotropic π-electron hyperfine interactions,[5] one expects a hyperfine splitting *A* parallel to the π-orbital axis of the aromatic nitrogen atom to be approximately twice the isotropic splitting, and the hyperfine splitting *B* perpendicular to the π-orbital axis to be much less than even the isotropic splitting. These expectations are borne out, for example, by the anisotropy of the N^{14} hyperfine interaction in di-*t*-butyl nitroxide[6] where $A/a = 2.35$ and $B/a = 0.33$. We therefore expect an N^{14} hyperfine splitting of $\sim 2.35 \times 6 = 14$ gauss when the plane of cpz^+ is perpendicular to the applied field. The triplet splittings seen in the parallel flow spectrum (Figure 1c) are *ca.* 17 gauss, whereas no splittings are seen in the perpendicular flow experiments. These are just the results expected if the plane of cpz^+ is perpendicular to the helix axis. The asymmetry in the spectra in Figures 1b and 1c is attributed to incomplete orientation of the DNA helices.

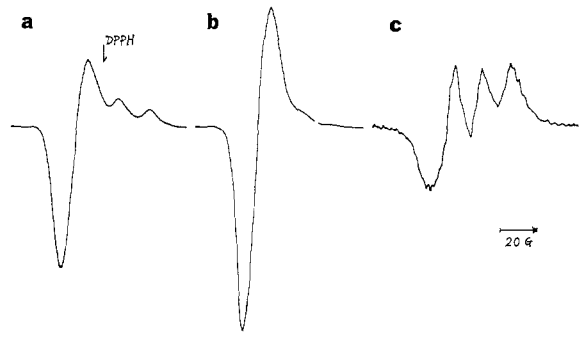

Figure 1. Paramagnetic resonance of the chlorpromazine cation bound to DNA: (a) "no flow" (see text), (b) perpendicular flow, (c) parallel flow.

Our argument favoring perpendicularity of cpz^+ to the helix axis is actually more general than that given above. When $|A| >> |B|$, the hyperfine splittings just detectable in the no flow spectrum of Figure 1a must be equal to $|A|$, irrespective of the relative orientation of cpz^+ to the helix axis. Thus, the observed equality of the splittings in Figures 1a and 1c is a necessary condition for perpendicularity of the cpz^+ plane to the helix axis. A sufficient condition for perpendicularity is that this equality must persist for all laminar shear rates, no matter how high; this is certainly true up to the maximum shear we have used (9000 sec.$^{-1}$).

The observed *g*-factor anisotropies are also in complete agreement with the intercalation geometry and current knowledge of *g*-factors in π-electron radicals.[7] From Figure 1b, $g_\perp$ is estimated to be 2.006, and from Figure 1c, $g_{||}$ is estimated to be 2.003.

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(4a) NOTE ADDED IN PROOF. The resonance of cpz^+ in the presence of *E. coli* transfer RNA is similar to that in Figure 1a, showing that cpz^+ also binds to RNA.
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The Intramolecular Insertion Mechanism of α-Haloneopentyllithium

Sir:

Transformation of neopentylidene iodide to 1,1-dimethylcyclopropane (**2**) by methyllithium[1] is typical of many in which α-elimination has hitherto been presumed to require a divalent carbon intermediate.[2] We

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