

RECENT ADVANCES IN ISOCYANATE CHEMISTRY¹

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I. INTRODUCTION

Significant industrial progress in isocyanate chemistry has occurred only within the past twenty years despite the fact that numerous references to both synthesis and reactions are to be found in the literature (241). Greatest progress has been made in the fields of polymers and polymer modification (96). Technological effort was stimulated by the development of diisocyanates, which are peculiarly adapted to polymer synthesis as a consequence of their reactivity.

A review of the synthesis and general reactions of isocyanates was published in 1948 (184). The purpose of this résumé is to extend this review to include not only the numerous contributions published since its preparation but also some new contributions from our laboratories.

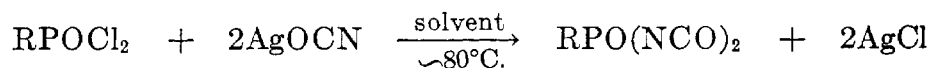
¹ Contribution No. 207 from the Jackson Laboratory. Excerpts from this paper were presented by R. G. Arnold before the Division of Rubber Chemistry at the 129th Meeting of the American Chemical Society, Cleveland, Ohio, May 16, 1956.

II. SYNTHESIS

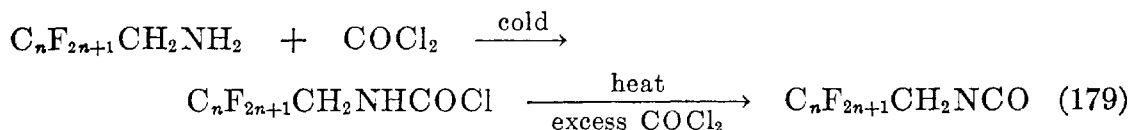
Several new mono- and polyisocyanates are described in the current literature (25, 26, 38, 97), and numerous patents have been issued (28, 29, 42, 109, 110, 122, 130, 149, 153, 154, 169, 179, 202, 218, 219). Although recent developments have provided a large selection of isocyanates of unique structure, the synthetic methods are basically the same as those described in earlier reviews (184, 207). The preparative methods of greatest utility involve

- (a) the phosgenation of amines (72, 73, 121, 122, 141, 153),
- (b) the decomposition of acid azides (214),
- (c) the dehydration of hydroxamic acids (242),
- (d) the double decomposition reaction between a cyanate salt and an ester of an inorganic acid (26, 241), and
- (e) the thermal decomposition of ureas (25, 171, 221) and urethans (27a, 27b, 50, 207).

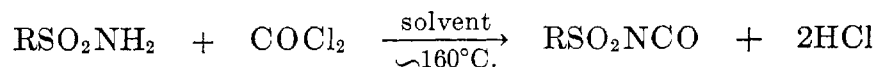
Three new classes of isocyanates have been developed in recent years. Among these are (a) organophosphorus isocyanates (2, 3, 97),



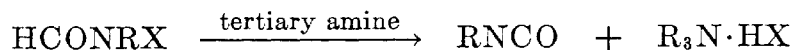
(b) fluorinated isocyanates,



and (c) sulfonyl isocyanates (130):

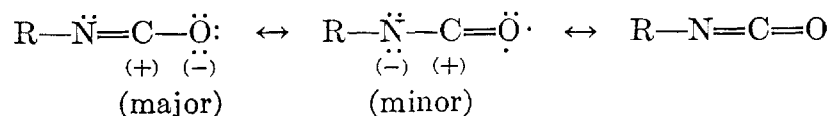


A new synthetic method utilizing *N*-haloformamides has been reported also (110).

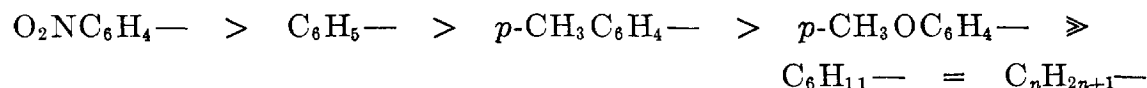


III. REACTIONS OF ISOCYANATES

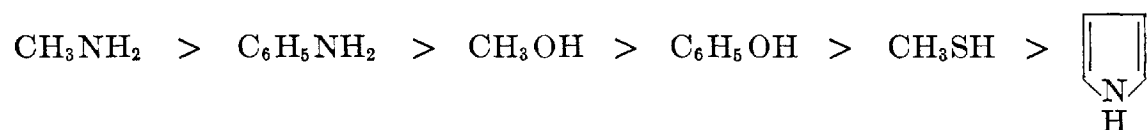
The reactions and reactivity of isocyanates can best be understood by considering the electronic structure of the isocyanate group and the effect on this structure of various groups attached to the nitrogen atom. A qualitative consideration of the resonance hybrids from the standpoint of the molecular orbital theory indicates that the electron or charge density is greatest on the oxygen (highest net negative charge) and least on the carbon (highest net positive charge), the nitrogen atom being intermediate with a net negative charge.



The reactions of isocyanates with active hydrogen compounds involve attack by a nucleophilic center upon the electrophilic carbon of the isocyanate. Therefore, if steric factors are neglected, any electron-withdrawing group attached to the NCO moiety will increase the positive charge on the carbon atom, thereby increasing the reactivity of the isocyanate towards nucleophilic attack. Conversely, electron-donating groups will reduce the reactivity of the NCO group, as illustrated below:



Likewise, the reactivity of the agent attacking the electrophilic carbon of the NCO group will increase as its nucleophilicity increases, as shown in the following series:



Consideration of the above factors in most cases makes it possible to predict on a qualitative basis the relative reactivity of various isocyanates with compounds containing active hydrogen. However, failure to consider steric factors, such as those encountered in ortho-substituted aromatic reactants, can lead to erroneous predictions.

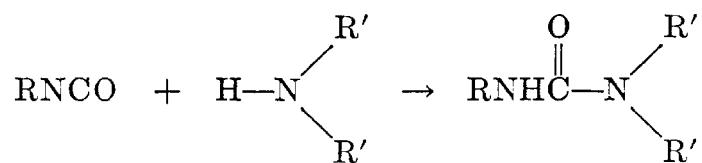
An indication of the effect of steric hindrance on the rate of isocyanate-amine reactions is given in table 1 (47). The data indicate that a substituent ortho to the isocyanate function hinders the reaction more effectively than a substituent ortho to the amine function.

A. Nitrogen-hydrogen bonds

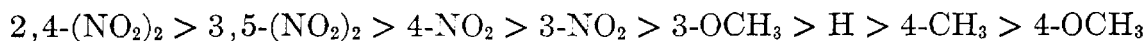
The reaction of isocyanates with compounds which contain nitrogen-hydrogen bonds is governed primarily by the basicity or nucleophilicity of the N—H bond.

TABLE 1
Effect of steric hindrance on the rate of isocyanate-amine reactions
(Amine, 0.1 M; isocyanate, 0.1 M in dioxane; 31°C.)

Amine	$K_b \times 10^{-10}$	Isocyanate	Time to 50% Reaction
			<i>minutes</i>
Aniline.....	4.6	Phenyl	43
<i>o</i> -Toluidine.....	3.3	Phenyl	60
Aniline.....	4.6	<i>p</i> -Tolyl	54
	4.6	<i>o</i> -Tolyl	202
<i>o</i> -Toluidine.....	3.3	<i>o</i> -Tolyl	>1000



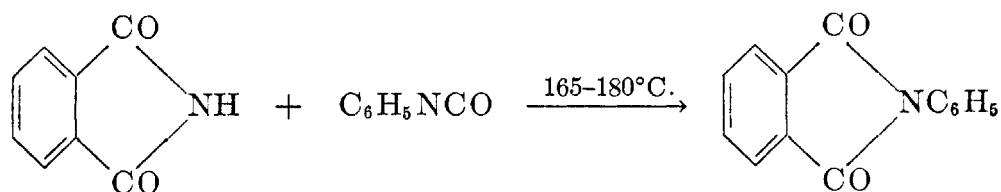
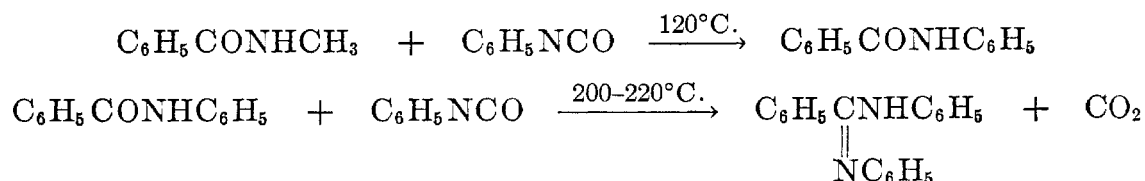
The effect of nuclear substituents on the reactivity of aryl isocyanates with arylamines has been reported (163). Isocyanate activity was found to decrease in the order



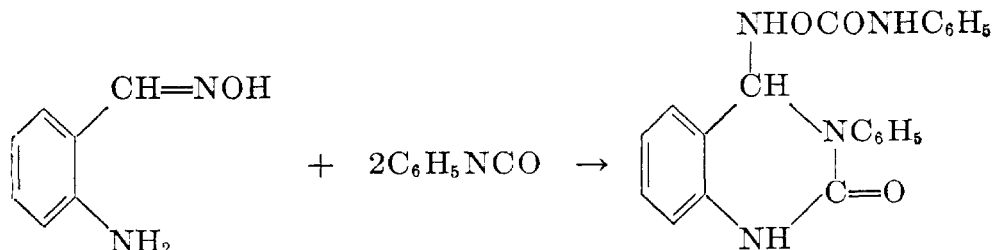
whereas the amine activity increased in the same order. Pyridine and certain carboxylic acids were shown to be catalysts.

