935. *The Mechanism of the Reaction of Aryl* iso*Cyanates with Alcohols and Amines. Part VII.* The "Spontaneous" Reaction with Amines.*

By John W. Baker and D. N. Bailey.

Kinetic investigations of the reaction $Ar{\cdot}NCO + NH_2R \longrightarrow Ar{\cdot}NH{\cdot}CO{\cdot}NHR$ for four *iso*cyanate–amine pairs in dry benzene solution at 20°, and with rigorous exclusion of moisture, are described. Analysis of the results shows that a product-catalysed reaction is superimposed upon a true "spontaneous" reaction, both of which follow a mechanism: $Ar{\cdot}NCO + A \rightleftharpoons \text{Complex}$; $\text{Complex} + NH_2R \longrightarrow \text{Products}$; where $A = Ar{\cdot}NH{\cdot}CO{\cdot}NHR$ and NH_2R, respectively. These mechanisms are complicated by the fact that the solubility of the sparingly soluble, precipitated products decreases as the $[NH_2R]$ falls, and by supersaturation phenomena due to the fact that the rate of formation (r_f) of the product exceeds its rate of deposition (r_d) in the early stages of the reaction. Some time after deposition of the product commences, r_d becomes greater than r_f until, finally, equilibrium conditions $r_f = r_d$ are attained and the second-order plot then becomes linear. By quantitative determination of these various factors the whole course of the reactions of the various *iso*cyanate–amine pairs under varying experimental conditions is satisfactorily accounted for. The nature of the catalysis by NH_2R and $Ar{\cdot}NH{\cdot}CO{\cdot}NHR$ is discussed.

Early examinations of the reaction between aryl *iso*cyanates and amines to give ureas were restricted either to determination of relative velocities, derived by analysis of the products when a mixture containing one equivalent each of two different amines was allowed to compete for only one equivalent of *iso*cyanate,[1] or by weighing the urea formed when the *iso*cyanate and amine had reacted for a fixed time at a definite temperature.[2]

After the work here described was completed Arnold, Nelson, and Verbane[3] gave a preliminary account of some (unpublished) work by Craven on kinetic studies of the reaction between phenyl *iso*cyanate and some aryl primary amines in dioxan solution at 31°. The reaction was studied only in homogeneous solution before appreciable separation of the carbanilide product began. In view of the complications which we now elucidate the conclusion that "initial rates of reaction . . . show substantial variations in their dependence upon amine concentration" is readily understandable, as also is the finding that "specific examples display considerable individuality."

The analytical method for determination of aryl *iso*cyanates, and the technique developed for kinetic study of the *iso*cyanate–alcohol reaction,[4] have now been extended to detailed kinetic examination of the amine–*iso*cyanate reaction in dry benzene solution at 20° with rigid exclusion of moisture.

The mechanism: $Ar{\cdot}NCO + \text{Base} \underset{k_b}{\overset{k_i}{\rightleftharpoons}} \text{Complex}$; $\text{Complex} + A \xrightarrow{k_p} \text{Product} + \text{Base}$; leading to the relation $k_{bi} = k_i k_p[\text{Base}]/(k_b + k_p[A])$, previously established for the experimentally determined second-order coefficient k_{bi} for the tertiary base-catalysed alcohol reaction ($A = ROH$),[4b] suggested that a similar relation (A = base = reacting amine, NH_2R) might hold for the spontaneous *iso*cyanate–amine reaction, leading to the expression $[NH_2R]/k_{bi} = 1/k_c = k_b/k_i k_p + [NH_2R]/k_i$, so that a plot of $[NH_2R]$ against $1/k_c$ would be linear. Preliminary experiments with aniline and phenyl *iso*cyanate at once showed that, although the value of k_{bi} does vary with the initial concentration of

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* Part VI, preceding paper.

[1] Davis and Ebersole, *J. Amer. Chem. Soc.*, 1934, **56**, 885.

[2] Naegali, Tyabi, Conrad, and Litwan, *Helv. Chim. Acta*, 1938, **21**, 1100, 1127.

[3] Arnold, Nelson, and Verbane, *Chem. Rev.*, 1957, **57**, 47.

[4] Baker *et al.*, *J.*, (*a*) 1947, 713; 1949, (*b*), 9, (*c*) 19, 24, 37.

aniline, no such simple relation is valid. The high solubilities of arylurethanes permitted kinetic examination of the alcohol–*iso*cyanate reaction in a homogeneous medium, but the much lower solubilities of ureas cause crystallisation of these products in the early stages of the amine–*iso*cyanate reaction to give heterogeneous conditions. Satisfactory determination of unchanged *iso*cyanate (to follow the course of the reaction) is possible in such heterogeneous media by filtration through a sintered-glass micro-filter-stick attached to the end of the pipette used to remove samples, but it was soon found that the heterogeneous conditions introduce serious complications into the study of the reaction mechanism.

The disentangling of these factors and the elucidation of mechanism was achieved only by detailed analysis of a large number of experimental results obtained under widely varied experimental conditions with a number of different *iso*cyanate–amine pairs, but the resultant picture is best described by reversing this order and first summarising the nature of these complications and then discussing typical experimental results which substantiate the conclusions reached.* This paper deals only with the " spontaneous " reaction between an amine and an *iso*cyanate without addition of any *extraneous* catalyst. The base-catalysed reaction under the influence of an added tertiary base will be discussed in Part VIII (following paper).

