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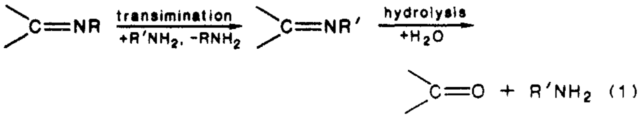
Intramolecular Base Catalysis in *N*-Benzylideneaniline Transimination by (Dimethylamino)alkylamines in Methanol[1]

Summary: The internal tertiary amino group in 2-(dimethylamino)ethylamine and 3-(dimethylamino)propylamine catalyzes proton transfer between nitrogen atoms of the *gem*-diamines formed in the course of the title reaction.

Sir: Recently, Okuyama et al.[2] reported that certain groups of amines catalyze the hydrolysis of *N*-(2-methoxybenzylidene)-2-methoxyethylamine through transimination and that this catalysis is very efficient when bifunctional amines carrying internal tertiary amino groups are used. This latter behavior was ascribed to intramolecular acid–base catalysis of (i) the initial transimination step and of (ii) the hydrolysis of the intermediate Schiff base formed (eq 1). Okuyama's results prompt us to report that we have observed similar intramolecular base catalysis when studying transimination of *N*-benzylideneaniline (**1**) by (dimethylamino)alkylamines *directly* in methanol (eq 2).

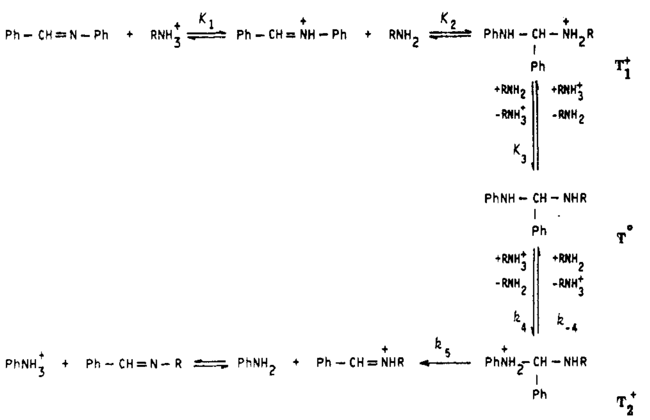


$$\mathrm{PhCH{=}NPh + H_2N(CH_2)_nNMe_2 \rightarrow PhCH{=}N(CH_2)_nNMe_2 + PhNH_2} \quad (2)$$

$$n = 2 \text{ or } 3$$

General catalysis of the Schiff base transimination reaction by acids and bases has been attributed to their promotion of the partly rate-limiting proton transfer between the two nitrogen atoms of the *gem*-diamine intermediate.[3] Despite the gem position of the two nitrogen atoms, proton transfer cannot occur intramolecularly by direct jump, but usually requires the intervention of a base, or acid, with intermediate formation of T^0 or T^{2+}, the neutral or diprotonated forms of the *gem*-diamine. When proton transfers from or to nitrogen atoms are fast enough, it is asssumed that the step which limits the rate is that which corresponds to the attack or expulsion of the less basic amine molecule. Because it is also expected that the partly rate-limiting proton transfer is that immediately adjacent to the attack or expulsion of the less basic amine,[3,4] and because the strong acidity of T^{2+} should make the acid-catalyzed pathway inefficient, the rate should depend both on the protonation/deprotonation step to/from T_2^+ and on aniline cleavage from the same ionic species (Scheme I).

Scheme I



N-Benzylideneaniline transimination by propylamine (**2a**), 2-methoxyethylamine (**2b**), 2-(dimethylamino)ethylamine (**2c**), and 3-(dimethylamino)propylamine (**2d**) was followed by UV spectroscopy, the absorbance decrease at 270 nm being monitored in methanol containing different buffer concentrations of free amine ($\mathrm{RNH_2}$) and of the corresponding conjugate acid ($\mathrm{RNH_3^+}$).[5] As expected from the above mechanism, the observed first-order rate constants, k_ψ, are linearly dependent on $[\mathrm{RNH_3^+}]$ at constant amine concentration. In the case of monofunctional amino compounds, **2a** and **2b**, the second-order rate constants k_{II} ($k_\psi/[\mathrm{RNH_3^+}]$) also depend on free amine concentration, with a leveling-off effect at high concentration (Figure 1). Since free amine concentration effects should cancel out if proton transfer were fast relative to aniline expulsion, this behavior can easily be accounted for by base catalysis of the T_1^+ to T_2^+ process by the amine itself. According to the above mechanism, k_ψ can be expressed by eq 3, and the second-order rate constant can be written as in eq 4. By plotting $1/k_{\mathrm{II}}$ vs. $1/[\mathrm{RNH_2}]$, excellent linear relationships are observed with intercepts corresponding to $1/(k_{\mathrm{II}})_{\max}$ (the reciprocal of the asymptotic second-order rate constant at high amine concentration, i.e., when the rate is completely controlled by aniline expulsion). The ratios between slopes and intercepts give k_5/k_{-4} values of 0.060 M and 0.105 M for **2a** and **2b**, respectively.

