

**934.** *The Mechanism of the Reaction of Aryl isocyanates with Alcohols and Amines. Part VI.*<sup>1</sup> *Preliminary Investigations with Amines: Complex-formation by Amines and Ureas in Benzene Solution.*

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Early in a kinetic investigation of the reaction  $\text{Ar}\cdot\text{NCO} + \text{NH}_2\text{R} \longrightarrow \text{Ar}\cdot\text{NH}\cdot\text{CO}\cdot\text{NHR}$  in dry benzene solution at 20° (following papers) it was found that the ureas formed have pronounced catalytic effects. The solubilities of these products are greatly affected by the concentration of  $\text{NH}_2\text{R}$ , and, to a smaller extent, by that of  $\text{Ar}\cdot\text{NCO}$  and of a tertiary base catalyst, present in the reaction media. As an essential preliminary to an analysis of the complex kinetics of the reaction these solubility changes have been quantitatively determined, and their nature is briefly discussed.

EARLIER work (Parts I—V)<sup>1</sup> demonstrated that the “spontaneous” reaction between aryl *isocyanates* and alcohols is more complicated than that represented by the simple bimolecular mechanism  $\text{Ar}\cdot\text{NCO} + \text{ROH} \longrightarrow \text{Ar}\cdot\text{NH}\cdot\text{CO}\cdot\text{OR}$  and involves the attack of one molecule of the alcohol upon an initially (and reversibly) formed 1 : 1 molecular complex of alcohol and *isocyanate*. In the presence of a tertiary base, a base-catalysed reaction is superimposed which similarly involves alcohol attack on an initially formed 1 : 1 molecular complex of the *isocyanate* and the tertiary amine. Such mechanisms were later confirmed by independent results.<sup>2</sup> In the “spontaneous” reaction weak catalysis by the urethane product was also demonstrated.<sup>1</sup>

In extension of these investigations to the *isocyanate*–amine reaction it early became apparent that the formation of heterogeneous media, due to crystallisation of the much less soluble ureas formed, introduces serious complications, especially when it was established that these products have much more pronounced catalytic effects than do the urethanes in the corresponding reaction with alcohols. When attempts were made to standardise such autocatalysis by working in media saturated with the urea product, it was found that the solubilities of the ureas are greatly affected by the concentration of the reactant amine and, to a much smaller extent, by the *isocyanate* and tertiary amine concentrations in the media. In order to interpret the complicated kinetics in our study of the amine–*isocyanate* reaction it was, therefore, necessary to obtain solubility data for the different urea products in the presence of the various amines and *isocyanates* used in the investigation.

Such data are recorded in Tables 1—4. Rigid exclusion of moisture was maintained throughout, the solubilities being determined by direct weighing from saturated solutions in equilibrium with undissolved solid at 20.0°. The following abbreviations are used: Carb. A =  $\text{NHPH}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{Et}-p$ ; Carb. B =  $\text{NHPH}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_{11}$  ( $\text{C}_6\text{H}_{11}$  = *cyclohexyl*); Carb. C =  $\text{CO}(\text{NHPH})_2$ ; Carb. D =  $\text{NHPH}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_4\cdot\text{OMe}-p$ . All concentrations are in mole l.<sup>-1</sup>.

<sup>1</sup> Parts I—V, J. W. Baker *et al.*, *J.*, 1947, 713; 1949, 9, 19, 24, 27.

<sup>2</sup> Dyer, Taylor, Mason, and Samson, *J. Amer. Chem. Soc.*, 1949, 71, 4106.

From plots of these results it was possible, assuming that the increases in solubility due to any one entity are additive, to determine the saturation concentration of the catalytic urea product at any stage in a reaction between an *isocyanate* and an amine. Within the experimental concentration ranges employed, the dominant effect is that due to the presence of the reactant amine, and neglect of the effect of both *isocyanate* ( $\sim 0.07M$ ) and tertiary amine ( $0.003-0.3M$ ) concentrations involves an error of only  $\sim 0.5\%$  in the calculated saturation concentration of the urea, an error too small to be significant. The important point emerges that, whilst, as reaction proceeds, loss of *isocyanate* has little effect on the saturation concentration of the catalytic urea product, the corresponding fall in reactant amine concentration is highly significant in this respect.

