

# Noncatalytic mono-*N*-methylation of aniline in supercritical methanol: the kinetics and acid/base effect†

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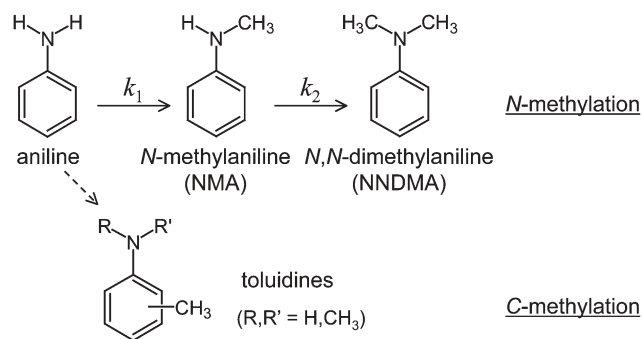
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Aniline is easily *N*-methylated in supercritical methanol without catalyst at 350 °C and 0.237 g cm<sup>-3</sup> to give mono-*N*-methylaniline with high selectivity, and the reaction rate is increased by a small amount of base (LiOH, NaOH, KOH, and CH<sub>3</sub>ONa), indicating a difference in the reaction mechanism from the ordinary acid-catalyzed one.

*N*-methylanilines are useful chemical intermediates for dyes and pharmaceuticals, and are industrially synthesized by a vapor-phase methylation of aniline with methanol.<sup>1,2</sup> In the conventional method, however, strong acid catalyst is indispensable for the production of methyl cation as an electrophile, and the selectivity of mono-*N*-methylaniline (NMA) is significantly lowered by the side-reactions, a further *N*-methylation to *N,N*-dimethylaniline (NNDMA) and a *C*-methylation to toluidines, as shown in Scheme 1.

In supercritical methanol ( $T_C = 239$  °C,  $P_C = 8.1$  MPa, and  $\rho_C = 0.272$  g cm<sup>-3</sup>), by contrast, aniline is readily *N*-methylated without catalyst to give NMA with high selectivity.<sup>3</sup> The supercritical *N*-methylation can provide a simple and clean process by eliminating the problems associated with the use of acid catalyst and the separation of the byproducts. It has been rarely explored, however, why the supercritical methylation occurs in the absence



Scheme 1 Methylation of aniline and the rate constants involved.

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of acid catalyst. We thus try to elucidate the reaction mechanism by focusing on the difference between the noncatalytic *N*-methylation in supercritical methanol and the ordinary acid-catalyzed one. In this paper, we perform a kinetic analysis for the supercritical reaction in order to explain the high selectivity of NMA. We also report an interesting acid/base effect on the reaction rate: the supercritical *N*-methylation is accelerated not by acid but by base. A new reaction mechanism is proposed that can account for the experimental results.

Methanol solution of aniline was prepared at a concentration of 50 mM ( $M \equiv \text{mol dm}^{-3}$ ). The solution (3.18 cm<sup>3</sup>) was packed into a SUS-316 stainless batch reactor with an inner volume of 10.6 cm<sup>3</sup>. The air in the reactor was purged with argon. The sample was heated in a molten salt bath (Thomas Kagaku, Celsius-600H) at 350 °C. At the supercritical condition, the density of the sample solution is 0.237 g cm<sup>-3</sup>, and the pressure is estimated to be 22.8 MPa from the *PVT* data of pure methanol.<sup>4</sup> After a given reaction time (20 min to 6.0 h), the sample was quickly cooled in a water bath. The yields and selectivities of the products were determined by GC-MS and GC-FID (Hewlett Packard, HP-6890). The selectivity of NMA is defined as: (selectivity of NMA) = (yield of NMA)/(total yield of NMA and NNDMA)  $\times$  100 (%).

Fig. 1 shows the reaction time dependence of the concentrations of aniline, NMA, and NNDMA in the supercritical *N*-methylation without catalyst. Here we note that no toluidines were formed in this reaction. The concentration of aniline monotonically decreases with reaction time down to 1 mM at 4 h, while the yield of NMA shows a rapid increase with reaction time up to 78% at 2 h. Since

