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THE MECHANISM OF N-ALKYLATION OF WEAK N-H-ACIDS BY PHASE TRANSFER CATALYSIS[1]

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Abstract:*The alkylation of aromatic amines in the presence of inorganic bases is accelerated by a PT catalyst* even *if $KHCO_3$ is the base. $ArNR^{\ominus}$ ions seem not to be involved. A novel type of mechanism for a PTC process is proposed.*

Phase transfer catalysis (PTC) is a very effective method for the N-alkylation of activated compounds such as carboxamides, phosphon- and sulfonamides, and numerous heterocycles in the presence of a base and a quaternary ammonium salt catalyst [review:ref.[2]]. This is in line with the known fact that compounds up to a pK_a value of 20-24 can be alkylated in the presence of caustic soda and a PT catalyst. Surprisingly,however, further reports have accumulated on the acceleration of aromatic amine alkylations by a PT catalyst in the presence of aqueous or powdered alkali metal hydroxides[3]. A mechanism involving deprotonation of N-H bonds is assumed tacitly or explicitly inspite of the pK_a (aniline) = 27 and the fact that even the known $NEt_4^{\oplus}\ {}^{\ominus}NPh_2$ is decomposed by traces of water[4].

We have verified first the accelerating effect of a catalyst on aromatic amine alkylations in the presence of powdered NaOH (Table 1). It is apparent that PTC increases the rates by a factor of approximately 3 to 4. The various catalysts do not differ much in activity. With aliphatic amines, little or no increase in alkylation rates was found under various PTC conditions.

Further experimentation (Table 2) and literature search revealed these facts : (1) The alkylation is accelerated moderately by the presence of an onium salt even in the absence of an inorganic base. Catalysis[5] and autocatal-

Table 1. PTC Alkylations of Anilines (0.04 mole amine, 0.04 mole ethyl bromide, 0.001 mole catalyst, 0.04 mole crushed NaOH, 2h at 40°C in a sealed tube)

		% Conversion[b)]	% Yield (G.C. Analysis)	
Amine	Catalyst[a)]		N-Alkylation	N,N-Dialkylation
Aniline	PBu_4Br	80	48	16
	none	32	24	4
	Aliquat 336	66	44	11
	TEBA	95	51	22
	NBu_4HSO_4	87	45	16
	NBu_4Br	89	49	20
	$NHex_4Br$	72	44	14
4-Toluidine	NBu_4HSO_4	77	47	15
	none	16	12	2
4-Anisidine	NBu_4HSO_4	76	46	14
	none	25	19	3
2-Nitroaniline	NBu_4HSO_4	42	42	—
	none	—	traces	—

a) TEBA = $PhCH_2NEt_3Cl$; Aliquat 336 = technic. $(C_8H_{17})_3NMeCl$; b) Based on EtBr

Table 2. Influence of Base and Catalyst Presence on the Alkylation of N-Methylaniline (10 mmole aniline, 10 mmole hexyl bromide, 0.25 mmole catalyst in 10 ml toluene, 100°C, 15.5h)

			% Yield	
Inorganic Base	Catalyst	mmole Base	with Catalyst	without Catalyst
powdered KOH	NBu_4Cl	40	44	13
50% aq. NaOH	NBu_4Cl	100	70	12
50% aq. NaOH	NBu_4Cl	11	68	11
10% aq. NaOH	NBu_4Cl	20	44	12
solid K_2CO_3	NBu_4Cl	20	63	18
solid $KHCO_3$	NBu_4Cl	20	62	9
solid $KHCO_3$	NBu_4Br	20	60	9
solid $KHCO_3$	[18] crown-6 + KCl	20	15.5	9
solid $KHCO_3$	dicyclohexano-[18] crown-6 + KCl	20	14	9
solid $KHCO_3$	cryptand[222] + KCl	20	50	9
none	—	—	45	35

ysis[6] of such processes by amine hydrohalides and by various salts[6] have been known for long, but no specific explanation of the so called "electrolyte catalysis" was offered.

(2) Expectedly, the presence of inorganic bases suppresses the autocatalytic effect of the amine hydrohalide.

(3) A quaternary ammonium salt catalyzes more effectively than an amine hydrohalide.

(4) In the absence of an inorganic base, more and more of the amine is tied up as hydrohalide and the reaction becomes slow. Even weak bases like $KHCO_3$ increase the rate of alkylation if NBu_4Cl is present. Powdered potassium hydroxide - although the strongest base - gives less yield due to extensive tarring.

(5) NBu_4Br is almost as effective a catalyst as NBu_4Cl. This is important because bromide ions are liberated in the course of the reaction. Crowns + KCl are not useful, but cryptand[222] plus KCl can be applied as a catalyst[11].

These observations rule out the deprotonation of anilines and point towards halide ions as essential catalysts. Only quaternary ammonium cations keep the halide permanently in the organic phase if an inorganic base is present. In nonpolar solvents, halide counterions of catalysts function as bases in eliminations and other processes [review: ref.[2]], and the formation of ion pair complexes with HX or H_2O_2 have been demonstrated[7] in dichloromethane and benzene: $[NR_4^{\oplus}\ Cl^{\ominus}..HX]$, $[NR_4^{\oplus}\ Cl^{\ominus}..HOOH]$. The strongly basic and H-bonding properties of KF were reviewed recently[8], and freeze dried KF accelerates the aniline alkylation at room temperature[9].

It is reasonable to assume that amines and halide ions form similar hydrogen bonded complexes $[NR_4^{\oplus}\ X^{\ominus}..H\blacktriangleright NR'Ar]$ in which polarization towards the amide anion occurs without generation of the full negative charge. Precisely this type of intermediate was implicated from a kinetic study of homogeneous nitroaniline acylation[10]. The lesser catalytic activity of amine hydrohalides compared to quaternary ammonium halides is explained by such an intermediate without difficulty: The negative charge density at the N of the complexed aniline derivative, $[ArNRH_2^{\oplus}..X^{\ominus}..HNRAr]$, will be smaller than in the earlier mentioned complex due to the additional H-bonding of the cation.

The overall process comprises two steps: (a) reaction of aniline and RX catalyzed by intermediate NR_4X-aniline complexing, and (b) non-catalyzed deprotonation of the formed amine hydrohalide by the inorganic base at the phase boundary. Although the basic ideas assembled here are known, this mechanism is unique and novel among the phase transfer catalysis processes.

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[11] KCl was used in excess over crowns or cryptand. The poor performance of the crowns could not be improved by the use of KCl complexes that were preformed independently. It remains open to the question whether the [222] catalysis is simply due to its amine character which could result in quaternization under the reaction conditions.

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