KINETICS OF REACTIONS OF *para*-SUBSTITUTED PHENYL ISOCYANATES WITH AMINES AND ALCOHOLS

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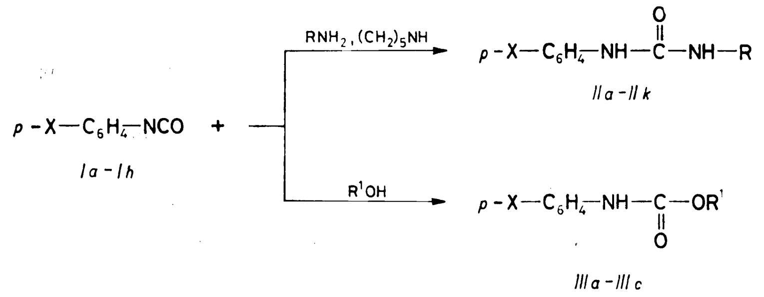
The reaction of *para*-substituted phenyl isocyanates with amines and alcohols was studied by stopped-flow method. The Hammett correlation obtained showed that the sensitivity of the above mentioned reactions toward substituent effects is the same as that of analogous reactions of phenyl isothiocyanates ($\varrho \approx 2$). The rate constants of these reactions were found to be affected more by steric effects than by solvent effects. An one step multicentre mechanism with partial charges in transition state has been proposed for the title reactions.



	X
Ia	OCH_3
Ib	CH_3
Ic	H
Id	F
Ie	Cl
If	Br
Ig	CN
Ih	NO_2

	X	R
IIa	OCH_3	C_4H_9
IIb	CH_3	C_4H_9
IIc	H	C_4H_9
IId	F	C_4H_9
IIe	Cl	C_4H_9
IIf	Br	C_4H_9
IIg	CN	C_4H_9
IIh	NO_2	C_4H_9
IIi	H	$(CH_3)_2CH$
IIj	H	$(CH_3)_3C$
IIk	H	$N(CH_2)_5$

	X	R^1
IIIa	H	C_4H_9
IIIb	H	$C_2H_5(CH_3)CH$
IIIc	H	$(CH_3)_3C$

SCHEME 1

The high polarity of multiple bonds and the strong electrophilic character of the carbon of the -N=C=O group are the reason why typical reactions of isocyanates are nucleophilic addition reactions. The reactions of isocyanates with nucleophiles were relatively often studied[1], mainly due to wide application of their products. However, a general mechanism of these reactions has not yet been proved unambiguously. Most authors[2-5] have preferred a mechanism involving cyclic transition state to that including a zwitterion intermediate[6]. The possible role of catalysis by the reaction components has also been discussed[2-7].

In our previous works[8-10] we were concerned with kinetics of reactions of isothiocyanates with HO-, H_2N- and HS-nucleophiles with the aim to determine and analyse their reactivity–structure relationships. For that reason in the present work we decided to compare previous results with data for analogous phenyl isocyanates obtained both by us and by other authors. The reactions studied are depicted in Scheme 1. They were followed by stopped-flow method under conditions of the pseudomonomolecular reaction.

EXPERIMENTAL

Compounds

Series of *para*-substituted phenyl isocyanates *Ia—Ih* was prepared by the Curtius rearrangement of the azides of corresponding carboxylic acids. The purity of the obtained compounds was checked by comparing their physicochemical characteristics with reported data[11].

Products

N-Phenyl-N'-alkylureas *II* were prepared by the reaction of equimolar amounts of the corresponding isocyanate with amine in dry diethyl ether. The raw product was isolated by filtration with suction, washed with small amount of the ether and dried. Analogous procedure was also used to prepare N-phenyl-O-alkyl carbamates *III*. UV spectra of the products were measured in cyclohexane.

N-(p-*Methoxyphenyl*)-N'-*butylurea* (IIa), m.p. 112°C. UV spectrum: λ_{max} 241 nm, log ε 3·85. For $C_{12}H_{18}N_2O_2$ (222·29) calculated: 64·84% C, 8·16% H, 12·60% N; found: 65·02% C, 8·07% H, 12·41% N.