The relative reactivity of primary amines with phenyl isocyanate is shown in table 2. The data (51a) illustrate the greater reactivity of aliphatic amines.

Many other reactions involving the nitrogen-hydrogen bond are reported in the literature (184). In general the expected reactions occur, that is, the formation of a substituted urea. However, a number of anomalous reactions have been reported in the case of the following substances: (a) *N*-substituted amides under severe reaction conditions (231, 232),



(b) *N*-substituted sulfonamides, which do not react with isocyanates although the unsubstituted derivatives do (171); (c) *o*-aminobenzaldoxime which, with phenyl isocyanate, gives 2-keto-3-phenyl-4-(β -hydroxylamine carbanilide)-1,2,3,4-tetrahydroquinazoline



in contrast to the meta and para isomers, which give the expected dicarbanilino derivatives (91); and (d) phenyl isocyanate when reacting with liquid ammonia in the presence of potassium amide, a reaction which produces carbanilide as well as the expected *N*-phenylurea (230).

TABLE 2
Relative reactivity of amines with phenyl isocyanate

Amine	Relative Reactivity	Amine	Relative Reactivity	Amine	Relative Reactivity
Ammonia	1	Propylamine	8.22	Amylamine	9.17
Ethylamine	9.72	Butylamine	9.17	Aniline	0.53

B. Oxygen-hydrogen bonds

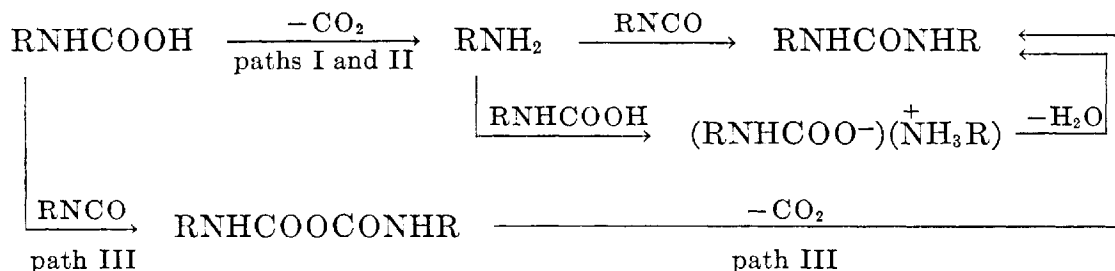
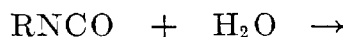
The reactions of isocyanates with compounds containing an oxygen-hydrogen bond represent one of the most important areas of isocyanate chemistry.

In general, they react rapidly with water at ordinary temperatures, giving rise to 1,3-disubstituted ureas and carbon dioxide (151):



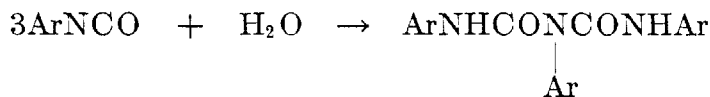
however, in the presence of sodium hydroxide the principal product is the primary amine.

The reaction of substituted aromatic isocyanates with water has been reported (163). On the basis of experimental evidence, three reaction paths for the formation of disubstituted ureas are proposed. The intermediate products formed by a particular isocyanate depend on the reaction conditions, the electronic structure, and the orientation of substituents on the aromatic nucleus. The



influence of substituent groups (163) on the ability of aromatic isocyanates to form the free amine rather than the urea is given in table 3.

The direct synthesis of triarylbiurets by the reaction of aromatic isocyanates and water has been reported (92).



The mechanism of this reaction is not known beyond the fact that it does not involve the intermediate formation of the urea. Conditions which favor this "direct" biuret formation include an aromatic solvent such as benzene or the isocyanate itself at 60–90°C. For example, in the case of phenyl isocyanate, triphenylbiuret is obtained in 1 hr. with only 2 per cent of carbanilide being formed. The reaction between phenyl isocyanate and carbanilide, even in the presence of water, is much too slow at 90°C. to account for this high conversion to the biuret.

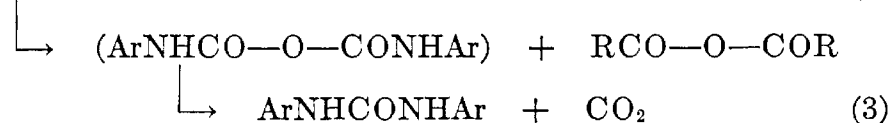
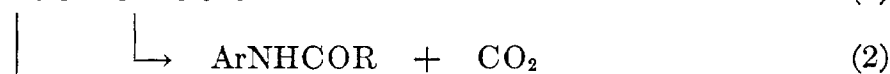
TABLE 3

Influence of substituent groups on the ability of isocyanates to form the free amine rather than the urea in reaction with water

R in RNCO	Product	R in RNCO	Product
2, 4, 6-Trinitrophenyl.....	Amine	3-Nitrophenyl.....	Amine + urea
2, 4-Dinitrophenyl.....	Amine	3-Methoxyphenyl.....	Urea
2-Nitrophenyl.....	Amine + urea	Phenyl.....	Urea
3, 5-Dinitrophenyl.....	Amine + urea	4-Methylphenyl.....	Urea
4-Nitrophenyl.....	Amine + urea	4-Methoxyphenyl.....	Urea

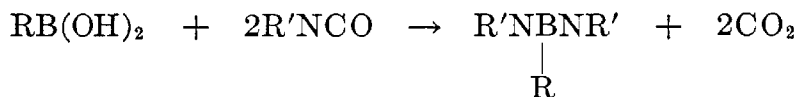
Alcohols and phenols react with isocyanates to yield carbamate esters (184). These derivatives are often used for the characterization of hydroxyl-containing compounds (87).

Weak aromatic and aliphatic carboxylic acids readily form mixed anhydrides with isocyanates (reaction 1), whereas stronger acids such as cyanoacetic, trichloroacetic, and formic acid form mixed anhydrides which spontaneously decompose into amides and carbon dioxide (reaction 2). The more stable mixed anhydrides decompose at elevated temperatures into disubstituted ureas, carboxylic acid anhydrides, and carbon dioxide (reaction 3) (161, 162, 171, 184).

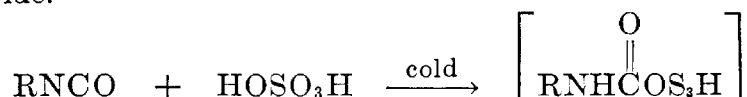


The decomposition of the mixed anhydride indicated in reaction 2 has been shown (86) to occur unequivocally by loss of the carbonyl function of the isocyanate as carbon dioxide (128).

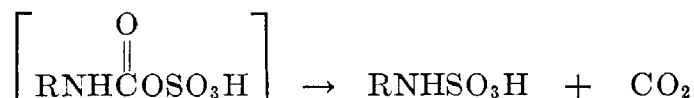
The reaction of a boronic acid and an isocyanate results in the formation of a boronamide and carbon dioxide (226).



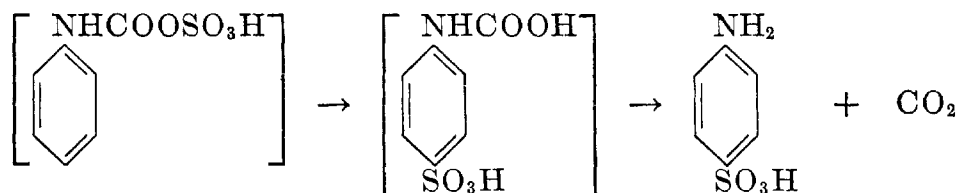
Sulfuric acid reacts with isocyanates in a manner similar to that described for carboxylic acids (27), in that the first step involves the formation of an unstable mixed anhydride.



With an alkyl isocyanate the mixed anhydride decomposes to a sulfamic acid and carbon dioxide.



In the case of phenyl isocyanate, on the other hand, the product is sulfanilic acid, which is probably formed by the route shown below.



It appears that the reaction is essentially a sulfonation of the aromatic ring by the mixed anhydride and that *N*-phenylsulfamic acid is not an intermediate in the process, since, at low temperatures, *N*-phenylsulfamic acid rearranges to orthanilic acid and not to the para derivative.

C. Carbon-hydrogen bonds

N-Substituted amides are formed as a result of nucleophilic attack on isocyanates by the carbanions of sodiomalonic esters and related compounds (184). The nucleophilic α -position of pyrrole (225) or the methylene group of *N*-alkyl-2-methylenedihydropyridine (195) and related compounds (45, 160) undergoes similar reactions.

N-Substituted aroylamides are also produced by the Friedel-Crafts synthesis (93). An intramolecular carbamoylation occurs when 1-naphthyl isocyanates are fused with mixtures of aluminum and sodium chlorides, yielding naphthostyryls (55). The fusion of phenyl isocyanates or the corresponding dimers under similar conditions yields 3-phenyl-2,4-dioxotetrahydroquinazolines (54). Treatment of α -butylphenethyl isocyanates with aluminum chloride in an inert solvent yields 3-butyl-3,4-dihydro-1(2*H*)-isoquinoline (5).

