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Migration of Methyl Groups between Aliphatic Amines in Water

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Glycine undergoes spontaneous decarboxylation in dilute aqueous solution at elevated temperatures to form methylamine.[1] During that process, we noticed the appearance of dimethylamine and trimethylamine in smaller amounts that increased gradually with time. These observations suggested the existence of disproportionation reactions of methylamines in water, for which there appears to be no direct precedent in the literature.[2] Here, we show that methyl groups migrate between aliphatic amines when they are incubated with their conjugate acids at elevated temperatures and that competition by water as a methyl acceptor is negligible. Half-titrated dimethylamine (0.02 M), for example, yields trimethylamine and methylamine in equal amounts (Scheme 1a), with no appearance of methanol. In addition to the apparent novelty of these reactions, these results are of interest in relation to the mechanism of methyl transfer in biological systems.

To determine the rates of methyl transfer between amines, we incubated aqueous amines, half-titrated with HCl, for various time intervals at high temperatures in stainless-steel bombs lined with PTFE After cooling, the reaction mixtures were removed and analyzed by proton NMR, using added pyrazine as an integration standard. Every member of the methylamine series was found to yield other members of the methylamine series. At each of a series of temperatures, the rate of disappearance of the starting material followed satisfactory first-order kinetics and yielded a linear Arrhenius plot when the logarithm of the initial rate of reaction was plotted as a function of the reciprocal of the absolute temperature. When the ratio of the protonated to the unprotonated species of mono-, di-, or trimethylamine was held constant but the total concentration of that amine varied, the initial rate of disappearance of the starting material was found to vary in proportion to the square of its concentration, as expected for a bimolecular reaction involving two molecules of amine (see for example Figure 1a).

When the total concentration of amine was held constant, and the rate of reaction was examined as a function of changing pH using the amine itself as the buffer,[3] the initial rate of appearance of the products was found to reach a maximum when the conjugate acid and the conjugate base were present at equivalent concentrations. Near this equivalence point, the rate of reaction varied with pH as expected for a second-order reaction between the protonated and the unprotonated species, as shown by the solid line in Figure 1a. At pH values much below this equivalence point, product formation continued at a much slower rate (Figure 1b). The persistence of reactivity at low pH, which has also been reported for other transalkylation reactions,[4,5] suggests that water may be acting as a general base catalyst.

In experiments in which the tetramethylammonium ion (Me_4N^+) was employed as the methyl donor and dimethylamine was the acceptor, trimethylamine was formed at an initial rate proportional to the concentrations of each of these two reactants. When this reaction was followed as a function of increasing pH, using dimethylamine itself as a buffer,[3] its initial rate of disappearance became half-maximal at the pH value where dimethylamine is half-converted to its uncharged form, approaching a constant value when dimethylamine is fully converted to its uncharged form but Me_4N^+ retains its positive charge (Figure 1c). Activation parameters based on the resulting Arrhenius plots are shown in Table 1.

Scheme 1

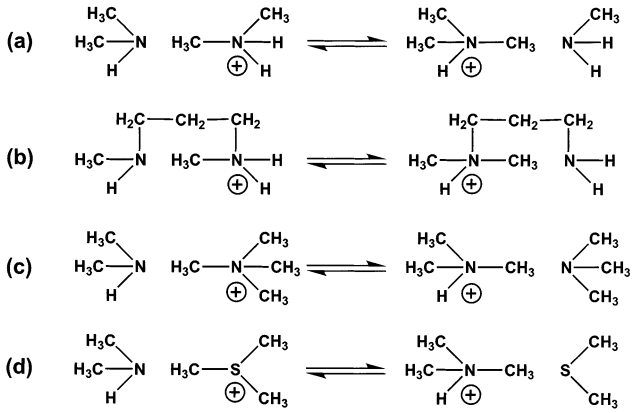

Table 1. Extrapolated Rate Constants and Activation Parameters from Arrhenius Plots, Based on 10 or More Rate Constants Obtained over a Range >50 °C, with Estimated Errors in $\Delta H^{\ddagger}$ and $T\Delta S^{\ddagger}$ of ±1.5 kcal/mol

	k (25 °C) ($M^{-1}\,s^{-1}$)	$\Delta H^{\ddagger}$, kcal/mol	$T\Delta S^{\ddagger}$, kcal/mol
dimethylamine + dimethylammonium	4×10^{-13}	25.9	−8.5
N,*N*′-dimethyl-1,3-propanediamine (s^{-1})	5×10^{-12}	30.4	−2.5
dimethylamine + tetramethylammonium	1.9×10^{-12}	30.1	−3.4
dimethylamine + trimethylsulfonium	1.5×10^{-8}	22.2	−5.9