N-(p-*Methylphenyl*)-N'-*butylurea* (IIb), m.p. 114°C. UV spectrum: λ_{max} 241 nm, log ε 4·10. For $C_{12}H_{18}N_2O$ (206·29) calculated: 69·87% C, 8·80% H, 13·25% N; found: 70·03% C, 8·75% H, 13·36% N.

N-*Phenyl*-N'-*butylurea* (IIc), m.p. 130—131°C. UV spectrum: λ_{max} 240 nm, log ε 3·69. For $C_{11}H_{16}N_2O$ (192·26) calculated: 68·72% C, 8·39% H, 14·57% N; found: 68·93% C, 8·42% H, 14·37% N.

N-(p-*Fluorophenyl*)-N'-*butylurea* (IId), 132°C. UV spectrum: λ_{max} 237 nm, log ε 3·64. For $C_{11}H_{15}N_2OF$ (210·25) calculated: 62·84% C, 7·19% H, 13·32% N; found: 62·90% C, 7·22% H, 13·53% N.

N-(p-*Chlorophenyl*)-N'-*butylurea* (IIe), m.p. 174°C. UV spectrum: λ_{max} 247 nm, log ε 3·86. For $C_{11}H_{15}N_2OCl$ (226·71) calculated: 58·28% C, 6·67% H, 12·36% N; found: 58·09% C, 6·61% H, 12·08% N.

N-(p-*Bromophenyl*)-N'-*butylurea* (IIf), UV spectrum: λ_{max} 245 nm, log ε 3·83. For $C_{11}H_{15}.N_2OBr$ (271·16) calculated: 48·73% C, 5·58% H, 10·33% N; found: 48·64% C, 5·61% H, 10·26% N.

N-(p-*Cyanophenyl*)-N'-*butylurea* (IIg), m.p. 130°C. UV spectrum: λ_{max} 268 nm, log ε 3·56. For $C_{12}H_{15}N_3O$ (217·27) calculated: 66·34% C, 6·96% H, 19·34% N; found: 66·15% C, 7·01% H, 19·22% N.

N-(p-*Nitrophenyl*)-N'-*butylurea* (IIh), m.p. 128—129°C. UV spectrum: λ_{max} 327 nm, log ε 3·85. For $C_{11}H_{15}N_3O_3$ (237·26) calculated: 55·69% C, 6·37% H, 17·71% N; found: 55·41% C, 6·35% H, 17·67% N.

N-*Phenyl*-N'-*isopropylurea* (IIi), m.p. 157°C. UV spectrum: λ_{max} 241 nm, log ε 5·43. For $C_{10}H_{14}N_2O$ (178·24) calculated: 67·39% C, 7·29% H, 15·60% N; found: 67·45% C, 7·86% H, 15·60% N.

N-*Phenyl*-N'-*tert-butylurea* (IIj), m.p. 171—172°C. UV spectrum: λ_{max} 242 nm, log ε 5·29· For $C_{11}H_{16}N_2O$ (192·26) calculated: 68·72% C, 8·39% H, 14·57% N; found: 68·91% C, 8·36% H, 14·41% N.

1-(N-*Phenylcarbamoyl*)*piperidine* (IIk), m.p. 171—172°C. UV spectrum: λ_{max} 241 nm, log ε 5·37. For $C_{12}H_{16}N_2O$ (204·27) calculated: 70·56% C, 7·90% H, 13·71% N; found: 70·40% C, 7·97% H, 13·69% N.

N-*Phenyl*-O-*butyl carbamate* (IIIa). UV spectrum: λ_{max} 234 nm; log ε 5·98. For $C_{11}H_{15}NO_2$ (193·25) calculated: 68·37% C, 7·82% H, 7·25% H; found: 68·22% C, 7·87% H, 7·36% N.

N-*Phenyl*-O-(1-*methoxypropyl*)*carbamate* (IIIb). UV spectrum: λ_{max} 234 nm, log ε 5·57. For $C_{11}H_{15}NO_2$ (193·25) calculated: 68·22% C, 7·82% H, 7·25% N; found: 68·41% C, 7·75% H, 7·21% N.