D. Sulfur-hydrogen bonds

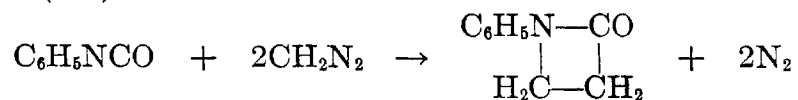
The thiol group reacts with isocyanates in the same way as its oxygen analog, except that it is very much less reactive (171). Hydrogen sulfide reacts with isocyanates to give disubstituted ureas and carbon oxysulfide (171).

E. Miscellaneous

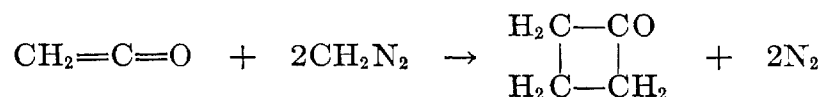
Lithium aluminum hydride reduces aryl and alkyl isocyanates to the corresponding methylamines in high yield (85, 180, 299).

Most Grignard reagents and organometallics react smoothly and rapidly with isocyanates, forming *N*-substituted amides (125).

Diazomethane and phenyl isocyanate combine to yield the β -lactam, 1-phenyl-2-azetidinone (206).

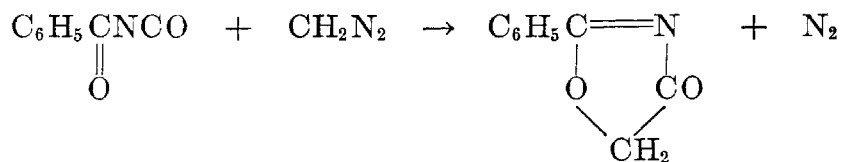


This reaction is analogous to that of ketene with diazomethane.



p-Bromophenyl isocyanate also yields the corresponding β -lactam with diazomethane, whereas α -naphthyl, *p*-nitrophenyl, benzyl, and benzoyl isocyanates do not form β -lactams.

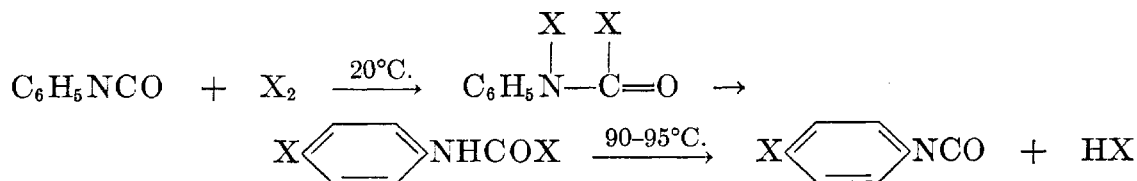
Benzoyl isocyanate and diazomethane react to produce 2-phenyl-4-oxazolone in 70 per cent yield.



Isocyanates give addition products with sodium bisulfite similar to those formed by aldehydes and ketones (171); in fact, isocyanates are capable of displacing the aldehyde or ketone from the sodium bisulfite adduct. Those from aliphatic isocyanates are more stable to hydrolysis, being capable of recrystallization from water, whereas the aromatic derivatives are sensitive to hydrolysis.

Dialkyl phosphites react with isocyanates to produce carbamoyl phosphonates (178).

Chlorine and bromine add to phenyl isocyanate, giving rise to a dihalide (94),



which may be rearranged to yield a mixture of the *o*- and *p*-halo-substituted aromatic isocyanates (89).

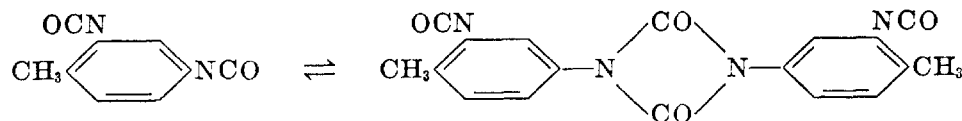
IV. POLYMERIZATION

A. Dimers

The dimers of isocyanates are obtained by treatment of the monomer with catalysts. Triethylphosphine was used in the preparation of phenyl isocyanate

TABLE 4
Dimerization of toluene 2,4-diisocyanate* (TDI) in benzene

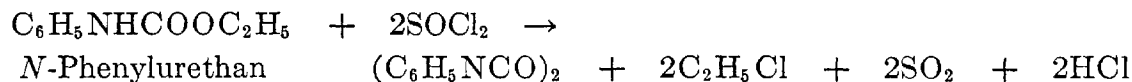
Catalyst, tributylphosphine



Starting Material	Temperature	Equilibrium Conversion
	°C.	per cent
Toluene 2,4-diisocyanate.....	25	74
Toluene 2,4-diisocyanate dimer.....	25	71
Toluene 2,4-diisocyanate.....	10	90

* Chemical Abstracts uses the name 4-methyl-*m*-phenylene diisocyanate for this compound.

dimer in 1858 (101, 102). Other alkyl- and arylalkylphosphines (13), pyridine (215), methyl-substituted pyridines (84), and triethylamine (142) are effective also. The dimer of phenyl isocyanate has been prepared also by the action of excess thionyl chloride on *N*-phenylurethan at room temperature (228),

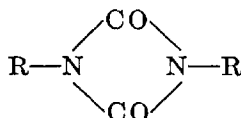


but this reaction appears to be limited to the phenyl derivative (175).

Aromatic isocyanate dimers are obtained readily and a large number have been reported, including some mixed dimers (see tables 5 and 6). Aliphatic isocyanates, in contrast, do not dimerize, although trimers have been made.

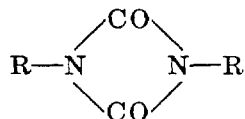
When pyridine is used as a catalyst for dimer formation, it is most conveniently applied as the solvent medium for the reaction (84, 215). Phosphine catalysts are much more active than pyridine and are used in trace amounts. A convenient method of controlling phosphine-catalyzed dimerizations has been described (13). It involves the addition to the reaction mass of an alkylating agent such as benzyl chloride in an amount stoichiometrically equivalent to the substituted phosphine present. Complete deactivation of the catalyst results. By this means the reaction may be mitigated or even quenched and then activated by the addition of more catalyst. The reaction product of the alkylating

TABLE 5
Monoisocyanate dimers



R	Melting Point	References
	°C.	
Phenyl.....	175	(102, 176, 215)
<i>m</i> -Tolyl.....	159-160	(176)
<i>p</i> -Tolyl.....	185	(176)
<i>p</i> -Ethoxyphenyl.....	181-182	(176)
2-Chlorophenyl.....	234-235	(176)
3-Chlorophenyl.....	153-154	(176)
4-Chlorophenyl.....	155-156	(176)
4-Bromophenyl.....	203-204	(176)
4-Nitrophenyl.....	208-211	(176)
4-Aminophenyl.....	—	(136)
4-Amino-3-methylphenyl.....	—	(136)
3-Amino-4-methoxyphenyl.....	—	(136)
3-Amino-5-chlorophenyl.....	—	(136)
4-Phenylazophenyl.....	270 (dec.)	(176)
4-(4'-Aminophenyl)phenyl.....	281-282 (dec.)	(176)
3-Bromo-2-hydroxy-5-methylphenyl.....	—	(177)
1-Naphthyl.....	Sublimed at 296	(176)
2-Naphthyl.....	196-197	(176)
4-Amino-1-naphthyl.....	—	(136)
Mixed dimer of 4-chlorophenyl and 4-tolyl isocyanates....	195	(176)

TABLE 6
Diisocyanate dimers



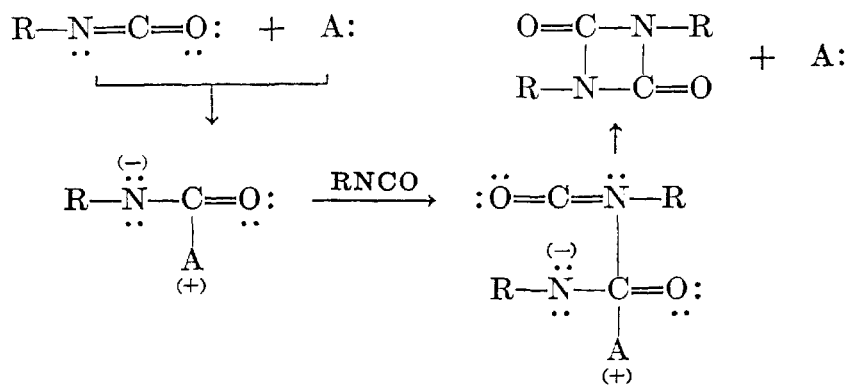
R	Melting Point °C.	References	R	Melting Point °C.	References
$\text{OCN}-\text{C}_6\text{H}_4-\text{CH}_3$	156	(17, 84, 136)	$\text{OCN}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_4-\text{OCN}$	179-181	(123)
$\text{OCN}-\text{C}_6\text{H}_4-\text{Cl}$	172-174	(12, 88)	$\text{OCN}-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{OCN}$	168-169	(12)
$\text{OCN}-\text{C}_6\text{H}_4-\text{CH}_2\text{O}$	197	(123)			

agent and the phosphine catalyst (probably a phosphonium salt) does not interfere with the dimerization process. Finally, when the conversion is complete, the reaction mass may be stabilized and effectively freed of catalyst traces by treatment with the alkylating agent.