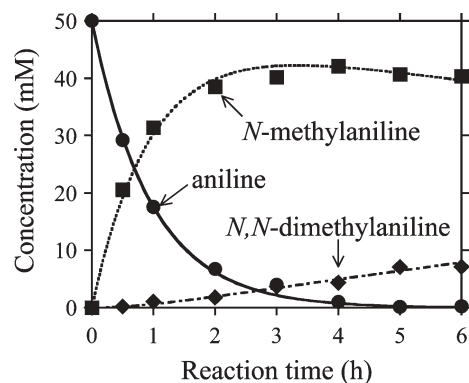


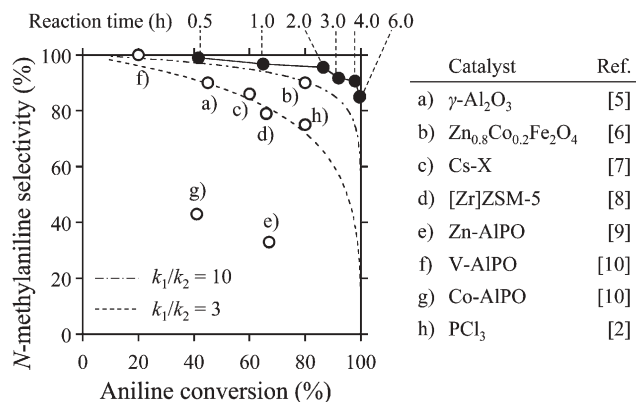
Fig. 1 Reaction time dependence of the concentrations of aniline (●), *N*-methylaniline (■), and *N,N*-dimethylaniline (◆) in supercritical methanol without catalyst at 350 °C and 0.237 g cm<sup>-3</sup>.

the yield of NNDMA at 2 h is only 3%, the selectivity of NMA at the reaction time is higher than 95%. At reaction times longer than 4 h, however, the yield of NMA shows a slow decrease because of the further *N*-methylation to NNDMA, resulting in a decrease in the NMA selectivity with reaction time.

In Fig. 2, the selectivity of NMA in the supercritical methylation is compared with those in acid-catalyzed reactions in the literature.<sup>2,5–10</sup> The NMA selectivity is plotted against the conversion of aniline. The higher the aniline conversion, the lower the NMA selectivity in general. In the supercritical *N*-methylation, however, both the aniline conversion and the NMA selectivity are sufficiently high when the reaction time is 2 to 4 h, in comparison with those in the conventional reactions with acid catalyst.<sup>11</sup>

The high selectivity of NMA indicates that the *N*-methylation rate constant of aniline to NMA ( $k_1$  in Scheme 1) is much larger than that of NMA to NNDMA ( $k_2$ ). The pseudo-first-order rate constants  $k_1$  and  $k_2$  were determined from the least-squares fitting of the time profile shown in Fig. 1. The kinetic analysis revealed that  $k_1 = 1.00 \pm 0.07 \text{ h}^{-1}$  is 28 times as large as  $k_2 = 0.036 \pm 0.06 \text{ h}^{-1}$ . The  $k_1/k_2$  ratio in the supercritical reaction (28) is markedly larger than those in acid-catalyzed reactions (typically *ca.* 3, and 10 at the largest, as shown in Fig. 2).<sup>12</sup>

We further investigate the acid/base effect on the supercritical *N*-methylation. Here we added HCl, H<sub>2</sub>SO<sub>4</sub>, LiOH, NaOH, KOH, and NaOCH<sub>3</sub> into the sample solution at a concentration of 0.5 mM, where a molar ratio of acid/base to aniline is 1 : 100. The effects on the rate constant  $k_1$ , the selectivity of NMA at 1 h, and the total yield of toluidines at 1 h are summarized in Table 1



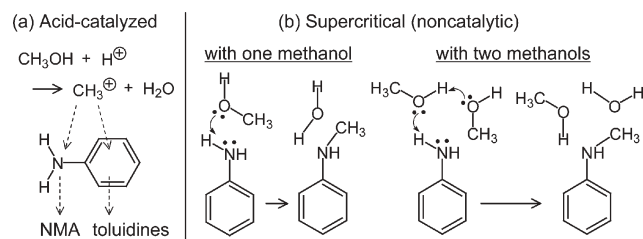
**Fig. 2** Selectivity of *N*-methylaniline vs. conversion of aniline: the values for the noncatalytic supercritical *N*-methylation at various reaction times (●) are compared with those for acid-catalyzed reactions in the literature (○). The dotted lines are the theoretical curves at  $k_1/k_2 = 10$  and 3.

**Table 1** Acid/base effects (0.5 mM) on the rate constant  $k_1$ , the selectivity of *N*-methylaniline at 1 h, and the yield of toluidines at 1 h

Acid/base	$k_1$ ( $\text{h}^{-1}$ )	<i>N</i> -methylaniline selectivity (%)	Toluidines yield (%)
HCl	$1.10 \pm 0.02$	89.8	1.4
H <sub>2</sub> SO <sub>4</sub>	$0.85 \pm 0.01$	93.0	1.7
No catalyst	$1.03 \pm 0.03$	96.8	0
LiOH	$2.29 \pm 0.05$	98.7	0
NaOH	$2.23 \pm 0.16$	98.6	0
KOH	$2.08 \pm 0.05$	97.8	0
NaOCH <sub>3</sub>	$2.34 \pm 0.10$	98.2	0