N-*Phenyl*-O-*tert-butyl carbamate* (IIIc). UV spectrum: λ_{max} 236 nm, log ε 5·64. For $C_{11}H_{15}.NO_2$ (193·25) calculated: 68·22% C, 7·82% H, 7·25% N; found: 68·45% C, 7·91% H, 7·32% N.

Kinetic Measurements

Reactions of *p*-substituted phenyl isocyanates *Ia*—*Ih* with selected amines and alcohols were followed by stopped-flow technique[12] (the instrument: Model 1705, Applied Photophysics, G.B.) in the following solvents: cyclohexane, dioxane and acetonitrile. Concentrations of isocyanates *I* and amines or alcohols were such that it ensured the pseudomonomolecular course of the reactions. The reaction course was recorded with a HP3437A voltameter and immediately evaluated by a HP-85 computer which was connected to the voltameter via a HP-IB 82937A interface. The apparent rate constants k' were determined from the relation $\log[\log(V_\infty/V_t)] = \text{const.} - k't/2{\cdot}303$, where V_t is the voltage in time t (proportional to the intensity of the light passing through the reactor in time t), V_∞ is the voltage at the end of the reaction (proportional to the intensity of the light which has passed through the reactor at the end of the reaction). The values of the real rate constant k were calculated as $k = k'/[C]$, where [C] is the concentration of a given amine or alcohol. The whole arrangement and its testing is described in more detail in our works[13,14]. The order of the studied addition reactions was verified by the reaction of phenyl isocyanate with nine different concentrations of butylamine in cyclohexane at 25°C and at λ 245 nm (Table I). Each k' value represents the average of ten measurements. The values of k' and butylamine concentrations $[BuNH_2]$ are related by the expression $k' = 17{\cdot}77\ [BuNH_2]$ with the correlation coefficient $r = 0{\cdot}998$. The increase of the rate constant k with butylamine concentration can be ascribed to the change in the polar properties of the reaction medium under given reaction conditions[2,15]. The dependence of the apparent rate constant k' on phenyl isocyanate concentration has been followed similarly. By using seven different concentrations of phenyl isocyanate at sufficient excess of butylamine (100 fold excess) we have found that k' is almost identical with the value presented in Table I, i.e. $17{\cdot}5 \,.\, 10^{-2}\ s^{-1}$. This value does not change even if the catalytic amount of N-phenyl-N'-butylurea is present at the beginning of the reaction. On the basis of the equation $\log k' = \log k + n \log [BuNH_2]$, the reaction order was found to be $n = 1{\cdot}08$ ($r = 0{\cdot}999$).

RESULTS AND DISCUSSION

Substituent Effect

The values of the rate constants k presented in Table II speak for the important effect of substituents on the rate of the reaction of *p*-substituted phenyl isocyanates with butylamine. The reaction with the nitro derivative *Ih* proceeded by about 300times faster rate as with the methoxy derivative *Ia*. The k values correlate well with the substitution parameters[16] σ_p according to the relation $\log k = 2{\cdot}005\ \sigma_p + \log 30{\cdot}5$ with the correlation coefficient $r = 0{\cdot}991$. It is of interest to compare now the reactivity of phenyl isocyanate and of phenyl isothiocyanate[10] toward butylamine in cyclohexane at 25°C. Under these reaction conditions the reaction of the unsubstituted phenyl isocyanate proceeds 300times faster than the reaction of the

TABLE I

Kinetic data on the reaction of phenyl isocyanate with butylamine in cyclohexane at 25°C (phenyl isocyanate concentration is $1{\cdot}05 \,.\, 10^{-4}\ mol\ l^{-1}$, $\lambda = 245$ nm)

$[BuNH_2] \,.\, 10^3$ mol l^{-1}	Excess $BuNH_2$	$k' \,.\, 10^{2\,a}$ s^{-1}
2	20	2·86
3	30	4·59
4	40	6·27
5	50	7·91
6	60	9·33
7	70	11·04
8	80	13·25
9	90	15·68
10	100	17·51

[a] k' apparent rate constant.