Among the phosphine catalysts the trialkyl derivatives are the most active. Dialkyl-aryl compounds, of which dimethylphenylphosphine is a good example, are more convenient in practice, however, because their action is more moderate, permitting better control of the exothermic dimerization reaction. When the phosphorus atom carries two phenyl groups, its efficiency as a catalyst is reduced, and triphenylphosphine exhibits no catalytic activity.

Isocyanate dimerization is an equilibrium reaction. The conversion to dimer increases with decreasing temperature, as illustrated (12) in table 4.

The known dimerization catalysts may all be described as nucleophilic agents. It is probable that dimerization occurs by the mechanism shown below:

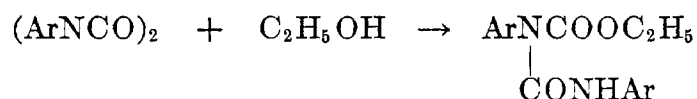


The availability of a pair of unshared electrons on the catalyst is not in itself sufficient, however. Obviously, structural or other factors must be involved. For example, dimethylphenylphosphine and dimethylaniline are about equal in base strength (50 per cent ethanol), but the phosphine is an extremely active catalyst and the amine is completely inactive.

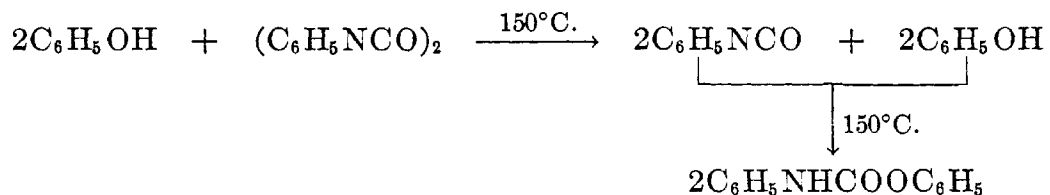
The dissociation of isocyanate dimers occurs only at elevated temperatures. The dimer of toluene 2,4-diisocyanate is almost completely converted to monomer at 175°C. and has been reported to dissociate at 150°C. (17). It has been shown that dimer dissociation follows first-order kinetics, as would be expected (212).

It has already been pointed out that the dimerization reaction involves an equilibrium. Thus, in solution in the presence of a phosphine catalyst dimers are dissociated even at low temperatures. For example, the dimer of toluene 2,4-diisocyanate is about 25 per cent dissociated at 25°C. in benzene solution and is 100 per cent dissociated at 80°C.

Alcohols react with isocyanate dimers to form allophanates (103).

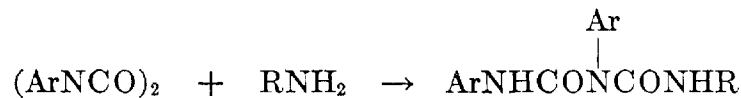


The reaction is slow, requiring prolonged heating of the dimer in alcohol. For this reason it is possible to employ ethanol as a solvent for the recrystallization of dimers. Phenol, at 100°C., does not react with phenyl isocyanate dimer (103) but a change does occur at 150°C.



Alcohols react with dimers in the presence of phosphine catalysts to yield the corresponding urethans, but this is probably the result of dissociation of the dimer to the free isocyanate rather than a direct attack on the dimer ring.

Amines combine with dimers to form biurets (103, 176).



With ammonia or aliphatic amines the reaction is rapid (103, 183). Aromatic amines are less reactive and, in fact, there is some evidence that they will not react at all (below the dissociation temperature of the dimer, of course) unless a catalyst is present. Triphenylbiuret has been prepared from phenyl isocyanate dimer and aniline at 100°C., but there is evidence that the dimer was contaminated with triethylphosphine (103). Purified phenyl isocyanate dimer and

TABLE 7
Effect of various reagents on phenyl isocyanate dimer

Reagent	Product	Reagent	Product
Hydrogen chloride (dry)	No reaction	Chlorine	<i>p, p'</i> -Dichlorophenyl isocyanate dimer
H ₂ , copper chromite or Raney nickel, 125°C., 5000 p.s.i.	No reaction	Bromine	<i>p</i> -Bromophenyl isocyanate dimer
Acid potassium permanganate	No reaction	Nitric acid	<i>p, p'</i> -Dinitrophenyl isocyanate dimer
Glacial acetic acid	No reaction	Sulfuric acid (100%)	Sulfanilic acid

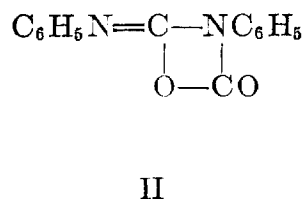
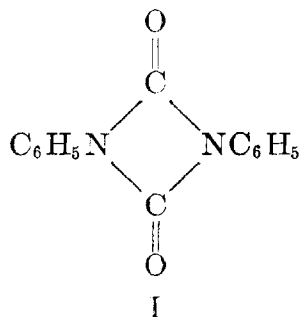
aniline do not react at 100°C.; in the presence of glacial acetic acid, however, a quantitative conversion to triphenylbiuret occurs at 25°C. within 3 hr. (124).

Ethylmagnesium bromide and methylmagnesium iodide react with phenyl isocyanate dimer to form carbanilide (176).

Aside from the reactions described above the dimer may be regarded as a relatively stable compound. For example, a number of nitrophenyl and nitronaphthyl isocyanate dimers have been catalytically reduced (palladium on charcoal) to the amino derivatives of the dimer, and these have been subsequently diazotized and coupled with suitable naphthols and phenols in aqueous medium (136). Table 7 lists a series of chemical reagents and their effect on phenyl isocyanate dimer.

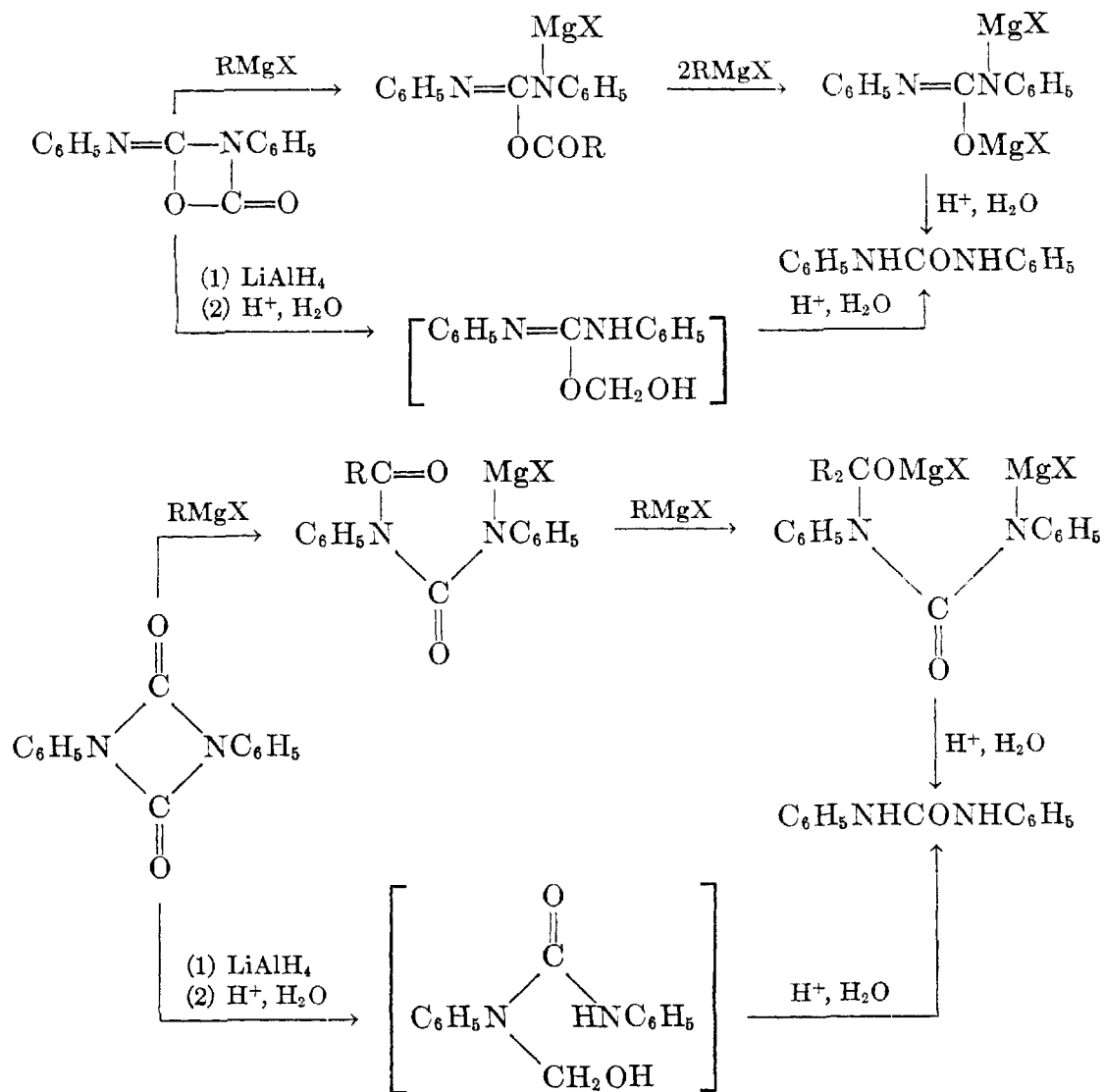
B. Structure and nomenclature

A 1,3-diaryl-1,3-diazacyclobutane-2,4-dione structure has been postulated for aryl isocyanate dimers (220). This structure has generally been accepted and the current nomenclature is based upon it. In 1939 *Chemical Abstracts* (43) indexed isocyanate dimers as uretidiones. Subsequently this was changed to uretidine dione, a term which is currently in use. The compounds are still commonly referred to simply as isocyanate dimers. The original structure is supported by recent crystallographic work (33), which shows that the dimer of phenyl isocyanate possesses a center of symmetry and is isostructural with *p*-terphenyl (see formula I).