$$k_\psi = \frac{K_1K_2K_3k_4k_5[\mathrm{RNH_3^+}][\mathrm{RNH_2}]}{k_{-4}[\mathrm{RNH_2}] + k_5} = k_{\mathrm{II}}[\mathrm{RNH_3^+}] \quad (3)$$

$$\frac{1}{k_{\mathrm{II}}} = \frac{k_{-4}}{K_1K_2K_3k_4k_5} + \frac{1}{K_1K_2K_3k_4[\mathrm{RNH_2}]} = \frac{1}{(k_{\mathrm{II}})_{\max}} + \frac{k_5}{k_{-4}(k_{\mathrm{II}})_{\max}[\mathrm{RNH_2}]} \quad (4)$$

In contrast to monofunctional amino compounds, the second-order rate constants k_{II} were found to be independent of amine concentration in the case of **2c** and **2d**, i.e., for amines carrying a tertiary group (Figure 1). Moreover, it is noteworthy that the mean value observed for **2c** (Table I), whose pK_a is very close to that of **2b**, does not differ significantly from the asymptotic maximum

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[1] Work presented at the 4th International Conference on Mechanisms of Reactions in Solution of the Royal Society of Chemistry, Canterbury, U.K., July 7, 1986.

[2] Okuyama, T.; Nagamatsu, H.; Kitano, M.; Fueno, T. *J. Org. Chem.* **1986**, *51*, 1516–1521.

[3] (a) Hogg, J. L.; Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 4772–4778. (b) Fischer, H.; DeCandis, F. X.; Ogden, S. D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 1340–1347.

[4] Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 826–831.

[5] At 270 nm, absorbance is essentially due to *N*-benzylideneaniline absorption; final absorbance values correspond to the products formed by complete transimination.

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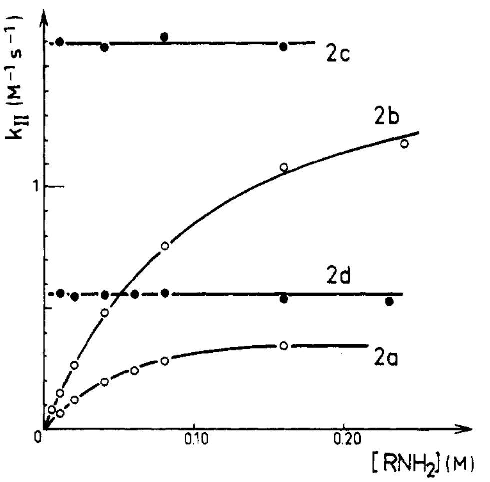


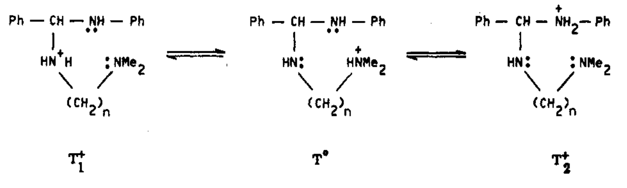
Figure 1. Amine concentration effect on the second-order rate constant (first order with respect to the substrate and to ammonium ion) for N-benzylideneaniline transimination by monofunctional amines (○) and (dimethylamino)alkylamines (●) (25 °C) [μ = 0.08 M (NMe$_4$Br); because of a slight downward curvature of the plots of k_ψ vs. [RNH$_3^+$] (RNH$_3^+$NO$_2^-$), k_{II} values were extrapolated to zero ammonium ion concentration].

Table I. Asymptotic Rate Constants at High Amine Concentration or Amine Concentration-Independent Rate Constants for Transimination of N-Benzylideneaniline by Monofunctional and Bifunctional Amines (25 °C)

compound	pK_a[a]	$(k_{II})_{max}$[b] (M^{-1} s^{-1})	k_{II}[b] (M^{-1} s^{-1})
propylamine (**2a**)	12.20	0.488 ± 0.020	
2-methoxyethylamine (**2b**)	11.52	1.75 ± 0.15	
2-(dimethylamino)ethylamine (**2c**)	11.60		1.59 ± 0.03
3-(dimethylamino)propylamine (**2d**)	12.04		0.55 ± 0.03

[a] In methanol; see ref 6. [b] The listed uncertainties are estimated error limits (about twice the standard deviations).