For brevity the various systems studied are denoted as follows:

A. $Ph\cdot NCO + p\text{-}NH_2\cdot C_6H_4\cdot CO_2Et \longrightarrow Ph\cdot NH\cdot CO\cdot NH\cdot C_6H_4\cdot CO_2Et$ (Carb. A)

B. $cyclo\text{-}C_6H_{11}\cdot NCO + NH_2Ph \longrightarrow Ph\cdot NH\cdot CO\cdot NH\cdot C_6H_{11}$ (Carb. B)

C. $Ph\cdot NCO + NH_2Ph \longrightarrow (Ph\cdot NH)_2CO$ (Carb. C)

D. $p\text{-}MeO\cdot C_6H_4\cdot NCO + NH_2Ph \longrightarrow Ph\cdot NH\cdot CO\cdot NH\cdot C_6H_4\cdot OMe$ (Carb. D).

In the " spontaneous " reaction between an *iso*cyanate and an amine in dry benzene solution the following factors influence the experimentally determined rate of reaction:

(1) Direct interaction between *iso*cyanate and amine to give the product.

(2) In agreement with Craven's finding (see ref. 3), the urea product is a much more effective catalyst for this reaction than is the very weakly catalytic urethane in the *iso*cyanate–alcohol reaction.

(3) The solubility of the product is greater the larger is the concentration of reacting amine from which it is formed. This factor is very large in system A, the solubility of Carb. A in a benzene solution of benzocaine being increased about 15-fold when the benzocaine concentration is increased from 0 to 0·5M.[5] Thus as the reaction progresses the amount of catalytic urea formed increases but, because the concentration of reacting amine is continually falling, so also is the solubility of this product in the reaction medium.

(4) The low solubilities of the ureas cause crystallisation of the product in the early stages of reaction, but, in homogeneous solutions initially containing no urea, considerable supersaturation builds up. Even in heterogeneous media, in the presence of the solid urea, the initial rate of product deposition (r_d) from the reaction medium is slower than its rate for formation (r_f) and it is only in the latter stages that the equilibrium $r_f = r_d$ is established, and the urea concentration (although still greater than the true solubility) then remains approximately constant for the remainder of the reaction because the reactant amine concentration has become small and changes little in these final stages of reaction. The second-order velocity coefficient then attains constancy.

(5) Both the true " spontaneous " and the product-catalysed reactions are not true second-order reactions but are both of the form already established for the *iso*cyanate–alcohol reaction, *viz.*:

$$\begin{aligned} &iso\text{Cyanate} + C \rightleftharpoons \text{Complex, followed by} \\ &\text{Complex} + NH_2R \longrightarrow \text{Products } (C = NH_2R \text{ or urea}) \end{aligned}$$

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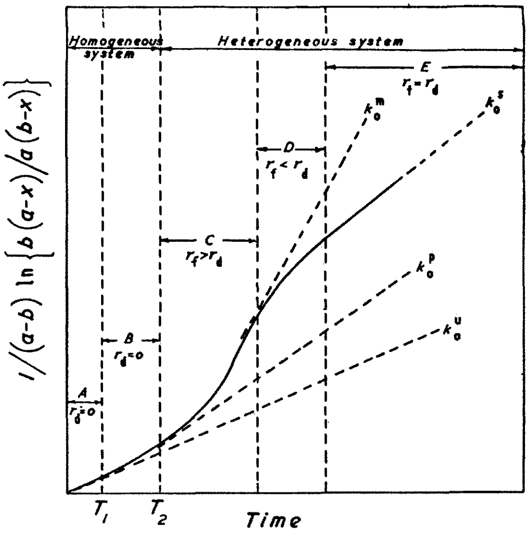
* For a detailed discussion see D. N. Bailey, Thesis, Leeds, 1955.

[5] Part VI, preceding paper.

The superimposition of all these factors means that the whole second-order plot for the reaction is a shallow S-shaped curve, merging finally into a linear plot, the general type of which is indicated schematically in the Figure. Depending on the speed of reaction, the catalytic effect of the product, and the supersaturation phenomena indicated in (4) above, the experimental plot for any single experiment may be represented by any one section *A*, *B*, *C*, *D*, or *E* of this curve or, of course, any combination of consecutive sections, and examples of all such plots were observed with various reactant pairs under suitable experimental conditions.

The results are discussed in terms of the apparent instantaneous second-order rate coefficients k_0 at different stages of the reaction. Such instantaneous k_0 values were determined either by drawing tangents to the second-order plot at the required reaction points, or by " small interval " determinations in the required region, whence an average value of the coefficient for mean concentrations of amine and product is obtained over a range where changes in these concentrations are very small. The two methods gave consistent values. Specific k_0 values, shown in the Figure, are defined as follows: k_0^{u} = the value of the second-order rate coefficient in homogeneous medium at the equilibrium saturated [Ar·NH·CO·NHR]; k_0^{p} is the value at the time when product begins to crystallise: k_0^{m} is the maximum value observed after crystallisation has commenced, and k_0^{s} is the final, constant value in heterogeneous media when an approximately constant concentration of product is maintained. All k_0 values are in mole^{-1} l. sec.$^{-1}$.



