

211. *Kinetics of the N-Alkylation of Diarylamines by Methyl Iodide in NN-Dimethylformamide.*

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The reaction of alkyl halides with diphenylamine in different solvents has been studied. The kinetics of the reaction of methyl iodide with diphenylamine and di-*p*-tolylamine has been measured in *NN*-dimethylformamide. This reaction takes place by a bimolecular substitution mechanism between the two un-ionised reactant molecules.

THE *N*-alkylation of diarylamine derivatives is generally carried out under drastic conditions,¹ so no proper kinetic investigation is feasible. We have carried out the alkylation so that the kinetics should be measurable, and thence deduced the mechanism of the reaction. Both the alkyl halides and the solvents led to experimental difficulties. With benzyl chloride the reaction could be carried out readily in ethanol, but side reactions constituted 25% of the total reaction of the halide. With benzyl chloride in benzyl alcohol, in kinetic experiments, the concentration of the free acid started to *fall* after a certain time. Benzyl alcohol and dry hydrogen chloride react with each other, forming (probably) benzyl chloride.² In inert solvents, such as benzene, nitrobenzene, dioxan, ethyl acetate, and acetone, diphenylamine and benzyl chloride did not react at 60° in

¹ Wedekind, *Ber.*, 1899, **32**, 511.

² Cannizzaro, *Annalen*, 1853, **88**, 130; Norris, *Amer. Chem. J.*, 1907, **38**, 631.

18—20 hr., and only reacted very slowly (about 1—2% in 18 hr.) in nitromethane, acetonitrile, dimethylformamide, or an excess of benzyl chloride.

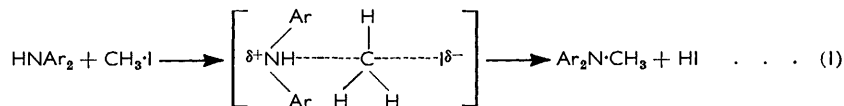
TABLE I. Second-order rate coefficients of the reaction of diphenylamine and of di-*p*-tolylamine with methyl iodide in dimethylformamide at 40°.

Diphenylamine (mole l. ⁻¹) ...	0.25	0.5	0.5	1.0	1.0	1.0			
Methyl iodide (mole l. ⁻¹)	1.0	0.5	1.0	0.25	0.5	1.0			
10 ⁶ k ₂ (l. mole ⁻¹ sec. ⁻¹)	3.72	3.80	3.65	3.72	3.76	3.61			
	3.80		3.72	3.80	3.72	3.62			
Di- <i>p</i> -tolylamine (mole l. ⁻¹) ...	0.25	0.25	0.25	0.5	0.5	0.5	1.0	1.0	1.0
Methyl iodide (mole l. ⁻¹)	0.25	0.5	1.0	0.25	0.5	1.0	0.25	0.5	1.0
10 ⁶ k ₂ (l. mole ⁻¹ sec. ⁻¹)	18.8	18.3	17.4	18.3	18.4	17.7	18.1	17.6	17.3

It seemed that in solvents of low dielectric constant the reaction did not take place; a higher dielectric constant was a necessary but not a sufficient condition. On the other hand, protogenic solvents of intermediate dielectric constants such as alcohols, etc., while giving conveniently measurable rates, gave also side reactions at a comparatively high rate. It was decided, therefore, to use dimethylformamide as solvent, as it has an intermediate dielectric constant ($\epsilon = 37.6$ at 20°). Although this solvent has no active hydrogen atom comparable to that in hydroxylic solvents, yet in certain circumstances³ it may give protons, and so can probably form hydrogen bonds, which seem to be necessary for the alkylation to take place under mild conditions.

In view of these considerations, the choice was narrowed to the reaction of diarylamines with methyl iodide in dimethylformamide at 40°. The results for diphenylamine and di-*p*-tolylamine are shown in Table I; with di-(*p*-nitrophenyl)amine and dipicrylamine the reaction was too slow to be followed. Reproducibility is good; the second-order rate coefficients are almost constant at the concentrations investigated.