The isomeric structure (II) has been proposed recently on the basis of the reactions between phenyl isocyanate dimer and Grignard reagents or lithium aluminum hydride (86a). It appears reasonable, however, that both structures

could yield the same final product, carbanilide, with these reagents, and the experiment is not yet definitive.



While crystallographic and infrared studies support structure I for the solid material, the possibility of rearrangements of the dimer in solution in the presence of reagents which may, secondarily, be catalysts cannot be ruled out.

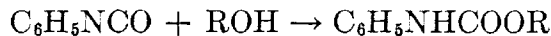
C. Trimers

Both aromatic and aliphatic isocyanates form trimers (*N*-substituted isocyanurates) when treated with appropriate catalysts (184).

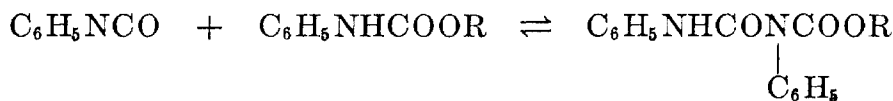
A new synthesis for aromatic isocyanate trimers has been reported (127). It is well known that, at moderate temperatures, the product of the reaction between an alcohol and an aromatic isocyanate is a carbanilate and that the reaction is catalyzed by tertiary amines (11). At elevated temperature (125°C.),

however, in the presence of the amine catalyst a good yield of isocyanate trimer is obtained. The reaction follows the course shown below:

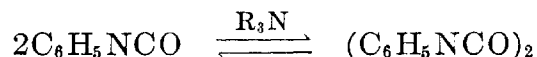
(a) Carbanilate formation:



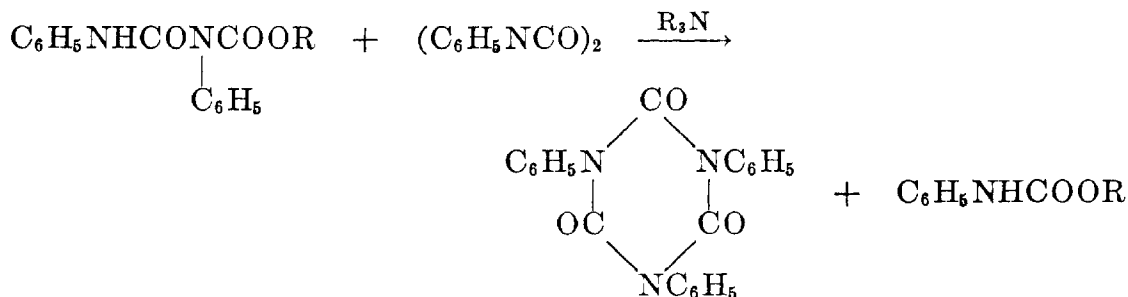
(b) Allophanate formation:



(c) Isocyanate dimerization:



(d) Isocyanate trimerization:



Thus the actual trimerization results from the reaction of allophanate and dimer and only occurs in the presence of the tertiary amine catalyst. Two of the three moles of isocyanate required by the reaction are derived from the starting dimer, and the third is supplied by the allophanate. It is obvious from this example that the method can be employed for the preparation of unsymmetrical isocyanate trimers.

The infrared absorption spectra of aromatic isocyanate trimers exhibit differences depending upon the orientation of the substituents on the aromatic rings (127). Tri-ortho-substituted aryl isocyanurates show a single carbonyl absorption at 5.87–5.90 microns, whereas the tri-para-substituted compounds exhibit three absorption peaks associated with the carbonyl group. Typical data are presented in table 8.

TABLE 8
Infrared absorption spectra of some substituted phenyl isocyanate trimers

Substituent	Carbonyl Absorption Peak	Substituent	Carbonyl Absorption Peak
	<i>microns</i>		<i>microns</i>
H.....	5.90	<i>p</i> -CH ₃	5.68, 5.86, 5.94
<i>o</i> -CH ₃	5.90	<i>p</i> -Cl.....	5.66, 5.85, 5.95
<i>o</i> -Cl.....	5.88	<i>p</i> -OCH ₃	5.70, 5.83, 5.95
<i>o</i> -NO ₂	5.87	<i>p</i> -NO ₂	5.67, 5.83, 5.94
<i>o</i> -OCH ₃	5.87		

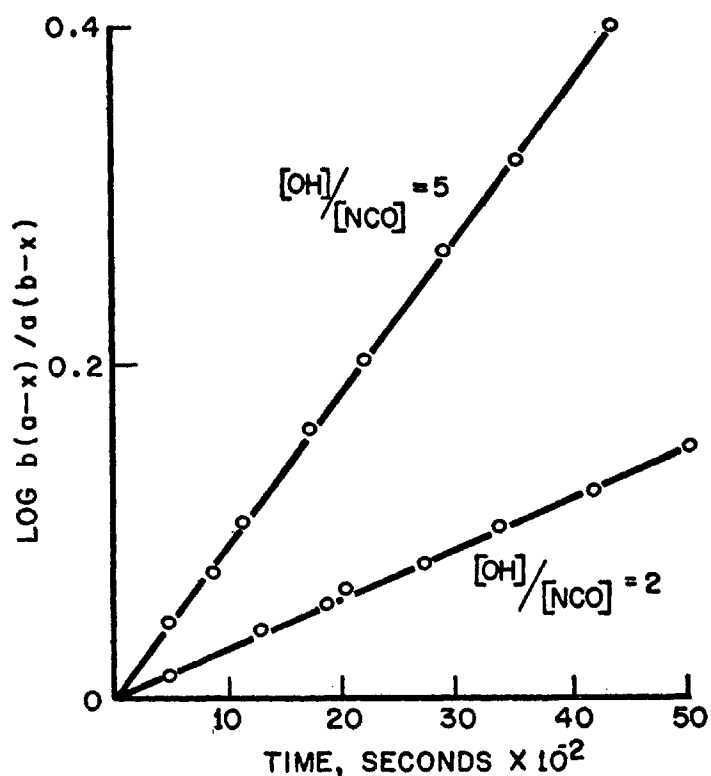
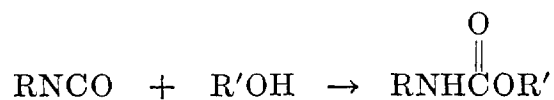


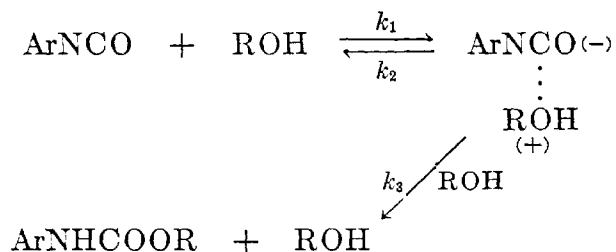
FIG. 1. Rate of reaction of *sec*-butyl alcohol with phenyl isocyanate in xylene at 25°C.

V. REACTION KINETICS

The stoichiometry of the reaction between an isocyanate and an alcohol is expressed by the simple equation:



The kinetics of the reaction, however, are not as straightforward as this equation would indicate. The reaction appears to follow second-order kinetics, with the complication that the rate constant obtained is dependent upon the ratio of the alcohol-isocyanate concentrations, as figure 1 illustrates (59). This reaction has been studied extensively (7, 8, 9, 10, 11). The mechanism shown has been suggested to account for the experimental kinetic data.



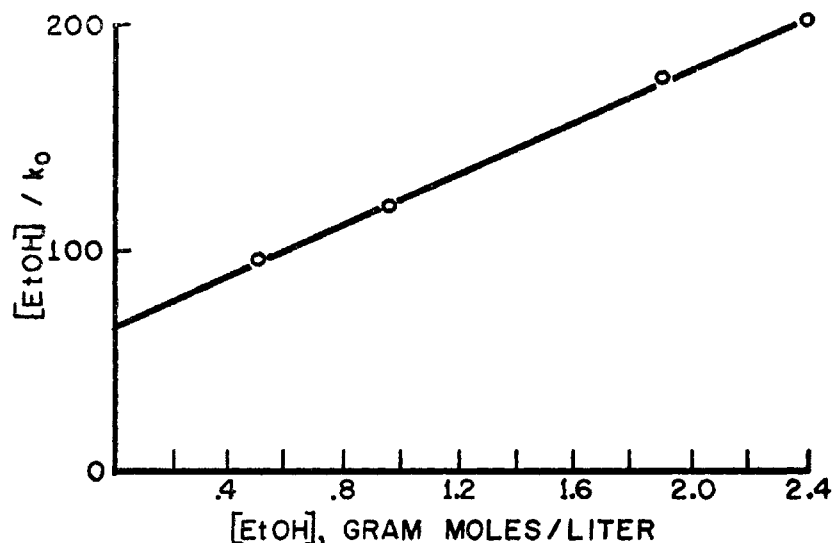


FIG. 2. Dependence of rate constant on alcohol concentration; reaction of ethyl alcohol with phenyl isocyanate in di-*n*-butyl ether at 20°C.