Under similar conditions, methyl groups were also found to migrate between the nitrogen atoms of *N*,*N*′-dimethyl-1,3-propanediamine in a first-order process, forming an equilibrium mixture containing nearly equivalent concentrations of 3-(dimethylamino)-propylamine and *N*,*N*′-dimethyl-1,3-propanediamine. At amine concentrations up to ∼1 M, this reaction (and its reverse) proceeded more rapidly than the bimolecular reactions described above, due to a more favorable entropy of activation (Table 1). This intramolecular reaction exhibits a larger $\Delta H^{\ddagger}$ that may reflect ring strain in the six-membered cyclic transition state.[6]

Biological reactions that involve the transfer of acyl or glycosyl groups often involve the formation of discrete intermediates that differ substantially in structure from the substrates and products. Such reactions can be accelerated by enzyme active sites that have or can easily adopt structures with binding determinants that are complementary to the structures of intermediate forms of the substrate that approach the transition state in structure, forming new H-bonds and other polar interactions that were not present in the ground-state enzyme−substrate complex.[7] Lacking such discrete intermediates, methyl-transfer reactions may be relatively difficult to catalyze except by desolvation[8,9] and approximation[5] effects that

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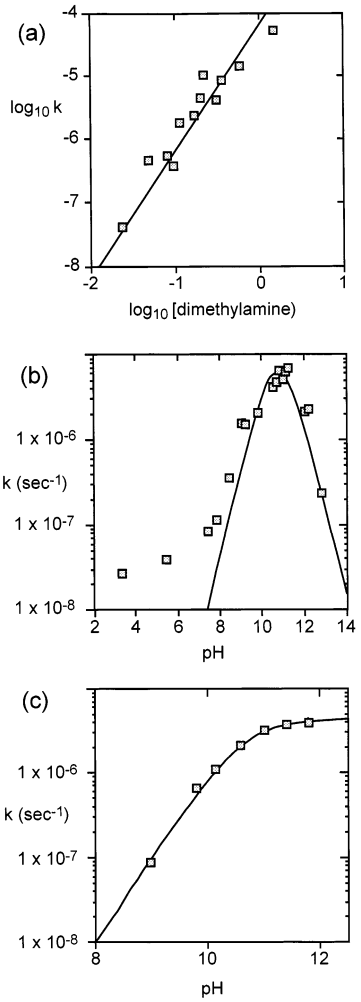

Figure 1. (a) Initial rate of conversion of half-titrated dimethylamine to methylamine and trimethylamine at 226 °C, plotted as a logarithmic function of changing initial concentration of dimethylamine. The line (slope = 2) is calculated for a reaction that is of the second order with respect to the total concentration of amine (Scheme 1a). (b) Initial rate of the same reaction at 226 °C, at a fixed total concentration of dimethylamine (0.5 M), plotted as a function of changing pH.[3] The line represents the behavior expected for the reaction shown in Scheme 1a. (c) Initial rate of reaction of dimethylamine (0.6 M) with tetramethylammonium chloride (0.25 M) at 171 °C, plotted as a function of effective pH.[3] The line represents the behavior expected for the reaction shown in Scheme 1c.

place the reactants in a position conducive to reaction. There are probably limits to the rate enhancements that can be achieved by these "physical" effects, so that the inherent reactivity of the substrate is of special importance.

If ammonium ions are capable of methyl transfer in water, then why are reactions that involve methyl transfer from ammonium ions[9] less common than reactions using S-adenosylmethionine (SAM) as a methyl donor?[10] To make a direct comparison of the inherent reactivities, we determined the rates of reaction of the trimethylsulfonium ion[11] with the tetramethylammonium ion as donors to a common acceptor in dilute aqueous solution. With dimethylamine as the acceptor, trimethylsulfonium ion was found to be $\sim 10^4$-fold more reactive than the tetramethylammonium ion at ambient temperature (Table 1). When the second-order rate constant for this trimethylsulfonium reaction (1.5×10^{-8} M^{-1} s^{-1}) is compared with the second-order rate constant (k_{cat}/K_m) for reaction of histamine with the SAM complex of guinea pig histamine *N*-methyl transferase ($\sim 7 \times 10^5$ M^{-1} s^{-1}),[12] this enzyme is seen to enhance the rate of reaction with a nitrogen nucleophile by a factor of 5×10^{13}.[13] Catechol O-methyltransferase has been shown to enhance the rate of methyl transfer from SAM to an oxygen nucleophile by an even greater factor, approximately 10^{17}.[5] Thus, enzymes reinforce the inherently superior reactivity of sulfonium compounds, making large contributions to the reactivity of SAM as judged by the rate enhancements that they produce.

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(13) It may be worth noting that the rate enhancement produced by histamine *N*-methyltransferase is similar, both numerically and in its detailed thermodynamic origins, to the rate enhancement produced by yeast hexokinase, whose action is probably based on similar principles (Sigmon, K. A.; Wolfenden, R., unpublished observations).

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