Schematic second-order plot for the reaction Ar·NCO + R·NH$_2$ $\longrightarrow$ Ar·NH·CO·NHR *in both homogeneous and heterogeneous media.*

T_1 = *Time when product formed saturates the medium.*
T_2 = *Time when deposition of solid product begins.*

The reaction of an *iso*cyanate with amines is much more rapid than is that with alcohols, and the rate increases with increase in the basic strength of the amine. Preliminary investigation to find an amine of suitable basic strength to give rates convenient for measurement over a wide range of amine concentration suggested system A as one suitable for initial study.

I(a). *System A in Dry Benzene in Initially Homogeneous Solution.*—The absence of side reactions was shown by the observation that the product Carb. A had m. p. 168—169°, unchanged by subsequent crystallisation, and gave correct analytical figures. The absence of reversibility was proved by the observation that no phenyl *iso*cyanate could be detected, by the sensitive analytical method used, when a saturated solution of Carb. A in dry benzene was kept at 20° for 196 hours. When a benzene solution of phenyl *iso*cyanate (0·07M), also saturated with Carb. A, was kept for five days at 20° no change in the *iso*cyanate concentration was detected. Hence, under the reaction conditions used, there is no further reaction between *iso*cyanate and Carb. A to give the biuret.

The choice of system A proved fortunate since, with varying initial concentration of the reactant amine, benzocaine, it revealed all the possible types of rate curves depicted in the Figure, although other systems were found to be more satisfactory for detailed investigation of certain sections of the curve. Table 1 summarises the results obtained in solutions where the initial [Ph·NCO] = 0·0710M but the [benzocaine] is varied: the values of k_0 are those obtained from the slopes of the approximately linear portions of the second-order plots.

The second-order plots of Nos. 6 and 7 are the full S-shaped type, whilst those for Nos. 1—5 are in the *A*, *B*, *C* sections of the Figure. The value of k_0 increases with time, *i.e.*, as the [Carb. A] increases, and the larger is the initial [benzocaine] the larger is k_0 at any given time. True linearity is not achieved until some time after crystallisation of Carb. A has begun. At this point the solution is supersaturated with product, but the figures in the last column of Table 1 indicate the irregular nature of the deposition from initially homogeneous media. This irregularity could be visually observed: in some experiments crystals were formed in the body of the solution and steadily dropped to the bottom of the vessel; in others crystal deposition occurred on the sides of the vessel; occasionally the whole solution became suddenly filled with a fine net-work of crystals. These physical differences were reflected in the observed values of k_0 and in the form of the second-order plot.

TABLE 1. *Reaction between p*-$NH_2·C_6H_4·CO_2Et$ *and* Ph·NCO (0·0710M) *in dry benzene at* 20°.

No.	10 × Initial [benzocaine] (M)	$10^5 k_0$	When deposition begins % reaction	When deposition begins 10^2[Carb. A] = *C* * (M)	Solubility † 10^2 [Carb. A] at point of deposition = *S*(M)	Supersaturation of Carb. A = (*C* − *S*) (10^{-2}M)
1	5·091	—	57	4·08	2·46	1·62
2	4·018	11·3	43	3·03	1·98	1·05
3	3·215	10·4	31	2·19	1·63	0·56
4	2·679	9·47	32	2·31	1·36	0·95
5	1·339	5·71	39	2·78	0·68	2·10
6	0·669	5·21	20	1·35	0·40	0·95
7	0·335	4·59	22	0·76	0·28	0·48

* Determined from % reaction. † From data in Part VI.

TABLE 2. *Catalytic effects of* Ar·NH·CO·NHR *on the reaction,* Ar·NCO + $NH_2R \longrightarrow$ Ar·NH·CO·NHR, *in initially homogeneous solution in dry benzene at* 20°.

Initially [Ar·NCO] = [NH_2R] = ~ 0·07M.

System	10^2[Ar·NH·CO·NHR] (M) (*a*)	10^2[Ar·NH·CO·NHR] (M) (*b*)	$10^5 k_0^a$	$10^5 k_0^b$	k_0^b/k_0^a
A	0·06	0·76	1·70	9·66	5·68
B	0·01	0·34	0·171	0·955	5·5
	0·10	0·85	0·463	1·87	4 *

* Initial [NH_2Ph] = 0·5584M.

The marked catalytic effect of the product is demonstrated by the results in Table 2 which includes data from two different systems. The hypothesis that a simple autocatalytic reaction occurs was first tested and disproved. This would require $dx/dt = k_c'(a - x)(b - x)(x)$, which, by integration, gives

$$k_c' = (1/t)\{ab(a - b)\}.\,[a \ln\{bx/(b - x)\} - b \ln\{ax/(a - x)\}]$$

which would require a linear plot between t and the expression in square brackets. This test was applied to data obtained in many runs in homogeneous solution but in no case was a linear plot obtained.

In an attempt to standardise conditions, attention was next directed to a study of the reaction in the presence of varying excesses of added solid product, always more than sufficient to keep the *medium* saturated with regard to product. Such conditions might be expected to eliminate sections *A*—*D* of the curve and give only the linear section *E*.

I(b). *The System A in Dry Benzene in Heterogeneous Media.*—This system was first examined by using fixed initial concentrations of *iso*cyanate and amine but varying amount of solid product. The results are in Table 3. All these runs gave *approximately* linear second-order plots passing through the origin, although more detailed examination sometimes revealed slight curvature [see para. III (1)]. These results definitely prove the absence of heterogeneous catalysis on the surface of the solid present. The slight fall (~20%) in the values of k_0^s observed when a very large amount of solid is present is explained in paragraph IV.