The reaction takes place probably through a bimolecular (S_N2) mechanism:



In this, the rate-determining step is the formation of the intermediate, and it is reasonable to suppose that both reactants start in their molecular, uncharged form. The following argument can be put forward to support this scheme: The large effect of the polarity of the various solvents fits either a bimolecular mechanism between two *uncharged* molecules, or a unimolecular one with the ionisation of the alkyl halide as the rate-controlling step.⁴ The second possibility is eliminated by the strictly second-order kinetic form. Another possible mechanism would involve reaction of a pre-formed diarylamine anion (Ar₂N⁻) with a neutral alkyl halide molecule in the rate-determining step; this should give second-order kinetics, but would be influenced adversely by the polarity of the solvent, being between one charged and one neutral entity.⁴ Still, the polarity might enhance the rate by displacing the equilibrium $\text{Ar}_2\text{NH} \rightleftharpoons \text{Ar}_2\text{N}^- + \text{H}^+$ strongly towards the right; the reaction would then be faster because of the influence of polarity on the *amount* of one of the reacting species, *i.e.*, the diarylamine anion. However, since the acidity of diarylamines is strongly enhanced by electron-withdrawing substituents such as nitro-groups, and diminished by electron-repelling substituents such as methyl groups, then if the magnitude of the ionisation of the diarylamine influences the rate of the reaction, di-*p*-tolylamine should react more slowly than diphenylamine, and di-*p*-nitrophenylamine much faster. In fact the opposite is true. Hence we prefer the mechanism (1).

³ Given, *J.*, 1958, 2686; Wawzonek, Blaha, Berkey, and Runner, *J. Electrochem. Soc.*, 1955, **102**, 235.

⁴ Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 347.

EXPERIMENTAL

Materials.—All solvents were redistilled pure commercial products. Diphenylamine (B.D.H.), recrystallised several times from ethanol until colourless, had m. p. 53—54°. Di-*p*-tolylamine (m. p. 79°) was prepared according to Girard *et al.*⁵ Di-(*p*-nitrophenyl)amine (m. p. 218—221°) was prepared according to Gnehm and Werdenberg.⁶

TABLE 2. *Reaction of various alkyl halides (1M) with diphenylamine (1M) in different solvents and with the solvents alone.*

RX	Solvent	Temp.	Reaction with NHPH ₂ and solvent		Reaction with solvent alone	
			Reaction time (hr.)	% Reaction of RX *	Reaction time (hr.)	% Reaction of RX *
CH ₂ PhCl	Abs. EtOH	60°	16	20	16	5
"	CH ₂ Ph·OH	60	16	23	16	2
"	"	40	24	7	24	0
"	H·CO·NMe ₂	60	15	1	15	0
EtBr	Abs. EtOH	60	48	32	17	3
Bu ⁿ Br	"	60	48	10	16	1
"	H·CO·NMe ₂	60	15	1	—	—
Pr ⁱ Br	Abs. EtOH	60	48	20	28	2
Bu ^t Cl	H·CO·NMe ₂	60	18	2	—	—
MeI	"	40	17	24	17	1

* Amount of HX formed, determined by titration.

Reaction Measurements (see Table 2).—The reactions were carried out in an oil-bath whose temperature was constant within $\pm 0.05^\circ$. The percentage of reaction after 16—48 hr. was determined by titration of 1 or 2 ml. samples, diluted with ethanol, with ethanolic potassium hydroxide, Bromocresol Green being the indicator. The appearance of the final blue (basic) colour was usually taken as the end-point, but if the reaction mixture was yellow or light red it was easier to titrate to the green (intermediate) colour of the indicator.

Controls. Benzyl alcohol reacted with dry hydrogen chloride at 40—60°: the reaction was carried out in closed ampoules, so acid could not evaporate. Hydrogen chloride also reacted with dimethylformamide slowly at 40° and rapidly at 100°. In these reactions the products were not identified but loss of acid was determined by titration. No measurable reaction took place between hydriodic acid and dimethylformamide at 40° during 17 hr.

Rate measurements. The appropriate amount of diarylamine was weighed in a 25 ml. measuring flask and dissolved in about 20 ml. of dimethylformamide. When this had reached the reaction temperature methyl iodide was added from an accurate pipette, and the flask was immediately filled to the mark with dimethylformamide at 40°, and shaken thoroughly. Samples of 2 ml. were taken with pipettes (also kept at 40°). The first sample was taken within 1 min. of mixing, and subsequent samples at intervals of about 30 min. The samples were diluted with 3 ml. of ethanol [for di-(*p*-nitrophenyl)amine with 5 ml. of acetone, to avoid precipitation] and titrated with 0.01N-ethanolic potassium hydroxide (Bromocresol Green indicator). A "blank" was conducted, whose results indicated the reaction of methyl iodide with solvent. As shown in Table 3, this reaction was comparatively slow, and was assumed to run concurrently with, but independently of, the main reaction. The "blank" values were subtracted from the measured values. The nature of this "blank" reaction was not clarified, but even in 5—6 hr. it used less than 0.5% of the methyl iodide present.