unsubstituted phenyl isothiocyanate. Comparison of the values of the rate constants of the studied isocyanates and the corresponding isothiocyanates[10] as well as the values of the slopes (ϱ_{NCO} and ϱ_{NCS}) of the given dependences show that the reactions of phenyl isocyanates are faster but almost as sensitive to substituent effects ($\varrho \approx 2$) as those of phenyl isothiocyanates. This allows us to assume that the same mesomeric structures can play role in the reaction of both phenyl isothiocyanates and phenyl isocyanates[17] and hence that the mechanism of the reactions could be the same in both cases. The fact that phenyl isothiocyanates are less reactive than phenyl isocyanates comports with the total charges on the carbons of –NCO and –NCS groups calculated by[17] MNDO method. The charge on the carbon of the –NCO group (0·396 e) is markedly greater compared to that on the carbon of the NCS group (0·247 e). In the *p*-substituted series *Ia*–*Ih* there exists the correlation between the rate constants *k* and the total charges *Q* on the carbon of –NCO group in the form $\log k = 151{\cdot}59\ Q - 58{\cdot}78$ ($r = 0{\cdot}955$).

Reaction of Phenyl Isocyanate with Selected N *and* O *Nucleophiles in Cyclohexane at* 25°C (*Steric Effects*)

The effect of nucleophility and steric effects of the reagents were studied by using the properly chosen nucleophiles (Table III). In accordance with the assumed increase of nucleophility, in the case of the little sterically hindered reagents, also the rate of the above mentioned reactions is increased, as demonstrated by comparison

TABLE II

Kinetic data on reactions of *p*-substituted phenyl isocyanates *Ia*–*Ih* with butylamine in cyclohexane at 25°C (phenyl isocyanates concentration is c. 1 . 10^{-4} mol l^{-1})

Compound	X	λ nm	$[BuNH_2] . 10^2$ mol l^{-1}	k'^a s^{-1}	k l mol^{-1} s^{-1}
Ia	OCH_3	245	1·07	0·11	10·5
Ib	CH_3	250	1·08	0·17	16·1
Ic	H	245	1·00	0·18	17·5
Id	F	240	0·98	0·44	45·0
Ie	Cl	255	1·03	1·07	104·3
If	Br	250	1·04	0·89	85·1
Ig	CN	280	1·08	8·38	775·8
Ih	NO_2	280	1·06	14·33	1 351·5

[a] *k'* values were measured at 100fold excess of butylamine with respect to phenyl isocyanates; λ values are optimum wavelengths for given measurement.

of kinetic data in Table III: n-BuOH: sec-BuOH : n-BuNH$_2$: (CH$_2$)$_5$NH = 1 : 14 : : 27 : 1 245. The reactivity of piperidine, (CH$_2$)$_5$NH, is thus 1 200times greater than that of n-butanol and about 50times greater than the reactivity of n-butylamine. From the following relations of the relative rate constants for the amines (n-butylamine: isopropylamine: tert-butylamine = 5·3 : 6·5 : 1) and for the alcohols (n-butyl alcohol : sec-butyl alcohol : tert-butyl alcohol = 1·5 : 20·4 : 1) it follows that in the series of both the amines and the alcohols the steric hinderance at the tertiary carbon has such a strong effect that it prevails over the effect of the higher nucleophility of the attacking atom and the corresponding reaction proceeds here at the slowest rate. It is further worthy of mentioning that the marked difference between the reactivity of n-butyl alcohol and sec-butyl alcohol is no more observed with the corresponding amines (n-butylamine and isopropylamine). On the basis of determined rate constants of the reactions of phenyl isocyanate with N- and O-nucleophiles, the following sequence of the nucleophiles according to their increasing reactivity can be written:

$$(CH_3)_3COH < H_3C(CH_2)_3OH < (CH_3)_3CNH_2 < CH_3(C_2H_5)CHOH <$$
$$H_3C(CH_2)_3NH_2 < CH_3(C_2H_5)CHNH_2 < (CH_2)_5NH\,.$$

Reactions of p-Substituted Phenyl Isocyanates I *with Butylamine in Different Solvents*

The solvent effect in the reactions of *p*-methoxyphenyl, phenyl and *p*-chlorophenyl isocyanate was examined by using three solvents : cyclohexane, dioxane and aceto-

TABLE III

Kinetic data on reactions of phenyl isocyanate with different N and O nucleophiles in cyclohexane at 25°C (phenyl isocyanate concentration is c. 1 . 10^{-4} mol l^{-1})