TABLE 3. *Dependence of* k_0^s *on weight of undissolved Carb. A present in the medium.*

Initially: [Ph·NCO] = 0·0714M; [p-$NH_2·C_6H_4·CO_2Et$] = 0·2204M. Equilibrium saturation [Carb. A] varies throughout any one run from 0·0123 to 0·0114M.

No.	12	13	14	15
Wt. (g.) of Carb. A in excess of that (0·0700 g.) required for saturation	0·0696	0·2114	0·4244	0·8206
$10^5 k_0^s$	6·57	6·39	5·66	5·65

Under such saturated conditions, since the solubility of the product increases as the initial concentration of the reacting amine is increased, so also does k_0^s. This is shown by the results in Table 4. Except for experiments at very low concentrations (Nos. 20 and 21) where maximal experimental errors occur, a plot of k_0^s against mean [Carb. A] gives a good straight line; hence k_0^s is directly proportional to the concentration of the product. This suggests that the rate data might be satisfied by the relation $k_{bi} = k_s + k_c'$ [Carb. A], *i.e.*, by:

TABLE 4. *Variation of* k_0^s *with initial* [$NH_2·C_6H_4·CO_2Et$] *in solutions initially saturated with Carb. A.* Initial [Ph·NCO] = 0·0739M.

No.	16	17	18	19	20	21
Initial 10^2[$NH_2·C_6H_4·CO_2Et$] (M)	49·25	31·10	25·92	12·96	6·48	3·24
Mean 10^3 [Carb. A] (M)	24·2	15·9	13·6	7·2	4·6	3·0
$10^5 k_0^s$	12·8	9·67	8·26	6·7	5·06	4·89

$$dx/dt = k_s (a - x)(b - x) + k_c' (a - x)(b - x)x, \qquad . \quad . \quad . \quad \text{(i)}$$

where k_s = rate coefficient for a true " spontaneous " reaction and k_c' is the catalytic coefficient for the product, Carb A. This relation may be transposed thus: $dx/dt = k_c'(a - x)(b - x)(K + x)$ where $K = k_s/k_c'$, integration of which gives:

$$\begin{aligned} k_c't = [1/(K + a)(K + b)(b - a)][b \ln a(K + x)/K(a - x) + a \ln K(b - x)/ \\ b(K + x) + K \ln a(b - x)/b(a - x)] \quad . \quad . \quad . \quad \text{(ii)} \end{aligned}$$

This relation would only be generally valid if both the " spontaneous " and the product-catalysed reaction were true second-order reactions, *i.e.*, if both k_s and k_c' are independent of the concentration of the reacting amine, postulates shown not to be valid by a more detailed examination of the instantaneous rate coefficients in homogeneous media.

II. *Analysis of the Variation of* k_0 *in Homogeneous Media.*—Typical values of such instantaneous rate coefficients k_0 at various points in runs in homogeneous media are given in Table 5, where only the results for the largest and smallest initial values of [NH_2R] are recorded. The intermediate values of [NH_2R] showed similar variations in k_0.

The plots of instantaneous k_0 against [Carb.] are all linear, but (1) the value of the intercept on the k_0 axis when [Carb.] = 0 (*i.e.*, k_s) increases and (2) the slope of the lines decreases, as the initial [NH_2R] is increased. Hence, in equation (i) the value of k_s is larger the higher is the initial concentration of reactant amine and k_c' is a function of the reciprocal of the initial concentration of reactant amine, although the concentration change *in any one experiment* is insufficient to cause detectable deviations from linearity. Thus, although each individual run is correctly represented by the equation $k_0 = k_s + k_c'$[Carb.], *both* k_s and k_c' are dependent on the initial [NH_2R]. This close similarity to the previously found relationship in the alcohol–*iso*cyanate reaction suggests analysis of the results in terms of the following schemes of reaction mechanism:

TABLE 5. *Dependence of* k_0 *on initial* [NH_2R] *and on* [*Carb.*] *in homogeneous solutions.*

System A. Initial [Ph·NCO] = 0·0710M.

(1) Initial [$NH_2·C_6H_4·CO_2Et$] = 0·5091M.

10^3[Carb. A] (M)	2·2	3·8	10·1	16·4	24·4	32·0
10^5k_0	3·50	4·28	5·43	7·07	9·25	11·2

(2) Initial [$NH_2·C_6H_4·CO_2Et$] = 0·0335M.

10^3[Carb. A] (M)	0·3	0·6	2·4	4·2	5·9	7·6
10^5k_0	1·50	1·70	2·55	4·99	8·56	9·66

System B. Initial [C_6H_{11}·NCO] = 0·0700M.

(3) Initial [NH_2Ph] = 0·0698M.

10^3[Carb. B] (M)	0·1	0·21	0·93	1·7	3·35
10^5k_0	0·17	0·24	0·45	0·65	0·95

(4) Initial [NH_2Ph] = 0·8375M.

