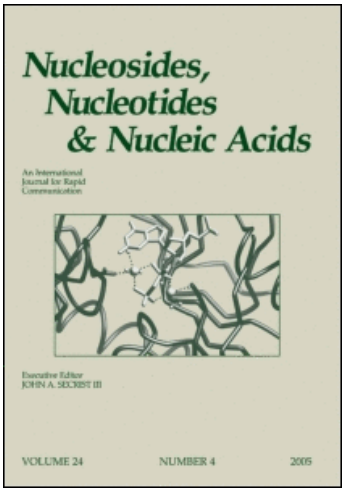

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Reactions of Adenosine with Bromo- and Chloromalonaldehydes in Aqueous Solutions: Kinetics and Mechanism

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REACTIONS OF ADENOSINE WITH BROMO- AND CHLOROMALONALDEHYDES IN AQUEOUS SOLUTIONS: KINETICS AND MECHANISM

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ABSTRACT. The kinetics of the reactions of adenosine with bromo- and chloromalonaldehydes to give ethenoadenosine and ethenoformyladenosine has been studied under various conditions. The rate of disappearance of adenosine and the product distribution seen to be dependent on the halogen on the malonaldehyde. Different mechanistic alternatives are discussed, although definite conclusions can not be drawn.

Halomalonaldehydes react with DNA bases forming etheno and formyletheno adducts, which are known to be mutagenic and fluorescent. The formyletheno adducts are particularly interesting, since their formyl function enables further derivatization.

The pseudo first-order rate constants of disappearance of adenosine was followed as a function of pH and XMA[a] concentration. The formation of εado and εcado was observed, and rate constants of these processes were calculated. The disappearance initially shows a first-order dependence on the aldehyde concentration, but seems to start leveling off at high concentration (~ 50 mM). The dependence of the rate on pH is small, the rate slowly increased as pH increases. The reactions are not particularly fast. Under all conditions, the reactions of BMA are faster than those of CMA. The halogen on MA also seems to have an influence on the effect of pH on the product distribution: with CMA the effect is rather small, whereas with BMA there is a clear change in the preference: at low pH the formation of the εcado is favoured, whereas at pH 6, εado is the predominant product.

[a]Abbreviations: BAA, bromoacetaldehyde; CAA, chloroacetaldehyde; BMA, bromomalonaldehyde; CMA, chloromalonaldehyde; εado, ethenoadenosine; εcado, formylethenoadenosine ; MA,malonaldehyde ; XAA and XMA are for haloacetaldehyde and halomalonaldehyde, respectively.

The reactions of corresponding XAAs were studied for comparative purposes. The only product in these reactions is εado. Similarly to the situation with MAs, the reactions of BAA are faster than those of CAA. Reactions of acetaldehydes are also 20-30 times faster than those of MAs. The reactions show a first-order dependence on the aldehyde concentration. The pH dependency is slightly steeper than with MAs although, a first-order dependence is not observed in this case either.

To study the stability, the rate constants of the disappearance of etheno and formyl-etheno were determined. Both products are rather stable: at pH 4.7, the half-lives of the cleavage of etheno and formyletheno adducts were 25 and 45 days, respectively.

The kinetics data do not allow any strict conclusions about the mechanism of the reaction of XMAs with adenosine. It seems likely, however, that neither of the mechanisms previously suggested for this reaction is correct. In both of them, the etheno adduct is formed by a reaction between corresponding XAA and adenosine, whereas the formyletheno product is formed by the addition of XMAs to adenosine. Nair *et al*[1] proposed an XAA released from the adduct formed upon the initial nucleophilic attack on the XMA. On the other hand[2], MA spontaneously yields some acetaldehydes.

Our data show that the formation of εado in the reactions between adenosine and XMAs is too fast to be explained by the cleavage of the carbinolamine intermediate. The reaction could also not be expected to follow first-order kinetics or show a dependence on XMA concentration. As further evidence, N^6-formyl adenosine, which should be formed upon the release of XAA, and which appears to be stable, was not observed among the reaction products. Spontaneous cleavage of XMAs to XAAs seems equally unlikely: no cleavage of XMAs in buffer solutions in 5 days was observed by NMR. In the case adenosine catalyses the cleavage of XMAs to corresponding XAAs, clear first-order could not be expected either, but the process would consist of two consecutive reactions.

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