Nucleophile	λ nm	[Nu] . 10^{2a} mol l^{-1}	k' s^{-1}	k l mol^{-1} s^{-1}
$C_4H_9NH_2$	243	1·00	0·18	17·5
$(CH_3)_2CHNH_2$	245	1·04	0·22	21·3
$(CH_3)_3CNH_2$	245	1·00	0·03	3·3
$(CH_2)_5NH$	245	1·00	8·17	816·7
C_4H_9OH	240	1·00	0·01	0·7
$C_2H_5(CH_3)CHOH$	240	1·00	0·10	9·5
$(CH_3)_3COH$	240	1·08	0·01	0·5

[a] Nu nucleophile.

nitrile (Table IV). Kinetic data obtained show that the studied reactions proceed faster in polar solvents (170times faster in dioxane and 120times faster in acetonitrile compared to cyclohexane). From Table V it follows further that the differences in logarithms of the rate constants for a given substituent are practically constant. This indicates that the polarity of solvents does not affect the slopes of the reactions (i.e. ϱ).

Proposed Mechanism

Reactions of phenyl isocyanates with butylamine are typical nucleophilic additions, Ad_N, that can proceed in general either by a synchronous or by an asynchronous

TABLE IV

Kinetic data on reactions of *p*-substituted phenyl isocyanates *I* (Scheme 1) with butylamine in different solvents at 25°C (compoud *I* concentration is c. 1 . 10^{-4} mol l^{-1})

X	Solvent[a]	λ nm	$[BuNH_2] . 10^2$ mol l^{-1}	k' s^{-1}	k l mol^{-1} s^{-1}
OCH_3	ACN	245	1·01	12·52	1 239·4
H	ACN	245	0·96	20·35	2 120·2
Cl	ACN	255	1·01	132·76	13 144·8
OCH_3	DIO	245	0·99	17·18	1 734·9
H	DIO	245	0·99	32·40	3 285·8
Cl	DIO	255	1·01	177·72	17 595·5

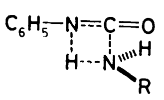
[a] ACN acetonitrile, DIO dioxane.

TABLE V

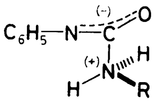
Logarithms of rate constants of reactions of *p*-substituted phenyl isocyanates *I* with butylamine (Scheme 1) in cyclohexane (CHX), acetonitrile (ACN) and dioxane (DIO) and their differences for given substitent in the solvent pairs

X	log k			$\log(k_{ACN}/k_{CHX})$	$\log(k_{DIO}/k_{CHX})$
	CHX	ACN	DIO		
OCH_3	1·02	3·09	3·24	1·07	2·22
H	1·24	3·33	3·52	2·08	2·27
Cl	2·02	4·12	4·25	2·10	2·23

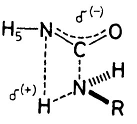
mechanism via cyclic (*A*) or zwitterionic (*B*) intermediate[1]. The observed increase of the rate of the reaction of phenyl isocyanate with butylamine in polar solvents cannot be accounted for by synchronous mechanism with intermediate *A* where solvent effect would operate less. Molecules of polar solvents are known to stabilize charges of zwitterion *B* which could be formed in the first step of the reaction, and thus to lead to rate acceleration. However, the great negative values of the activation entropy $\Delta S^{\ddagger}$ and the small activation enthalpy $\Delta H^{\ddagger}$ of the reactions of isocyanates with amines[18] are strong arguments against the operation of the zwitterion intermediate *B*. Although such data cannot be presented by us for the reactions studied in our work because of the arrangement used, our assumptions can be based on the results of the studies of similar systems which show for the zwitterion intermediate the solvent effect of acetonitrile/cyclohexane[19] by an order of 10^4 or small values (e.g. acetonitrile/heptane[20] the values of an order of 10) for the transition state of the type *A*. Hence, the obtained results along with literature data allow to conclude that in the transition state there is not any uniform formation of new σ bonds. Therefore, the nucleophilic addition of butylamine to phenyl isocyanate is not strictly synchronous but it takes place with formation of partial charges in intermediate *C*.



A



B



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