10^3[Carb. B] (M)	0·76	1·52	5·05	8·58	10·92
10^5k_0	0·71	0·87	1·21	1·65	2·02

For the true spontaneous reaction:

$$\left.\begin{array}{l} \text{Ar·NCO} + NH_2R \underset{k_5}{\overset{k_4}{\rightleftharpoons}} \text{Complex 1} \\ \text{Complex 1} + NH_2R \xrightarrow{k_6} \text{Ar·NH·CO·NHR} + NH_2R \end{array}\right\} \quad . \quad . \quad \text{(iii)}$$

whence, as in the alcohol reaction, stationary-state conditions give the relation

$$k_s = k_4k_6[NH_2R]/(k_5 + k_6[NH_2R]) \text{ or}$$
$$[NH_2R]/k_s = k_5/k_4k_6 + [NH_2R]/k_4 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad \text{(iv)}$$

For the product-catalysed reaction we then have:

$$\left.\begin{array}{l} \text{Ar·NCO} + \text{Ar·NH·CO·NHR} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Complex 2} \\ \text{Complex 2} + NH_2R \xrightarrow{k_3} \text{2Ar·NH·CO·NHR} \end{array}\right\} \quad . \; . \; . \; . \; . \; . \quad \text{(v)}$$

which gives the similar relation:

$$k_0 - k_s = k_c'[\text{Carb.}] = k_1k_3[\text{Carb.}]/(k_2 + k_3[NH_2R]) \text{ or}$$
$$1/k_c' = k_2/k_1k_3 + [NH_2R]/k_1 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad \text{(vi)}$$

The values of k_s and k_c' for various initial concentrations of reactant amine, determined from the slopes and intercepts of the linear plots obtained for data exemplified in Table 5, are given, for two systems only, in Table 6. As required by the suggested mechanisms, a plot of [NH_2R]/k_s against [NH_2R] is linear (except for the value in parentheses), thus satisfying equation (iv), as also is the plot of $1/k_c'$ against [NH_2R], in accordance with equation (vi). From the slopes and intercepts of these plots the following approximate values of the various velocity coefficients are obtained:

	10^3k_1	k_3/k_2	10^5k_4	k_6/k_5
(*a*)	1·77 (±5%)	6·7 (±15%)	2·46 (±4%)	18 (±20%)
(*b*)	1·7 (±8%)	2·1 (±20%)	0·9 (±30%)	1·8 (±60%)

Confirmation of the self-consistency of the analysis was obtained by substituting the appropriate values of k_s and k_c' from Table 6 in equation (ii) (p. 4656) for each individual run in homogeneous solution. Linear plots were obtained in all cases for the whole course of each run, over the range of initial benzocaine concentrations 0·0335—0·5091M.

TABLE 6. *Variations of* k_s *and* k_c' *with initial* $[NH_2R]$ *in the reaction of* $Ar{\cdot}NCO{-}NH_2R$.

(*a*) System A, initial $[Ph{\cdot}NCO]$ = 0·0710M: (*b*) System B, initial $[C_6H_{11}{\cdot}NCO]$ = 0·0700M.

(*a*)						
Initial $10^2[NH_2R]$ (M)	3·35	6·69	26·79	32·15	40·18	50·91
10^5k_s	1·05	1·20	2·15	2·00	2·15	2·85
$[NH_2R]/k_s$	3190	5575	12,470	16,080	18,690	(17,860)
$10^3k_c'$	10·7	6·51	4·01	3·92	3·43	2·60
$1/k_c'$	94	153	249	255	292	385

(*b*)			
Initial $10^2[NH_2R]$ (M)	6·982	55·84	83·75
10^5k_s	0·15	0·40	0·65
$[NH_2R]/k_s$	46,550	139,600	128,800
$10^3k_c'$	2·89	1·87	1·24
$1/k_c'$	346	568	808

(Data for system B are restricted, but reveal the same general pattern.)

III(1). *Supersaturation Phenomena.*—The following results show that, even in the presence of undissolved product, the concentration of dissolved product still builds up to a supersaturated value. In runs in heterogeneous and in homogeneous media the constant values of heterogeneous k_0 (k_0^s) and the instantaneous values of homogeneous k_0 at the solubility concentrations of product (k_0^u), at very closely similar concentrations of reacting amine, are compared in Table 7. Although the values of $[NH_2R]$ in homogeneous media are each slightly higher than are the corresponding values in the heterogeneous system, the differences are themselves too small to cause significant differences between k_0^u and k_0^s. Yet k_0^s is always ~20—40% greater than k_0^u. It follows that, even when undissolved solid is present, the concentration of dissolved product cannot immediately fall to its true solubility value. Careful examination of the instantaneous k_0 values in initially homogeneous systems at, and immediately after, the first deposition of solid product, shows

TABLE 7. *Comparison of the values of* k_0^s *(heterogeneous systems) and* k_0^u *(homogeneous systems) at [Carb.] = solubility.*

Initially $[Ar{\cdot}NCO]$ = 0·07M.

System A

Heterogeneous			Homogeneous	
Mean $[NH_2{\cdot}C_6H_4{\cdot}CO_2Et]$ (10^{-2}M)	$10^5k_0^s$	Solubility [Carb. A] (10^{-2}M)	Mean $[NH_2{\cdot}C_6H_4{\cdot}CO_2Et]$ (10^{-2}M)	$10^5k_0^u$
47·29	12·8	2·42	48·49	9·2
38·43	11·1	2·00	38·18	9·0
29·50	9·67	1·59	30·56	8·3
24·66	8·26	1·36	25·43	7·6
11·05	6·07	0·72	12·67	4·5
5·47	5·06	0·46	6·23	4·2
2·10	4·89	0·30	3·05	4·2

System B

Mean $[NH_2Ph]$ (10^{-2}M)	$10^5k_0^s$	Solubility [Carb. B] (10^{-2} mole $l.^{-1}$)	Mean $[NH_2Ph]$ (10^{-2}M)	$10^5k_0^u$
106·4	2·59	1·03	—	—
79·8	2·11	0·784	82·97	1·62
51·28	1·68	0·580	55·26	1·44
24·60	1·35	0·421	—	—
4·95	1·04	0·317	6·66	1·08

that the value k_0^{p} at this point first continues to increase to k_0^{m} and then decreases to the equilibrium, constant value k_0^{s}, which, however, is always greater than k_0^{u}. This is illustrated by typical data for two systems in Table 8.