(see ESI for more and detailed data). Surprisingly, the rate constant  $k_1$  is increased by base,<sup>13</sup> whereas it is unaffected or rather reduced by acid, indicating a difference in the reaction mechanism from the ordinary acid-catalyzed one. The selectivity of NMA is also enhanced by base, and no toluidines are produced in the base-catalyzed reaction. A small amount of base, therefore, can improve the highly selective mono-*N*-methylation of aniline in supercritical methanol. We further found, as shown in the ESI in detail, that the higher the concentration of base, the larger the  $k_1$ , at least up to  $4.8 \text{ h}^{-1}$  at 2.5 mM with negligible decrease in the NMA selectivity. In the presence of acid, on the other hand, the selectivity of NMA is reduced, and toluidines are by-produced, as in conventional acid-catalyzed reactions.

For explanation of the results above, *i.e.*, (i) noncatalytic reaction, (ii) no toluidine formation, (iii) high NMA selectivity, and (iv) acceleration by base instead of acid, we propose a new reaction mechanism for the supercritical *N*-methylation, as described in Fig. 3 in comparison with that for the acid-catalyzed one. The main difference between the two mechanisms is “which of the two elementary processes plays an important role in the *N*-methylation: an electrophilic attack of a methyl group or a dissociation of an N–H bond”. In the conventional reaction mechanism, acid catalyst is necessary for the production of methyl cation as an electrophile.<sup>14</sup> The methyl cation attacks not only the amino nitrogen but also the aromatic ring of aniline, yielding toluidines as well as NMA. Under the electrophilic substitution mechanism, NMA is readily *N*-methylated to NNDMA, because an electron-donating ability of the methyl group of NMA promotes a further electrophilic attack onto the amino nitrogen, leading to the low selectivity of NMA. On the other hand, the supercritical reaction is triggered by the dissociation of an N–H bond, where a methanol molecule abstracts the amino proton from aniline. In the noncatalytic reaction mechanism, the aniline molecule itself behaves as an acid. The presence of base makes easier the abstraction of an amino proton; the polarization of the N<sup>δ−</sup>–H<sup>δ+</sup> bond of aniline and the O<sup>δ−</sup>–H<sup>δ+</sup> bond of methanol can be enhanced by a large negative charge of OH<sup>−</sup> through hydrogen bond formation with their protons. The reaction proceeds locally around the amino group, thus yielding no toluidines. Two methanol molecules can participate in the reaction to form a six-membered ring structure, as shown in Fig. 3b, where a proton transfer occurs between the methanol molecules along their hydrogen bonding. Similar reaction mechanisms involving a cyclic transition state are often proposed for *N*-methylation of aniline on a zeolite surface<sup>15</sup> and for noncatalytic organic reactions in supercritical water, *e.g.*, a decarboxylation of formic acid and a



**Fig. 3** Comparison of the reaction mechanism between (a) the acid-catalyzed methylation of aniline and (b) the supercritical *N*-methylation without catalyst.

dehydrogenation of ethanol.<sup>16</sup> The small  $k_2$  in the supercritical reaction can be explained by the two reasons: (i) the dissociation of an amino proton from NMA is hindered by the electron-donating ability of the methyl group of NMA, and (ii) the methanol molecule(s) involved in the noncatalytic reaction mechanism has a steric hindrance larger than that of methyl cation in the acid-catalyzed one, preventing further methylation of NMA. The noncatalytic *N*-methylation is never specific to the methanol density studied here (see the ESI for the density and temperature dependence of  $k_1$ ). In the vapor phase, however, the noncatalytic pathway has a negligible contribution, because methanol density in the gas phase is much lower than that in the supercritical state.

In conclusion, we propose a new reaction mechanism for the noncatalytic *N*-methylation of aniline in supercritical methanol to explain the high selectivity of NMA and the acid/base effect on the reaction rate. For a better understanding of the reaction mechanism, it is essential to investigate both experimentally and theoretically the three roles of methanol – a solvent, a reactant, and a proton-transfer catalyst – as well as the acid–base equilibria in supercritical methanol, which will be studied in our subsequent work.

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- 11 Solid acid catalysts, such as metal oxides and zeolites, are often used in the laboratory (Refs. 5–10), whereas a homogeneous catalyst,  $\text{PCl}_3$ , is used in a commercial process (Ref. 2).  $\text{PCl}_3$  is highly toxic and corrosive, and is methanolysed to produce HCl and  $\text{CH}_3\text{Cl}$ .
- 12 No *C*-methylation was taken into account in the calculation of the theoretical curves shown in Fig. 2.
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