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# PROTIUM/DEUTERIUM EXCHANGE IN OXAZINEDIONES

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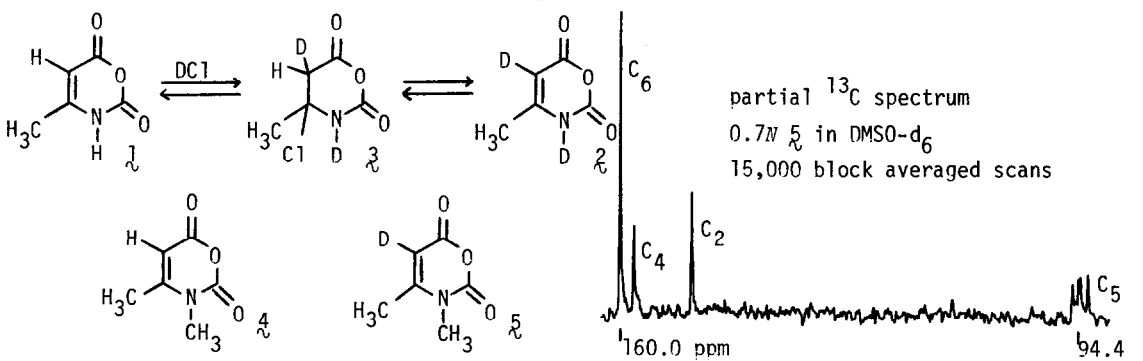
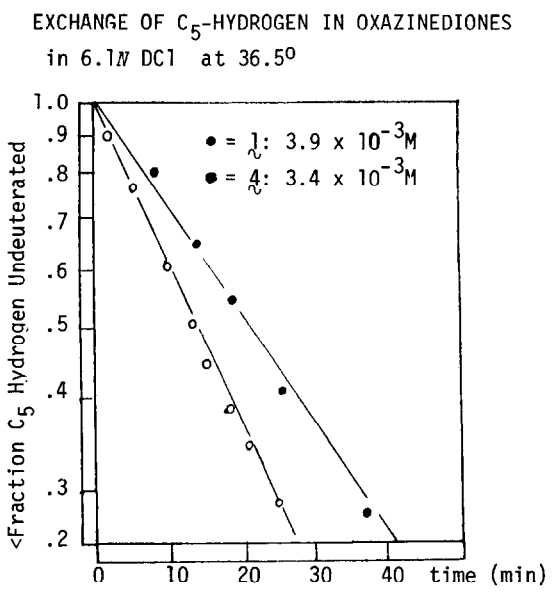
Recent interest in the 1,3-oxazine-2,6-dione ring system[1], an isosteric equivalent of uracil and thymine, as an antimetabolite and anti-leukemic agent[2], prompts us to report on the relative exchangeability of the protons of 4-methyl-1,3-oxazine-2,6-dione, 1, in acidic media, which may have bearing on the mode of action of this compound and its alkylated derivatives.

In the presence of acid, a priori, one would predict rapid exchange at the amidic N-H site, somewhat slower exchange at the vinylogous enolic methyl site, and slow, in any, exchange at the olefinic C-H site. Surprisingly, when 1 was treated with 6.1*N* DCl in $D_2O$, in a reaction monitored by $^1$H-nmr, the olefinic resonance disappeared faster than did the methyl resonance. The $^{13}$C-nmr confirmed this observation, where signals attributable to 3,5-dideuterio-4-methyl oxazinedione 2 ($J_{C_5-D}$ 27.6 Hz) were observed. The N,4-dimethyloxazinedione 4 similarly exchanged its olefinic proton (with first order rate about 50% greater than 1).

Preparative scale amounts of 5-deuterio-oxazinediones 2 (mp 178) and 5 (mp 86-87) were obtained by passage of a stream of DCl through a $D_2O$ solution of 1 or 4, neutralization, and extraction into ethyl acetate. The shown $^{13}$C-nmr of 5 shows a broadened central line in the $C_5$ triplet (94.4 ppm) due to a trace of 4 invisible in the $^1$H-nmr; the $C_5$ of 4 relaxes much more efficiently than the deuterium bonded $C_5$ of 5.






The only reasonable explanation for this exchange phenomenon is rapid addition-elimination via a species such as 3 A simple protonation-deprotonation scheme predicts exchange at the methyl group—unobserved in our system.

That protium-deuterium exchange at the olefinic position occurs readily in such a weakly nucleophilic system as aqueous DCl implies that 1 is a particularly potent Michael acceptor. Structural resemblance of oxazinediones to pyrimidinediones has led to the suggestion that biological activity in these compounds stems from their ability to "become an active site-directed irreversible inhibitor because of their anhydride function"[3], or that rapid hydrolysis of 5-halooxazinediones generates haloacetaldehydes which are the active inhibiting species.[2] In contrast, the present results imply that 1 and 4 (and by analogy other oxazinediones) function as alkylating agents; i.e. the enone and not the anhydride is involved.

Studies on the hydrolysis of oxazinediones[4] have not defined the complete sequence of intermediates on the path (in the case of 1, e.g.) to acetone, ammonia, and two moles of carbon dioxide. It is tempting to suppose that the enhanced rate of protium-deuterium exchange in 4 relative to 1, and the faster rate of aqueous hydrolysis of 4 relative to 1[4b] arise from a common cause; namely addition-elimination to 3 or a protonated equivalent. Confirmation of the propensity of oxazinediones to undergo addition-elimination reactions is shown by the synthesis of 5-halooxazinediones by treatment of the parent ring system with positive halogen.[4a,5]

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References:

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