TABLE 8. *Increase in k_0 in initially homogeneous systems after deposition of the urea product.*

System A.

(1) Initially: $[\mathrm{Ph{\cdot}NCO}]$ = 0·0710M; $[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ = 0·3215M; [Carb. A] = 0. Solubility [Carb. A] = 0·0163M: at deposition [Carb. A] = 0·0219M.

$[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ (M)	=	0·2996	0·2956	0·2887
10^5k_0	=	10·4 (k_0^{p})	11·1 (k_0^{m})	9·4

(2) Initially $[\mathrm{Ph{\cdot}NCO}]$ = 0·0710M; $[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ = 0·2679M; [Carb. A] = 0. Solubility [Carb. A] = 0·0136M: at deposition [Carb. A] = 0·0231M.

$[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ (M)	=	0·2448	0·2431	0·2265
10^5k_0	=	10·1 (k_0^{p})	12·8 (k_0^{m})	7·6

System B. Initially $[\mathrm{C_6H_{11}{\cdot}NCO}]$ = 0·0700M.

No.	Initial $[\mathrm{NH_2Ph}]$ (M)	$10^5k_0^{\mathrm{u}}$	$10^5k_0^{\mathrm{p}}$	$10^5k_0^{\mathrm{m}}$
1	0·06982	1·08	1·26	1·46
2	0·5584	1·44	1·94	2·11
3	0·8375	1·62	2·41	3·09

			[Carb. B] (10^{-3}M) to account for			[Carb. B] (10^{-3}M)	
			(*a*)	(*b*)	(*c*)	(*a*) formed	(*b*) deposited
No.	$10^5(k_0^{\mathrm{m}} - k_0^{\mathrm{u}})$	$10^5(k_0^{\mathrm{m}} - k_0^{\mathrm{p}})$	solubility	k_0^{m}	$k_0^{\mathrm{m}} - k_0^{\mathrm{p}}$	$p \longrightarrow m$	$p \longrightarrow m$
1	0·38	0·20	3·17	4·5	0·7	2·4	1·7
2	0·67	0·17	5·80	9·4	1·0	3·1	2·1
3	1·47	0·68	7·84	19·6	5·4	6·9	1·5

Thus the concentration of dissolved product to account for the value of k_0^{m} is greater than the true solubility value, and, during the period of the run between k_0^{p} and k_0^{m}, only a fraction of the new product formed has been deposited, the remainder further increasing the concentration of dissolved product notwithstanding the already supersaturated character of the medium. In harmony with this, similar small variations in the instantaneous values of k_0 could sometimes be observed in *initially* heterogeneous runs for which the second-order plot is approximately linear (cf. Ib, p. 4656), the apparent "straight line" sometimes being a very shallow S-shaped curve. This is illustrated for system A in Table 9.

TABLE 9. *Small variations in k_0 for the system A in the presence of excess of solid Carb. A.*

Initially $[\mathrm{Ph{\cdot}NCO}]$ = 0·0739M; $[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ = 0·3110M.

$[\mathrm{NH_2{\cdot}C_6H_4{\cdot}CO_2Et}]$ (10^{-2}M)	Solubility [Carb. A] (10^{-2}M)	10^5k_0	[Carb. A] to account for k_0 (10^{-2}M) *
30·55	1·67	8·2	1·58
29·92	1·63	9·35	1·86
29·29	1·61	10·4 (k_0^{m})	2·14
28·75	1·58	9·95	2·01
28·29	1·56	8·7	1·70

* From runs in homogeneous media.

Except in the very early stages of reaction (line 1, Table 9) the concentration of dissolved product necessary to account for the observed value of k_0 is always greater than the solubility value, even although an excess of undissolved solid is present throughout. Such phenomena are even more pronounced in System B in the presence of excess of solid Carb. B. Thus, (*a*) with initial concentrations $[\mathrm{C_6H_{11}{\cdot}NCO}]$ = 0·0700M, $[\mathrm{NH_2Ph}]$ = 1·116M, the second-order plot is a shallow S-shaped curve (Figure, $C + D + E$); (*b*) with $[\mathrm{C_6H_{11}{\cdot}NCO}]$ = 0·5593M, $[\mathrm{NH_2Ph}]$ = 0·5580M, the curve corresponds to type $D + E$; whilst (*c*) with

$[C_6H_{11}\cdot NCO] = 0{\cdot}0700$M, $[NH_2Ph] = 0{\cdot}2794$M, a straight-line plot (*E* only) is obtained, (cf. below).