Using this mechanism the apparent second-order rate constant of the reaction, k_0 , may be expressed as a function of the alcohol concentration:

$$k_0 = k_1 k_3 (\text{ROH}) / (k_2 + k_3 (\text{ROH}))$$

Rearranging:

$$(\text{ROH})/k_0 = k_2/k_1 k_3 + (\text{ROH})/k_1$$

The straight line obtained by plotting $(\text{ROH})/k_0$ against (ROH) (figure 2) supports the correctness of the assumptions. This reaction has been examined in both di-*n*-butyl ether and benzene. Association and solvation play an important role in controlling the kinetics by virtue of the effect of these factors on the concentration of free alcohol in the solution. Because of such secondary effects perturbations were observed, but the assumptions as to the nature of the primary reaction appear sound.

From the foregoing it is obvious that the alcohol is playing a dual role as catalyst and reactant. Tertiary amines, with the exception of the *N*-dialkylanilines (7, 8, 9, 10), catalyze the reaction and are more effective in this role than alcohols. The second-order rate constant observed in an amine-catalyzed reaction is a linear function of the concentration of the tertiary amine.

$$k_0 = k_1 k_3 (\text{R}_3\text{N}) / [k_2 + k_3 (\text{R}_3\text{N})]$$

Rearranging:

$$(\text{R}_3\text{N})/k_0 = k_2/k_1 k_3 + (\text{R}_3\text{N})/k_1$$

Evidence adduced in the case of the alcohol-isocyanate reaction indicates that isocyanates are highly sensitive to the action of nucleophilic catalysts. Even the *N*-phenylurethan which is the product of the combination of phenylisocyanate with an alcohol is a weak catalyst for the reaction (11). Consequently,

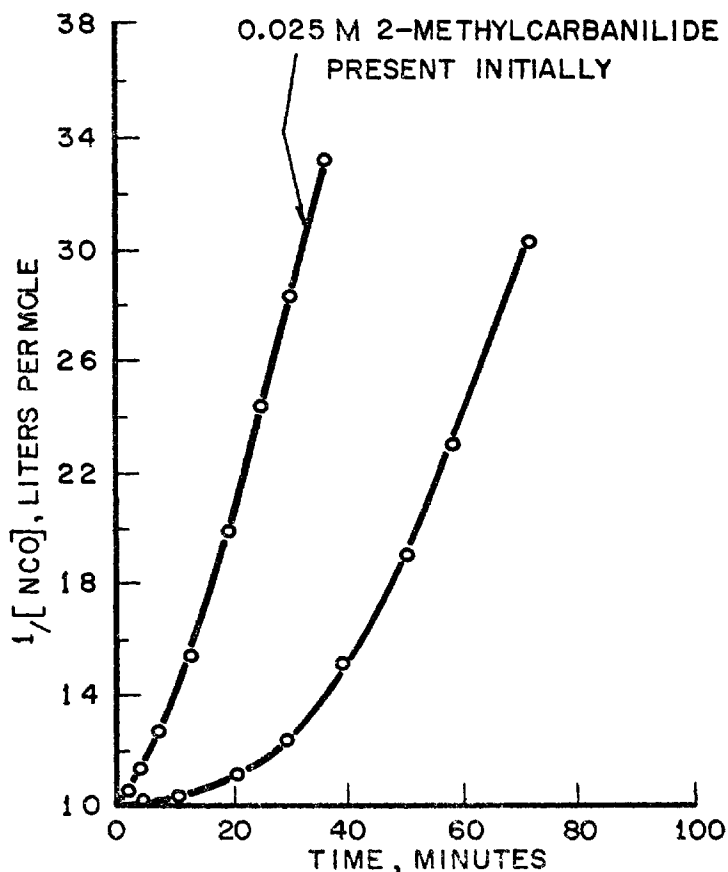


FIG. 3. Rate of reaction of 0.1 *M* phenyl isocyanate with 0.1 *M* *o*-toluidine in dioxane at 31°C.

it is to be expected generally that reactions involving other nucleophilic reagents, such as amines, water, mercaptans, and their nucleophilic reaction products, will exhibit anomalous kinetics rather than the simple second-order relationship suggested by the stoichiometric equations. That this expectation is well founded is illustrated by results obtained with phenyl isocyanate and *o*-toluidine, which combine to form 2-methylcarbanilide. The results shown in figure 3 demonstrate that the reaction is not simple second order and that it is strongly catalyzed by the urea which is the product of the reaction (47). The scheme which is illustrated is consistent with the kinetic data.

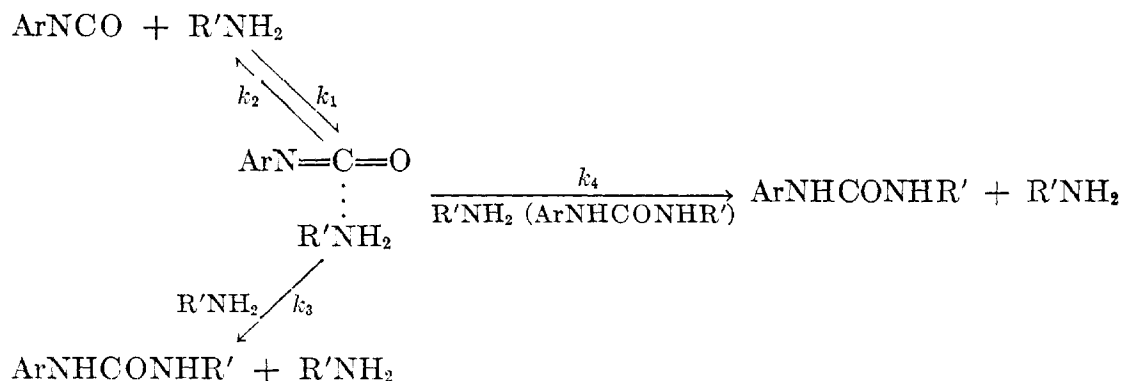


TABLE 9
Initial rates of amine-isocyanate reactions
 $R_0 = k(I)(A)^n$

Amine	Isocyanate	n
<i>p</i> -Toluidine.....	Phenyl	~1.0
Aniline.....	Phenyl	1.7
<i>o</i> -Toluidine.....	Phenyl	1.85

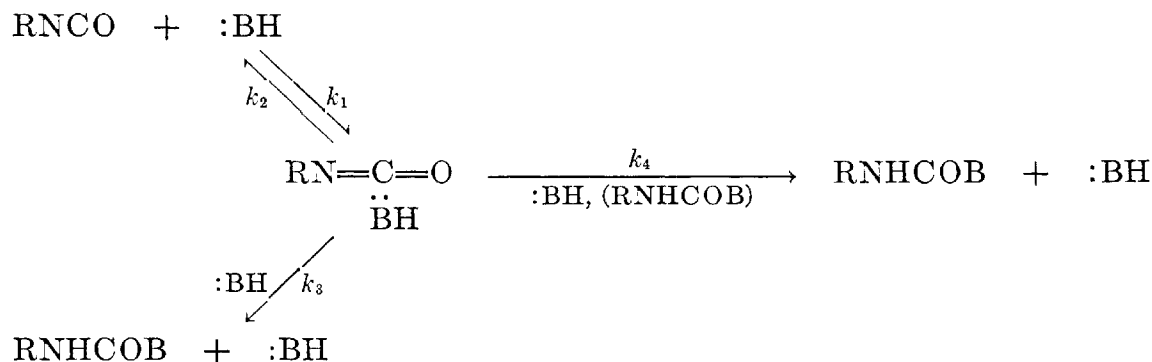
This sequence is identical in principle to that presented for the phenyl isocyanate-alcohol reaction. The differences between the amine and the alcohol reactions reside in the relative catalytic activity of the reactants and products. The carbanilide formed in the amine reaction is a much stronger catalyst for the reaction than is the urethan which is the product in the alcohol reaction. For this reason the kinetic expressions become more complicated, since they must include a term for the carbanilide concentration. Further, the amine itself is a more active catalyst than is alcohol. This is indicated by the fact that a tertiary amine accelerates the isocyanate-alcohol reaction and the apparent second-order rate constant becomes dependent upon the amine concentration, whereas a tertiary amine does not appreciably increase the rate of the isocyanate-amine reaction.

While the general principles described above apply to the kinetics of amine-isocyanate reactions, specific examples display considerable individuality. The initial rates of the reactions measured before appreciable quantities of product carbanilides have formed show substantial variations in their dependence upon the amine concentration, as illustrated in table 9. Furthermore, the catalytic activities of the product carbanilides show considerable variation. Development of the kinetic expressions on the basis of the same assumptions used for the alcohol-isocyanate reaction discussed above allows the assessment of the ratio of the specific rate constants k_3 and k_4 (see scheme for the amine-isocyanate reaction). The value of this ratio (k_3/k_4) provides an indication of the relative catalytic activity of the product carbanilides. The value of this ratio for the reaction between phenyl isocyanate and *o*-toluidine is 0.02; for phenyl isocyanate and aniline, 0.073; and for phenyl isocyanate and *p*-toluidine, 0.40. The apparent catalytic activity of the product carbanilides decreases in the same order.