TABLE 1. Solubility of Carb. A in dry benzene solutions of (a)  $NEt_3$ , (b)  $NH_2Ph$ , (c)  $p-NH_2 \cdot C_6H_4 \cdot CO_2Et$ , and (d)  $Ph \cdot NCO$ , at  $20^\circ$ .

(a) $10^2[NEt_3]$ .....	0	0.99	2.49	4.99	9.99	24.97	34.95	49.94	99.88
$10^3[Carb. A]$ .....	1.65	1.5	1.6	1.8	2.1	3.3	3.9	4.6	6.1
(b) $10^2[NH_2Ph]$ .....	0	5.0	10.0	50.0	75.0	100.0			
$10^3[Carb. A]$ .....	1.65	1.5	1.6	3.3	5.0	6.7			
(c) $10^2[p-NH_2 \cdot C_6H_4 \cdot CO_2Et]$ ...	0	2.63	5.26	10.52	21.04	29.46	33.66	42.08	
$10^3[Carb. A]$ .....	1.65	3.0	4.0	6.9	11.7	15.3	17.9	22.6	
(d) $10^2[Ph \cdot NCO]$ .....	0	5.0	10.0	25.0	50.0	75.0			
$10^3[Carb. A]$ .....	1.65	1.64	1.69	1.71	1.92	2.18			

TABLE 2. Solubility of Carb. C in dry benzene solutions of (a)  $NH_2Ph$  and (b)  $Ph \cdot NCO$ , at  $20^\circ$ .

(a) $10^2[NH_2Ph]$ .....	0	25.02	50.05	75.07	100.1	
$10^3[Carb. C]$ .....	0.424	0.6	1.0	1.3	2.2	
(b) $10^2[Ph \cdot NCO]$ .....	0	5.00	10.00	25.03	50.05	75.08
$10^3[Carb. C]$ .....	0.424	0.429	0.424	0.448	0.481	0.537

TABLE 3. Solubilities of various  $NN'$ -disubstituted ureas in dry benzene solutions of aniline at  $20^\circ$ .

$10^2[NH_2Ph]$ .....	0	5.0	10.0	25.0	50.0	75.0	100
$10^3[Carb. A]$ .....	1.65	1.5	1.6	—	3.3	5.0	6.7
$10^3[Carb. B]$ .....	2.91	3.30	3.41	4.22	5.78	7.57	9.80
$10^3[Carb. C]$ .....	0.42	—	—	0.6	1.0	1.3	2.2
$10^3[Carb. D]$ .....	0.54	0.59	0.67	0.82	1.19	1.68	2.39

TABLE 4. Dependence of solubility of Carb. A in dry benzene at  $20^\circ$  on (a)  $p-NH_2 \cdot C_6H_4 \cdot CO_2Et$ , (b)  $NH_2Ph$ , and (c)  $NEt_3$ .

Reagent	$K_b$	Increase in solubility (M) of Carb. A due to	
		[reagent] = 0.5M	1.0M
a	$2.9 \times 10^{-12}$ *	0.0237	(0.047)
b	$4.6 \times 10^{-10}$	0.00165	0.00505
c	$5.65 \times 10^{-4}$	0.00295	0.00445

\* For Me ester.

These solubility dependences clearly point to complex formation between the entities present in solution, most probably due to hydrogen bonding, of which many types are possible in the systems examined, *e.g.*,  $>C:O \rightarrow H-N<$ ,  $\geq N \rightarrow H-N<$ ,  $>O \rightarrow H-N<$  and, in addition, complex-formation of the type  $\geq N \rightarrow C \overset{O}{\parallel}$ . Such complex-formation would be favoured by the inability of the solvent benzene to associate with the various solutes.