III(2). *Interpretation of the Whole Reaction Course.*—The whole course of the S-shaped curve (see Figure) can now be interpreted. Depending on the value of r_f (and hence on the initial amine concentration), the effect of reactant amine concentration on the solubility of the product, and the value of r_d (supersaturation phenomena), the experimental results might (as they do) correspond to any portion of this total curve. In initially homogeneous medium increasing concentration in solution of the product causes a continuous rise in k_0 (portion *A*). This continues into the supersaturated region until, at k_0^p, crystallisation begins (*B*). At this point $r_f > r_d$ and hence supersaturation increases, causing a further rise of k_0 to its maximum value k_0^m (*C*). The increased distribution of crystal nuclei throughout the medium now greatly increases r_d, which becomes $>r_f$, the concentration of dissolved product falls, and so does the value of k_0 (*D*) until, when equilibrium conditions $r_f = r_d$ are attained, the concentration of dissolved product remains approximately constant (but still higher than its true solubility value) and k_0^s remains constant for the remainder of the reaction, the second-order plot becoming linear (*E*).

In a very fast reaction, when r_f is very great, the consequent build up of supersaturation, and deposition of a large amount of solid urea, results in the attainment of the condition $r_d > r_f$ after only a short time interval, before initial readings are taken. Under these conditions, exemplified by case (*b*) (above), only sections $D + E$ of the curve are experimentally realised. Conversely, in a very slow reaction r_f is very small and never exceeds r_d: supersaturation conditions are never built up and $k_0^s = k_0^u$. Hence the second-order plot is linear (section *E* only) as exemplified by case (*c*) (above).

IV. *Reaction in Stirred Media.*—If this picture is essentially correct, efficient stirring of a heterogeneous reaction medium should greatly facilitate the attainment of the equilibrium $r_f = r_d$, in the medium already saturated with product and containing undissolved solid. Under such conditions the efficient distribution of crystal nuclei should reduce both the degree of supersaturation (and therefore the value of k_0) and the period during which $r_f > r_d$. Hence sections *C* and *D* of the curve should be telescoped into a very short time interval, and a good linear second-order plot should be obtained throughout the remainder of the run. Illustrative results are in Table 10. Experiments No. 29 and 30 show that, with stirring, a 10-fold variation in the amount of solid urea present has no effect on the rate, confirming the absence of surface catalysis or absorption phenomena. The expected fall in k_0 due to rapid stirring is realised. A similar effect is produced when very large amounts of solid are added (Table 3), the small reduction in the k_0^s value arising from the increased availability of solid nuclei. The explanation suggested for the variation in k_0 is the only one which satisfactorily accounts for all the experimental observations.

TABLE 10. *Effect of stirring on the rate of the reaction* $Ph\cdot NCO$–NH_2Ph (*System C*)

Initially: $[Ph\cdot NCO] = 0{\cdot}07$M; $[NH_2Ph] = 0{\cdot}175$M.

No.	Conditions *	Time of commencement of rapid deposition (min.)	Instantaneous 10^3k_0 at 15 min.
25	0·0231 g.; n.s.	10	1·80
29	0·0696 g.; s.	3	1·38
30	0·6611 g.; s.	3	1·41
31	0·0631 g.; r.s.	2·5	1·24

* Wt. of added Carb. C; n.s. = no stirring; s. = stirring; r.s. = rapid stirring.

V. *Reaction Mechanism and the Function of Catalysts.*—Although the experimental results are satisfactorily represented by the relation, $k_0 = k_s + k_c'[\text{Carb.}]$, yet $k_s = f[NH_2R]$ and $k_c' = f(1/[NH_2R])$, and hence any numerical values of k_s and k_c' are valid at only the one particular concentration of reactant amine. Explicit formulation of the *catalytic* function of reactant amine (eqn. iii) and product (eqn. v) is not possible for several reasons. First, it is not possible to vary the amine or product independently of one another. Secondly, since both mechanisms (iii) and (v) involve the reversible formation of different intermediate complexes, coupling of the two mechanisms through the reverse dissociation of these two complexes is possible, *i.e.*, they cannot, with certainty, be regarded as isolated, simultaneous paths for the formation of the product. No account of any association phenomena (Part VI) is possible. In spite of these limitations certain tentative deductions regarding the general nature of the catalytic action may be drawn.

(1) *The true " spontaneous " reaction.* The effect of varying (1) the amine and (2) the *iso*cyanate on the values of k_s obtained under constant amine and *iso*cyanate concentrations (both $\sim$0·07M) is as follows: (*a*) with phenyl *iso*cyanate the values are $10^5k_s = 1{\cdot}20$ and 14·4 for benzocaine and aniline respectively; (*b*) with aniline, $10^5k_s = 14{\cdot}4$, 12·6, and 0·15 for its reaction with phenyl, *p*-methoxyphenyl, and *cyclo*hexyl *iso*cyanate, respectively. The efficiency of the two bases thus runs parallel with their basic strengths and, for aniline, the velocity of the spontaneous reaction with Ar·NCO decreases in the order Ar = Ph $>$ *p*-MeO·$C_6H_4 \gg$ *cyclo*-C_6H_{11}, as was found for the corresponding reactions with alcohols.[4a] It is therefore probable that both amine and alcohol reactions involve closely similar mechanisms and hence the former also involves a nucleophilic attack of the amine at the carbonyl group of the *iso*cyanate: $\overset{\frown}{NH_2R}\ C(:NH)\overset{\frown}{=}O$. The kinetic results can give no explanation *why* further attack by a second amine molecule is necessary to complete the proton transfer, but several schemes can be envisaged.