Calculation of Rate Coefficients.—Rate coefficients were calculated from the integrated form of the second-order rate expression $dx/dt = k_2(a-x)(b-x)$. In most cases the measured values (*i.e.*, the corrected volumes of KOH used *versus* time) fell on a straight line, showing that the "initial rate" expression may be used for calculation. In those cases, since $dx/dt = k_2ab$ (a and b being the initial concentration of methyl iodide and of the diarylamine respectively), k_2 could be calculated directly from the slope. The two methods gave good agreement (see note to Table 3).

⁵ Girard, De Laire, and Chapoteaut, *Annalen*, 1866, **140**, 346.

⁶ Gnehm and Werdenberg, *Z. angew. Chem.*, 1899, **12**, 1051.

Analysis of Products.—Methyl iodide (1M) and diphenylamine (0.5M) were heated together at 40° for 3 days. The amount of hydrogen chloride then found by titration corresponded to 70% reaction of the amine. The solvent and excess of methyl iodide were evaporated *in vacuo*. Water and chloroform were added to the residue and the chloroform solution was evaporated. Concentrated hydrochloric acid was added to the residue, and precipitated diphenylamine

TABLE 3. *Reaction of diphenylamine (0.5M) with methyl iodide (0.5M) in dimethylformamide at 40°.*

Time (min.)	0.0093N-KOH (ml.)			NHPH ₂ reacted (%)	10 ⁴ k ₂ * (l. sec. ⁻¹ mole ⁻¹)	Time (min.)	0.0093N-KOH (ml.)			NHPH ₂ reacted (%)	10 ⁴ k ₂ * (mole ⁻¹)
	used	blank	corr.				used	blank	corr.		
1	0.05	0.05	0.00	0.00	—	150	2.15	0.30	1.85	1.72	3.83
30	0.45	0.10	0.35	0.32	3.62	180	2.55	0.35	2.20	2.05	3.79
60	0.85	0.20	0.65	0.60	3.36	210	3.00	0.40	2.60	2.42	3.84
90	1.30	0.25	1.05	0.98	3.62	270	3.85	0.50	3.35	3.12	3.85
120	1.75	0.25	1.50	1.40	3.88	330	4.60	0.50	4.10	3.82	3.85

* Mean of all values in this column: 3.74×10^{-6} l. sec.⁻¹ mole⁻¹; k₂ determined from graph of ml. of KOH (corr.) versus time: 3.80×10^{-6} l. sec.⁻¹ mole⁻¹.

hydrochloride filtered off. Sodium hydroxide was added to the filtrate until basic, and the *N*-methyldiphenylamine extracted with ether. Evaporation of the ether yielded 1.7 g. of an oil, *n*_D²⁰ 1.615 (Brühl⁷ gives 1.6107 for *N*-methyldiphenylamine).

The reaction of di-*p*-tolylamine (0.5M) and methyl iodide (1.0M) was complete after 3 days. After evaporation of the solvent *in vacuo*, the residue was washed with dilute aqueous potassium hydroxide (5%) and taken up with ether. After evaporation, an oil was obtained (85% yield) which solidified on standing (m. p. 33° undepressed on admixture with an authentic sample⁸ of the *N*-methyl derivative).

Green by-product. In all experiments with diphenylamine and benzyl chloride the reaction mixture was deep emerald-green. A similar colour developed more slowly in all experiments where diphenylamine reacted with alkyl halides in benzyl alcohol and also when diphenylamine was heated with a solution of hydrogen chloride in benzyl alcohol. No colour developed if no reaction took place between the amine and the alkyl halide, *e.g.*, with *n*-butyl chloride. The intensity of the green colour seemed to depend on the amount of air in contact with the mixture: mixtures degassed and filled into ampoules *in vacuo* developed only a very faint green tinge.

A few mg. of the impure green dye were prepared as follows: diphenylamine (1 mole) was refluxed with benzyl chloride (1 mole) in ethanol (1 l.) for 10 hr. After cooling, the mixture was filtered from the benzylidiphenylamine (73 g.), and water added to the filtrate. The lower, dark green layer, consisting mainly of benzyl chloride, was separated and a large excess of dry ether was added to it; a dark green precipitate was formed (~34 mg.) which was soluble in ethanol and in acetic acid and insoluble in ether and in water. Its ethanolic solution was green in acid and red in basic media. The ultraviolet-light absorption of the green form in ethanol showed a broad maximum at 450—475 mμ and a sharp peak at 640 mμ. For comparison, a green substance was prepared from diphenylamine by oxidation with ferric chloride,⁹ but it had absorption maxima at 430 and at 750 mμ. Our substance could not be purified and was not further investigated.

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⁷ Brühl, *Annalen*, 1886, **235**, 21.

⁸ Girard, *Bull. Soc. chim. France*, 1875, **24**, 120.

⁹ Vogel, "Quantitative Inorganic Analysis," 2nd Edn., Longmans, Green & Co., London, 1951,