Examination of Table 4 reveals that the basic strength of the amine is evidently not the factor mainly concerned in complex formation. The greatest solubility increase

occurs when the group  $\text{CO}_2\text{Et}$  is present in both the urea and the amine, *i.e.*, in the interaction of benzocaine (*a*) with Carb. A, the solubility of which is accurately represented by the linear relation  $[\text{Carb. A}] = 0.00165 + 0.0469[p\text{-NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{Et}]$  mole  $\text{l}^{-1}$  over the range  $[p\text{-NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{Et}] = 0$  to  $0.5\text{M}$ . The extrapolated value in  $1\text{M}$ -solution in Table 4 (included for comparison) is derived from this relation, although a saturated solution of benzocaine itself in dry benzene at  $20^\circ$  is only  $0.6\text{M}$ . Such association should occur in benzocaine itself, and, in agreement with this, cryoscopic determinations of its apparent molecular weight in benzene solution revealed that this increases from 166 (monomeric =  $165.1$ ) in very dilute solutions to 184 in  $0.22\text{M}$ -solution, equivalent to  $11.5\%$  dimerisation.

It therefore seems most probable that the observed solubility effects are also mainly due to hydrogen-bonding association, although the number of different possibilities makes it impossible to specify the predominant type.

### EXPERIMENTAL

*Materials.*—The various ureas were prepared by direct interaction of the appropriate pure dry isocyanate and amine (in slight excess), either without solvent or in pure dry benzene, at room temperature, followed by repeated crystallisation from methanol and drying over phosphoric oxide in a vacuum. Thus were obtained: *N-p*-ethoxycarbonylphenyl-*N'*-phenyl-, m. p.  $169^\circ$  (Found: C, 67.6; H, 5.65; N, 9.7. Calc. for  $\text{C}_{16}\text{H}_{16}\text{O}_3\text{N}_2$ : C, 67.6; H, 5.7; N, 9.9%); *N-p*-methoxyphenyl-*N'*-phenyl-, m. p.  $192^\circ$ , *N-cyclohexyl-N'*-phenyl-,<sup>3</sup> m. p.  $184^\circ$  (Found: C, 71.8; H, 8.1; N, 13.1. Calc. for  $\text{C}_{13}\text{H}_{18}\text{ON}_2$ : C, 71.5; H, 8.3; N, 12.8%), and *NN'*-diphenyl-urea, m. p.  $239^\circ$  (from acetone). Other materials were purified as described in Part VII (following paper).

*Solubility Determinations.*—A standard solution of the reagent (freshly distilled if liquid) in pure dry benzene was prepared by direct weighing and solutions of various concentrations were prepared from this by suitable dilution. Excess of the solid urea was stirred with 100 c.c. of the solution at  $30^\circ$  and the whole was then allowed to come into equilibrium with undissolved solid during 18 hr. at  $20^\circ$ . The saturated solution (10 c.c.) was removed through a sintered-glass filter-stick, weighed, and evaporated on a steam-bath for 90—120 min. (aniline) or 30 min. ( $\text{NEt}_3$  and benzocaine), dried at  $110^\circ$  for 1 hr. to constant weight, and stored over phosphoric oxide for 0.5 hr. before weighing. Blank experiments showed that the standard procedure caused no change in weight of the urea, or of benzocaine when this was also present, and that other amines were completely removed. When phenyl isocyanate was present removal of this and the solvent was effected in a vacuum over phosphoric oxide, rigid precautions for the exclusion of moisture being maintained throughout the solubility determination.

*Molecular Weight of Benzocaine.*—This was determined in the usual manner by cryoscopic measurements in pure dry benzene ( $17.66 \text{ g.} : k = 5.12^\circ$ ).

Wt. (g.) of $p\text{-NH}_2\cdot\text{C}_6\text{H}_4\cdot\text{CO}_2\text{Et}$	0.1660	0.2553	0.3215	0.4339	0.5021	0.5730	0.6674	0.7278
$\Delta T^\circ$ .....	0.289	0.461	0.558	0.740	0.831	0.919	1.046	1.127
<i>M</i> .....	166	(159)	166	168	173	178	182	184

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<sup>3</sup> Skita and Rolfes, *Ber.*, 1920, **53**, 1248.