The lack of catalytic activity of 4-methylcarbanilide in the reaction between *p*-toluidine and phenyl isocyanate may well be a consequence of the relatively high base strength of *p*-toluidine, which overpowers the weakly basic carbanilide in performing the catalytic function for the reaction. When *p*-tolyl isocyanate is reacted with aniline, the same product carbanilide is formed, but the overall reaction is slower and is weakly catalyzed by the reaction product.

The kinetics of the reaction between water and aryl isocyanate indicate that this reaction also follows the same general pattern outlined for the alcohols and amines (213). In other words, water is a catalyst for its own reaction with an isocyanate.

On the basis of the studies which have been outlined it is possible to generalize the reactions of aryl isocyanates with alcohols, amines, and water.



Kinetic investigations undertaken in the field will have to account for at least four specific rate constants to explain these superficially simple reactions.

It is apparent that rate constants for the reactions of isocyanates with nucleophilic reagents, where they can be determined, will be specific rather than general, each one qualified by the conditions of solvent and catalysis under which it was obtained. Nevertheless, kinetic experiments have supplied data which give more exact meaning to the comparisons of the reactivities of various types of isocyanates and attacking reagents. For example, in table 10 the effect of changing the electronegativity of the group attached to the nitrogen atom of the isocyanate function on the reactivity of that function toward methyl alcohol (11) is shown. These data emphasize the much greater reactivity of aromatic as compared to aliphatic isocyanates and the wide range of activity available within the family of isocyanates.

VI. DIISOCYANATES

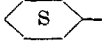
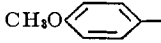



In the polymer field only di- and polyisocyanates are of interest. They are reactive building units capable, under the proper conditions, of forming high-molecular-weight materials. Application of di- and polyisocyanates has been extensive. The more reactive aromatic compounds are receiving the greatest attention.

The chemistry of isocyanates as defined by work with monoisocyanates is applicable with little or no modification. One feature of the transition, however, which has received some attention is the effect of one isocyanate function upon the reactivity of another when both are attached to the same aromatic nucleus. Rate studies performed on *o*- and *p*-tolyl isocyanate-amine systems (47) showed that *p*-tolyl isocyanate is the more reactive and one would be justified in suspect-

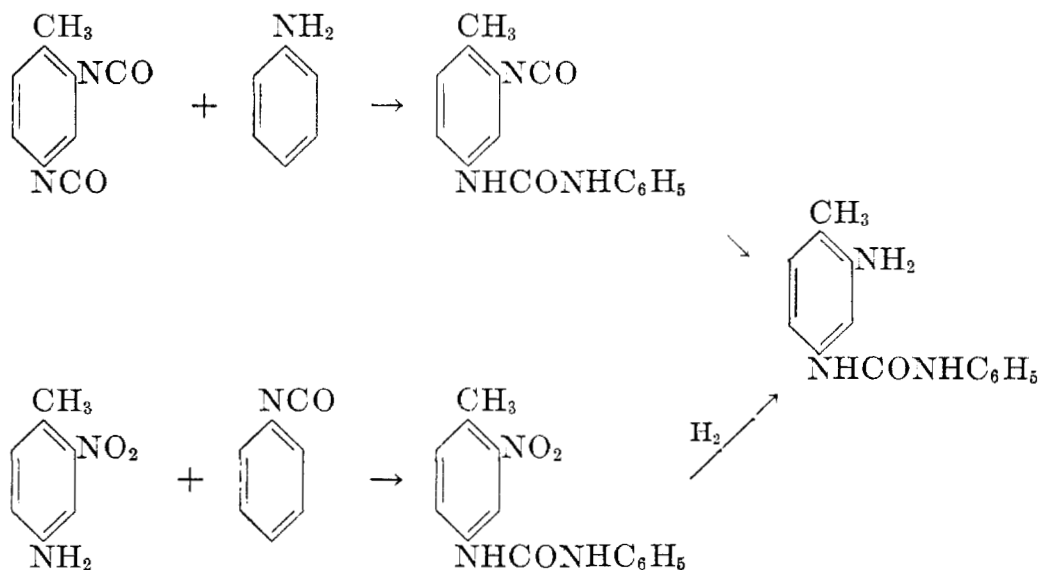
TABLE 10

Relative rate constants of RNCO with methyl alcohol in di-n-butyl ether at 20°C.

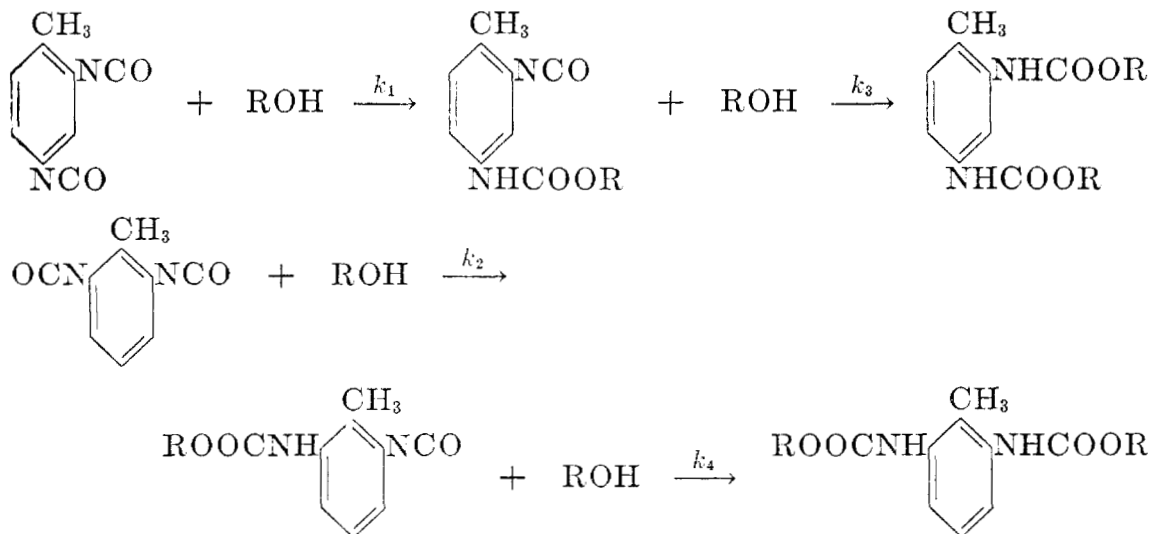
Catalyst, 0.0306 M triethylamine

R =					
	1	471	586	1076	142,800

ing that this is also true for the para isocyanate group in toluene 2,4-diisocyanate. However, to prove the absence of any anomalous effects the difference in reactivity of the isocyanate groups was established by the following procedure (4): Toluene 2,4-diisocyanate (1 mole) was reacted with aniline (1 mole) in tetrahydrofuran solution and the residual isocyanate group hydrolyzed with hydrochloric acid. Fractional recrystallization of the product gave 68 per cent of the theoretical yield of a compound which proved to be identical with an authentic sample of 3-amino-4-methylcarbanilide, as judged by melting point, mixed melting point, and infrared spectra. The remaining 32 per cent of the material consisted predominantly of a mixture of the two isomeric carbanilides which could not be separated readily.

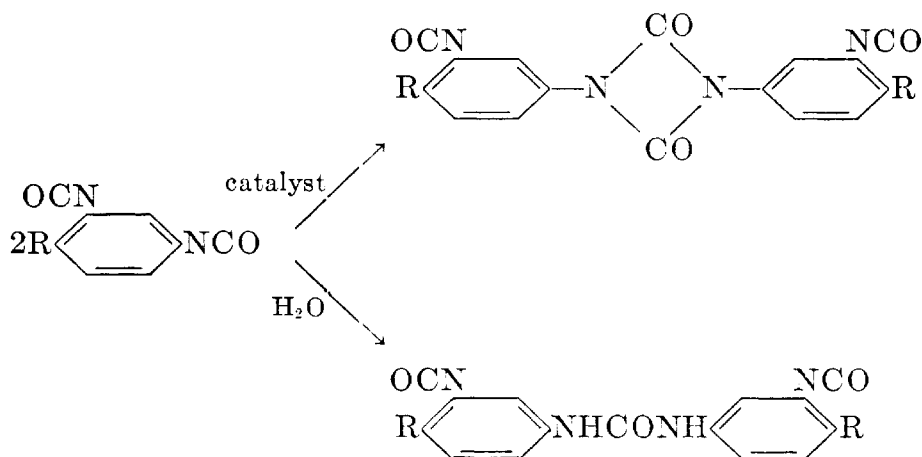


The preceding example indicates that the relative reactivities predicted from examination of the appropriate monoisocyanates are qualitatively correct in the case of toluene 2,4-diisocyanate. The following example, however, serves to demonstrate that predictions as to absolute reactivity are not justified.



As anticipated, k_1 is greater than k_2 , but accurate measurements of k_3 and k_4 (210) show that the ratio $k_3/k_4 = 1/2$. Thus, the reactivities of the two "ortho isocyanate" functions of the 2,4- and the 2,6-isomers differ by a factor of two, and neither is identical to that of the isocyanate function of *o*-tolyl isocyanate.

Among the diisocyanates of practical interest the most versatile are those bearing isocyanate groups which differ in their reactivity, since they allow the controlled stepwise synthesis of polymers or their intermediates. An example of the utilization of such differential reactivity is to be found in the preparation of diisocyanate dimers (17) and ureas (169), which are obtainable in high yield.



