

Methylase Models: Intramolecular Alkylation of a Phenol by an Adenosyl Sulphonium Salt

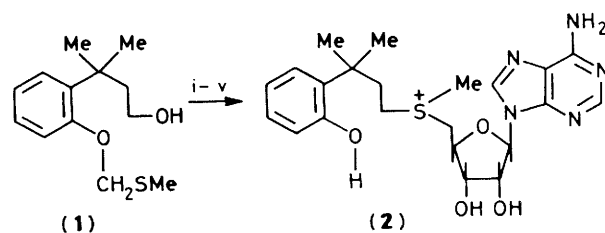
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The newly synthesized adenosylsulphonium ion, (2), undergoes a facile ring closure reaction in aqueous oxanion buffers; in contrast, amine buffers effect an intermolecular dealkylation in competition with the lyate reaction.

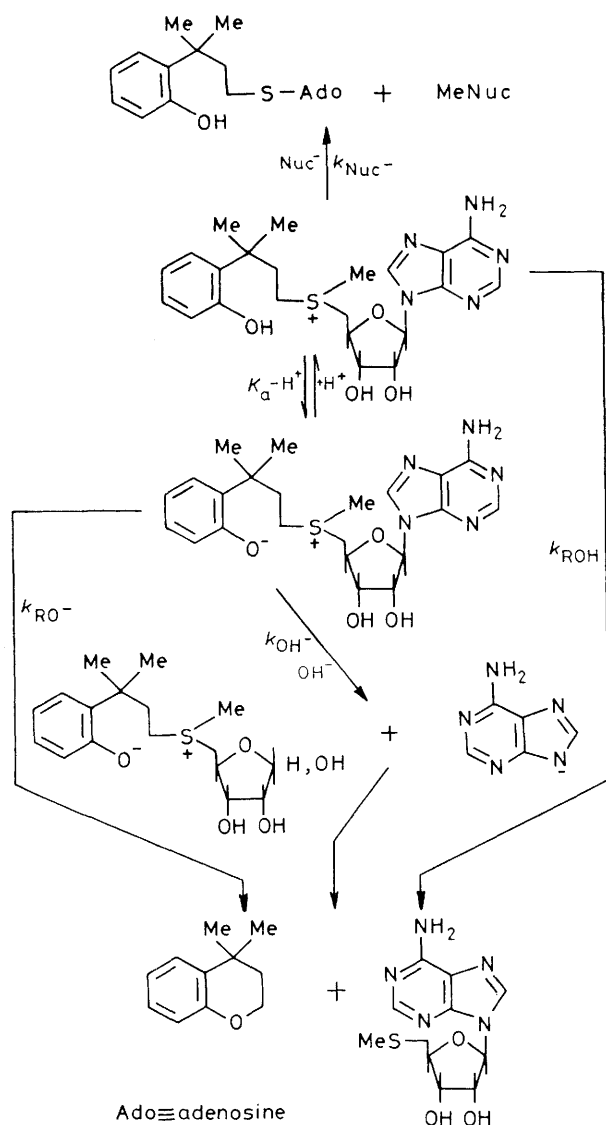
We have previously shown that the enzyme-catalysed methylation of pyro-catecholamines proceeds with inversion of configuration at the methyl carbon atom,¹ in agreement with a random, sequential kinetic mechanism.² In related model reactions, we have demonstrated that intramolecular alcohol³ and phenol⁴ alkylations by alkylmethyl-*p*-nitrophenylsulphonium salts are catalysed by general bases. We now report the extension of these model reaction studies to include alkylmethyl-5'-adenosylsulphonium salts [*e.g.* (2)]. In this case, the leaving group 5'-deoxy-5'-methylthioadenosine (MTA), is the same as for enzyme-catalysed aminopropyl transfer (*e.g.* spermidine synthase and spermine synthase).⁵ It is also electronically similar to *S*-adenosylhomocysteine, the leaving group in enzyme-catalysed methyl transfer.⁵ The present work represents the first example of a model reaction for enzyme-catalysed alkyl transfer, amenable to detailed kinetic studies, in which the leaving group is the biochemically relevant 5'-thioadenosine, MTA.

The desired substrate, (2), is obtained as shown in Scheme 1, starting with the *o*-substituted phenyl ether, (1).⁴ The general synthetic method follows procedures recently developed in our laboratory for the synthesis of complex adenosine-5'-thioethers.^{6,7} The reaction of (2) in aqueous buffers can be shown to proceed in a manner similar to that previously described with *p*-nitrothioanisole as the leaving group.^{3,4} Thus, (2) reacts at 40 °C over the range of pH 4–10, using acetate, phosphate, and carbonate buffers, to yield MTA and 4,4-



Scheme 1. Reagents and conditions: i, *p*-MeC₆H₄SO₂Cl, pyridine, 0 °C, 10 h; ii, KSAc, acetone, reflux, 4 h; iii, 5'-deoxy-5'-chloro-adenosine, Me₂SO, NaOH, ambient temp., 4 h, under N₂; iv, MeI, HCO₂H; v, ion exchange on Dowex 1, ClO₄⁻ form.

dimethylchroman. At pH > 10, adenine is observed in addition to MTA, as a result of a hydroxide-catalysed fragmentation. This reaction of adenosylsulphonium compounds and hydroxide is well known.⁸ Product analysis of the reaction solutions was carried out by h.p.l.c. using reverse-phase (Whatman ODS-2) chromatography; flow rate 1.0 ml min⁻¹. With 35% aqueous methanol as the mobile phase, adenine (*t_r* 10.2 min) and MTA (*t_r* 20.1 min) were easily quantitated, and 4,4-dimethylchroman (*t_r* 28.2 min) was determined using 70% aqueous methanol as the mobile phase. The compound [Me-¹⁴C](2) was synthesized, and its reaction studied in both oxanion (*e.g.* carbonate, phosphate, and acetate) and amine



Scheme 2

(e.g. *N*-methylmorpholine) buffers. The reactions were maintained at 40 °C for a period of at least 10 $t_{1/2}$, and then analysed for products by h.p.l.c. The reactions carried out in oxyanion buffers gave rise to [*Me*-¹⁴C]-MTA; no other radioactive product was observed. In contrast, the reactions carried out in amine buffers gave rise not only to [*Me*-¹⁴C]-MTA, but also to a radioactive material eluting very early on reverse-phase h.p.l.c.; t_R 3 min. These data are consistent with the formation of both MTA and an *N,N*-dimethylmorpholinium salt in the presence of the amine buffer. This result is in accord with our previous, more extensive studies on oxyanion-mediated general base catalysis vs. amine-mediated nucleophilic dealkylation at sp^3 carbon. A reaction scheme consistent with these results is shown in Scheme 2. Qualitatively, these data suggest that, in spite of a poorer dialkyl thioether leaving group, model sulphonium salts such as (2) react similarly to sulphonium salts in which *p*-nitrothioanisole is the leaving group.

This research was supported by a grant from the United States Public Health Service.

Received, 15th March 1982; Com. 292

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