(2) *The product-catalysed reaction.* The presence both of basic tervalent nitrogen centres and of acidic hydrogen, in the groups $H{-}\underset{|}{N}{-}\underset{|}{C}{=}O$ present in the urea products, makes it theoretically possible for them to function as either acid or base catalysts. Results obtained for the tertiary-base-catalysed reaction (following paper) show that, for constant concentrations of *cyclo*hexyl *iso*cyanate and aniline (both $\sim$0·07M) the values of $10^3k_c'$ for triethylamine and for the product Ph·NH·CO·NH·C_6H_{11} are 0·249 and 2·89 respectively, *i.e.*, the catalytic coefficient of the very much weaker product-base is $\sim$11 times greater than that of the strong base triethylamine. This suggests that the product is functioning as an acid catalyst, rather than as a base, facilitating the reaction by association of the acidic hydrogen with the carbonyl-oxygen atom, and thus increasing the requisite polarisation of the carbonyl group towards nucleophilic attack by the reactant amine, as in the formula $ArN{=}\overset{\delta+}{C}\overset{\frown}{=}O \rightarrow HN(Ar){\cdot}CO{\cdot}NHR$. The observed acid catalysis by organic acids on the amine–*iso*cyanate reaction [2,3] and on the phenol–*iso*cyanate reaction [6] probably functions by a similar mechanism. This acid-catalysed mechanism for the urea product does not, of course, exclude the possibility that the product might also function as a weak base catalyst in a manner similar to that postulated for the reactant amine.

EXPERIMENTAL

Materials.—Rigid precautions were taken to remove all traces of moisture from materials used and for their storage under completely anhydrous conditions.

Benzene.—" AnalaR " benzene was repeatedly refluxed over phosphoric oxide and fractionated through a good column. The fraction of constant b. p. was then repeatedly refluxed over fresh sodium wire and again fractionated. The sample, b. p. 79·7°/756 mm., was stored over sodium wire in a carefully dried vessel, fresh sodium being added from time to time. No carbanilide formation was observed after long storage of dry phenyl *iso*cyanate in this solvent.

Aniline.—" AnalaR " aniline was refluxed under reduced pressure over anhydrous potassium carbonate and was then kept sealed in contact with fresh amounts of this drying agent for several weeks. The middle fraction, obtained by careful fractionation through a good column, was repeatedly treated with 10 wt. % of powdered potassium hydroxide, refluxed for 1 hr. at

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[6] Tarbell, Mallatt, and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 2229.

200° over this drying agent, and then repeatedly fractionated (column) under reduced pressure. The sample, b. p. 86°/25·5 mm., was sealed in dry vessels. Samples were redistilled under reduced pressure immediately before use. Complete absence of moisture in the aniline was proved by the reproduction of various kinetic runs with aniline which had previously reacted with ~20 wt. % of dry phenyl *iso*cyanate: the unchanged aniline, recovered by fractionation under reduced pressure, had b. p. 71°/14 mm. In typical duplicate experiments the steady $10^5k_0{}^8$ values, (*a*) before *iso*cyanate treatment and (*b*) after such treatment, were: (1) (*a*) 90·5, (*b*) 88·8; (2) (*a*) 63·4, (*b*) 64·8.

iso*Cyanates*.—These were pure samples used in previous work.[4] They were repeatedly fractionated over phosphoric oxide and were again distilled from phosphoric oxide immediately before use: phenyl, b. p. 54°/15·5 mm.; *p*-methoxyphenyl, b. p. 113°/23 mm.; and *cyclo*hexyl *iso*cyanate, b. p. 59°/17 mm.

NN'-*Disubstituted Ureas*.—These were prepared from the appropriate amine and *iso*cyanate, recrystallised from an appropriate dry solvent to constant m. p., and stored over phosphoric oxide in a vacuum. Physical and analytical data are recorded in Part VI.

Apparatus.—All-glass apparatus, other than volumetric, was stored in an electric oven at 110° and then in a vacuum over phosphoric oxide before use. Pyrex reaction vessels were ignited just short of red heat and cooled in a vacuum over phosphoric oxide. Calibrated standard flasks and pipettes were washed only with dry solvents, dried in a current of dry air, and stored over phosphoric oxide in appropriate cylindrical desiccators immersed in the thermostat, which was of standard type maintained at 20° ± 0·005°.

Velocity Determinations.—Reaction vessels (except for stirred experiments) were of the pattern used previously.[4a] Because of the separation of solid product, samples were removed by pipettes to the ends of which were attached sintered-glass filter-sticks, suction being applied through a drying train. Unchanged *iso*cyanate was determined by the micro-adaptation of Stafford and Stagg's method, described in previous papers in this series.[4] Calibration curves, prepared for each *iso*cyanate, from concentrations 0 ⟶ 0·07M, were accurate straight lines passing through the origin; determined values corresponded to 100% ± 0·2% (0·07M region) to 100% ± 0·8% (0·02M-region) of the actual weight of *iso*cyanate present. Calibration curves were checked at intervals during the investigation, and each time a fresh sample of *iso*cyanate was employed.

In stirred experiments the modified reaction vessel consisted of a two-necked ground-joint flask fitted with a mercury-sealed stirrer. Reaction was started by final additions of the *iso*cyanate solution (at temperature equilibrium with the thermostat) through the side-neck, which was also used for withdrawal of samples.

The number of individual runs (each involving 10—15 determinations of k_0) was so large that recording of individual results is impracticable and summaries of the data are recorded in the various Tables.

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