Letters

On the Mechanism of Chlorpromazine Cation Radical Decay in Aqueous Solution

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Hammerich and Parker¹ have criticized a mechanism we proposed² for the hydrolysis of chlorpromazine cation radical (CPZ^{•+}) in aqueous buffers to form 50% yields of chlorpromazine sulfoxide (CPZO) and neutral precursor (CPZ). The rate law for the process has the form (1),

$$\frac{d[\text{CPZ}^{\bullet+}]}{dt} = \frac{-A_1[\text{B}^-][\text{CPZ}^{\bullet+}]^2}{([\text{CPZ}] + A_2)[\text{H}^+]} \quad (1)$$

where B⁻ is a buffer anion which acts as a catalyst (e.g., H₂PO₄⁻ or citrate anion) and A₁ and A₂ are constants. Hammerich and Parker were critical of our proposed mechanism [eqns. (2)–(4)] and offered an alternative [(5)–(8)] which has the same observed rate law [eqn. (1)] if certain assumptions are met.

Hammerich and Parker maintain that their mechanism [(5)–(8)] is simpler than ours [(2)–(4)] and is more consistent with other half regeneration mechanisms observed for other systems in nonaqueous solvents.

Apparently Hammerich and Parker were not aware of a paper we published in 1979³ which further discussed the role of water and protons in the reaction. In that work, it was shown that the reaction of CPZ^{•+} with acetate ion is pH independent once the variation of free acetate ion concentration with pH is considered. Furthermore, water need not be involved until the final step in the process. We have also shown more recently⁴ that the pH dependence of phosphate, acetate and several other nucleophiles is completely explained by the variation in concentration of various nucleophilic species (H₂PO₄⁻, HPO₄⁻², etc.). In 1979, the following mechanism was concluded³ for acetate attack of CPZ^{•+}.

Note that there is no pH dependence of the observed rate, since the proton is involved after the rate determining step. It was also pointed out in the same paper that the phosphate/CPZ^{•+} reaction has the same mechanism, except for proton loss from phosphate in the first step. In subsequent work,^{4,5} we showed in detail that the [H⁺] dependence indicated in eqn. (1) for the phosphate case stems solely from its effect on the distribution of HPO₄⁻² and H₂PO₄⁻ concentrations. Note that eqns. (9)–(11) (Ref. 3, Scheme II) are the same as proposed by Hammerich and Parker¹ for 10 methyl phenothiazine cation radical reacting with acetate ion in acetonitrile, except for the involvement of water. We are pleased to see these results confirmed for a different cation radical and solvent.

Hammerich and Parker are correct in their criticism of the intermediate produced in reaction

(2), particularly in light of our subsequent publications. While reactions (2)–(4) are consistent with the rate law available at the time, the anion radical (CPZBOH)^{•−} is a fairly unlikely intermediate. Furthermore, our subsequent work proved that reactions (9)–(11) apply to CPZ^{•+} reactions with acetate, phosphate and citrate, with the pH dependence of the rate stemming from variations in the concentrations of various nucleophilic species with [H⁺]. We should note that bifunctional nucleophiles (of the type R(CO₂[−])₂) can undergo a different series of reactions⁵ in parallel with eqns. (9)–(11), but this sequence is not relevant to the present discussion.

While the mechanism in reactions (9)–(11) is similar to those reported by others^{6,7} for different systems, it would have been extremely speculative to assume that CPZ^{•+} reacted the same way as thianthrene and diphenylanthracene without proof. We studied a different heterocyclic system, a different solvent, different nucleophiles, and both water and protons were involved. N-substituted phenothiazine cation radical reaction products and mechanism are highly dependent on radical structure,^{3,8} nucleophile structure⁹ and solution conditions, as was the case with the systems examined in Hammerich and Parker's work. While it is true that many systems, including CPZ^{•+}, follow a half regeneration mechanism (for certain combinations of radical and nucleophiles) each chemical system has its own qualities, and generalizations are dangerous. The mechanism which Hammerich and Parker criticized was modified by us a year later, but the major points remain. The original conclusions about the reactivity of CPZ^{•+} (as opposed to a dication), the involvement of the buffer as a catalyst, and the detailed kinetic analysis were new to that work, and formed the basis of several subsequent studies.

In conclusion, the mechanism proposed by Hammerich and Parker (reactions (5)–(8)) is not possible given results from our laboratory both published and in press. When the nucleophilic attack of CPZ cation radical is carried out in aqueous solution, the pH and buffer effects are explained by a careful determination of the species involved in the reaction. Most importantly, each radical/nucleophile combination has its own qualities, and the many interesting aspects of the work from both laboratories should not be excessively generalized.

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