R = CH_3 , CH_3O , or C_6H_5O .

In the preparation of polymers a degree of control over the orientation and structure of the segment derived from the diisocyanate is possible depending upon the magnitude of the difference in reactivity of the isocyanate groups.

VII. APPLICATION

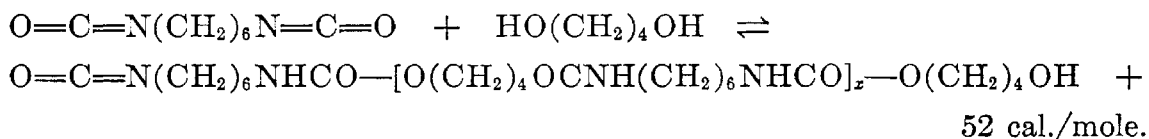
An examination of the formal and the patent literature provides an indication of the scope and intensity of industrial research activity in the isocyanate field. A detailed discussion of the recent patent literature is not warranted. However, a generalized outline of the types of products in which isocyanates are finding application is presented.

The reaction of di- or polyfunctional isocyanates with reagents such as water, amines, alcohols, etc., is generally comparable to their monofunctional counterparts. No abnormal reactivity in polymeric systems has been reported, and in general the reaction rates observed have been independent of the polymeric species participating. Because of the great reactivity of isocyanates, however, their reactions are rarely if ever devoid of undesirable side reactions. For this reason reactions involving the synthesis of high-molecular-weight products are somewhat difficult to control and reproduce. In this latter respect, however, isocyanate reactions do not differ markedly from other condensation systems.

A. Fibers

Condensation polymerization resulting from the reaction of a compound containing at least two isocyanate groups with other polyfunctional reagents

containing active hydrogen has opened a new and rapidly developing field in polymer chemistry. While many polymers have been investigated, only the linear polyurethans (Perlon U) derived from diols such as 1,4-butanediol and hexamethylene diisocyanate (18) are well known. They are usually made in aromatic chlorinated solvents at reflux.



Molecular weight \sim 10-12,000

These polymers are of interest as plastics and fibers because of their tensile strength, low water absorption, good electrical properties, and good resistance to outdoor exposure and acid. Their melting points are unusually sharp and attest to uniformity in molecular weight. The variation in melting point with structure is shown in table 11.

Polyurethans synthesized from hexamethylene diisocyanate and *cis*- and *trans*-2-butene-1,4-diol show small differences in properties, not attributable to *cis-trans* isomerism (144).

Polymers formed from 1,3-propanediol and 2,2-dimethyl-1,3-propanediol by reaction with hexamethylene diisocyanate are more crystalline than is that formed from 2-methyl-1,3-propanediol (31). Softening-point data are recorded in table 12.

B. Elastomers

The recent patent literature indicates an extensive interest in elastomers derived from isocyanates (6, 20, 21, 23, 32, 34, 35, 37, 58, 64, 70, 77, 99, 114-118,

TABLE 11
Melting points of some polyurethans

Number of Carbon Atoms in		Melting Point	Number of Carbon Atoms in		Melting Point
Diisocyanate	Glycol		Diisocyanate	Glycol	
		°C.			°C.
4	4	190	6	5	159
4	6	180	6	9	147
4	10	170	12	12	128
6	3	167			

TABLE 12
Softening points of polyurethans formed from hexamethylene diisocyanate and glycols

Glycol	Softening Temperature of Polyurethan (Approximate)	Glycol	Softening Temperature of Polyurethan (Approximate)
	°C.		°C.
1,2-Ethanediol.....	170	2-Methyl-1,3-propanediol.....	50
1,3-Propanediol.....	155	2,2-Dimethyl-1,3-propanediol.....	120
1,5-Pentanediol.....	235		

120, 129, 131, 133, 143, 145-148, 155-159, 166, 168, 194, 197-201, 235-237, 239). The intermediates employed include polyether glycols, polyester glycols derived from aliphatic, aromatic, and unsaturated components, and polyester amides of molecular weights in general of 1000 or greater. Aromatic and aliphatic isocyanates and isothiocyanates and thermally unstable or reactive adducts of isocyanates have been used in the polymerizations. The products themselves range from liquids to solids, some of which must be immediately molded and cured and some of which are stable to storage. Curing of the raw polymers to form finished elastomeric articles is effected variously by simple heating of the initial reaction product or by heating in the presence of added polyisocyanate or active halogen compounds or, with polymers containing unsaturated linkages, free-radical promoters such as di-*tert*-butyl peroxide.

C. *Plastics*

Elastomers represent only one segment of the isocyanate polymer field. Relatively high-molecular-weight, linear, low-melting glycols and diamines, when polymerized with diisocyanates, are the basic intermediates for elastomeric products, whereas low-molecular-weight or highly crystalline, higher-molecular-weight difunctional alcohols, amines, carboxylic acids, etc., and polyfunctional reagents form, with di- and polyisocyanates, the basis for plastics, coatings, films, and fibers (22, 36, 39, 41, 49, 52, 53, 57, 62, 76, 98, 111-113, 119, 137-140, 158, 164, 165, 167, 173, 186, 187, 189, 191-193, 196, 216, 222, 223, 227, 234, 238). One product derived from aliphatic diamines and diisocyanates and bearing intralinear secondary amino functions which may be acylated or hydroxy-alkylated is suggested as a plasma substitute (24). These products may be considered to be formed primarily by the reaction of isocyanates with alcohols, amines, carboxylic acids, water, and thiols, although often the intermediates are themselves preformed polyesters, polyamides, polyethers, polysiloxanes, and so on. There are also disclosed a few products which involve simultaneous reactions of not only isocyanate functions but other types of functional groups as well. In one example, a monoisocyanate bearing a carboxyl group is condensed with a diaminoalcohol to yield a fiber-forming polymer (224). In another, aromatic isocyanates bearing reactive halogen (benzyl) are polymerized in the presence of a Friedel-Crafts catalyst (74). A third example utilizes mono- or polyisocyanates which contain ethylenic bonds and which may be polymerized under such conditions that chain extension through reaction of both types of functions occurs (19).

D. *Foams*

Isocyanates, in their reactions with water and carboxylic acids, produce as a by-product of the polymerization a gas, carbon dioxide. As a consequence the polymerizing material is blown up to form a voluminous porous structure. When this phenomenon is properly controlled, foams with excellent structure and almost any desired density can be obtained (14, 15, 61, 63, 65, 67, 71, 75, 78-83, 90, 100, 106-108, 126, 209, 233). Depending upon the character of the intermediates these foams will be rigid or elastic. Foam "Prepolymers" are

reaction products of di- or polyisocyanates with the same intermediates used in the formation of bulk elastomers and plastics with the difference that excess isocyanate is used so that a low-molecular-weight viscous fluid is formed. Addition of the final reactant such as water or dicarboxylic acid is made just prior to use, the mixture is poured into a mold, and chain extension, cross-linking, and foaming occur simultaneously.

E. Polymer modification

Mono-, di- and polyisocyanates have been used to cross-link or otherwise modify the properties of polymers which are not themselves formed from isocyanates. Such products include alkyd resins (208, 211), cellulose ethers or esters (181), polyamides (104, 185, 190), and polyurethans (188).

F. Adhesives and pigment-bonding systems

Isocyanates have been useful in the formulation of adhesives. Rubber may be bonded to polar substrates with the aid of isocyanates (95, 170). Condensation products of isocyanates with polymers bearing carboxyl groups (217) or other groups which will react with isocyanates (152) have been employed as adhesives.

G. Catalysts for isocyanate reactions

Although isocyanates are described as reactive compounds, aromatic much more so than aliphatic, it is often advantageous to accelerate reactions with catalysts. This is particularly true in the formation of foams. Isocyanate-water reactions are catalyzed by tertiary amines (234) and by inorganic acids such as sulfuric and phosphoric (134, 135). Reactions between isocyanates and alcohols or carboxylic acids are accelerated by tertiary amines or phosphines (132), beryllium hydroxide (48), colloidal or soluble iron compounds (131), lactams (174), and combinations of basic substances and neutral metallic compounds such as nickel carbonyl or iron acetylacetonate (81).

H. Isocyanate generators

The extreme reactivity of isocyanates toward compounds containing active hydrogen makes them attractive as cross-linking or modifying agents for plastics, elastomers, resins, coating materials, textiles, and adhesives. In many of the above applications it is necessary to delay the desired isocyanate-substrate reaction until the final stages of fabrication or use. In order to achieve this objective certain isocyanate derivatives capable of undergoing thermal dissociation or exchange reactions with the active hydrogen site of the substrate are used to generate the isocyanate at the proper stage.

These isocyanate generators (16, 171) include the mono-, di-, or poly-reaction products of mono-, di-, or polyisocyanates with a secondary aromatic amine (16), tertiary alcohols (16, 105), amides (205, 238, 240), lactams (204, 238), monohydric phenols (203, 238), mercaptans (238), enolizable hydrogen compounds (16, 105, 171, 172, 203), heterocyclics (16, 69), hydrogen cyanide (171), and sodium bisulfite (16, 56, 171).

I. Miscellaneous

Other miscellaneous uses for isocyanates or polymers derived from them have been patented. These include the fixing of pigments on textiles and paper (46, 60, 66, 68), the bonding together or coating of fibers (51, 150, 182), and the preparation of cements of isocyanate-based polymers in appropriate solvents (30).

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