Scheme II



value observed for **2b** at high concentration of base. This clearly shows that the dialkylamino group makes the proton transfer fast by intramolecular base catalysis (Scheme II); the rate of transimination of **1** by **2c** and **2d** is wholly controlled by the expulsion of aniline and is similar to that observed for monofunctional amines when base concentration is so high that intermolecular proton transfer no longer controls the rate of the overall reaction. Moreover, when k_{II} values from Table I for **2c** and **2d** are plotted vs. pK_a, together with $(k_{II})_{max}$ for **2a** and **2b**, a rough straight line with a slope close to unity is observed. This is in agreement with what expected from a rate-limiting expulsion step with an early transition state.

It is noteworthy that the identity of the overall rate constants for amines of same basicity when proton transfer is fast—whether proton transfer occurs intramolecularly or intermolecularly—means that proton transfer and C–N bond cleavage are not energetically coupled processes, despite the good leaving group ability of aniline. C–N bond cleavage requires full protonation of nitrogen, in contrast to the C–O bond cleavage which, in the case of many tetrahedral intermediates,[7] is coupled with proton transfer.

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(6) The pK_a values of the RNH$_3^+$ ions were measured by UV spectroscopy with 4-nitrophenol as indicator [pK_a = 11.2 (Clare, B. W.; Cook, D.; Ko, E. C. F.; Mac, Y. C.; Parker, A. J. *J. Am. Chem. Soc.* **1966**, *88*, 1911–1916)].

(7) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; Chapter 3, Section D; Chapter 10, Section B. (b) Jencks, W. P. *Prog. Phys. Org. Chem.* **1964**, *2*, 63–128. (c) Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459. (d) Funderburk, L. H.; Jencks, W. P. *Ibid.* **1978**, *100*, 6708–6714.

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Novel Products from the Reaction of Tris(p-methoxyphenyl)phosphine with Neopentyl Iodide

Summary: The title reaction gave a mixture of eight phosphonium salts. Intermediacy of phosphonium inner salts, $\geqslant$P$^+$C$_6$H$_4$O$^-$-*p*, is suggested for their formation.

Sir: Recently, we have observed that in a reaction between tris(*p*-methoxyphenyl)phosphine and neopentyl iodide eight phosphonium salts were formed (1–8, see Table I). The reaction was carried out by using 3.52 g (0.01 mol) of the phosphine with 3.96 g (0.02 mol) of Me$_3$CCH$_2$I under N$_2$ at 150 °C for 18 h. Addition of 100 mL of ethyl acetate and 100 mL of anhydrous ether precipitated a mixture (4.3 g) of phosphonium salts. Their structures were assigned, without separation, from the ^{31}P and ^{1}H NMR spectra of the mixture. The ^{31}P spectrum showed four absorptions in the chemical shift region of neopentylphosphonium salts and four corresponding to the methylphosphonium salts. The ^{1}H NMR spectrum corroborated the structures of **1**, **2**, **5**, and **6** whose absorptions were clearly observed due to their higher concentrations in the mixture. The presence of methyltris(*p*-methoxyphenyl)phosphonium iodide in the mixture was established by comparison of its NMR data to that of a pure sample. Table I lists the spectral data and the approximate molar ratios of phosphonium salts estimated from the ^{31}P NMR spectrum.

The FAB mass spectrum of the mixture, run in glycerol–thioglycerol–methylene chloride as matrix, showed main peaks corresponding to the masses of the parent phosphonium ions: 367 (**5**), 423 (**1**, **6**), 479 (**2**, **7**), 535 (**3**, **8**), and 591 (**4**). Next in intensity were peaks at masses 353, 409, 465, and 521 due to the phosphonium species in which the methyl of a OCH$_3$ group has been substituted by H from matrix. There were three more peaks of much lower intensity at masses 337, 393, and 449. They are apparently due to the phosphonium ions in which a *p*-methoxy group has been replaced by H.

Apparently, quaternization of phosphorus in **1** activates the *p*-methoxy groups on the phenyl rings making them prone to nucleophilic attack by the unreacted phosphine to give methyltris(*p*-methoxyphenyl)phosphonium salt (**5**)

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