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Carbodiimides as important intermediates in the reaction of isocyanates with carboxylic acids

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Abstract. The reaction between isocyanates and carboxylic acids is known to lead to amides. We have studied the mechanism of catalysis of this reaction by phospholene oxides. The reaction between phenyl isocyanates and benzoic acid was monitored under various conditions using High-Pressure Liquid Chromatography. It was found that the catalyst reacts with the isocyanate under formation of a carbodiimide. The carbodiimide reacts with the carboxylic acid to form amide and isocyanate via an N-acylurea as intermediate. The catalyst is partly deactivated by the acid. The phospholene catalyst was only found effective in reactions with aromatic isocyanates.

Introduction

Diisocyanates are important monomers for wide variety of polymers, the most relevant ones being polyurethanes and polyureas. A less known application is the synthesis of polyamides by reaction of diisocyanates with carboxylic acids with elimination of carbon dioxide. The synthesis of polyamides has been investigated by several research groups^{1,2,3}. The mechanism of the reaction has also been studied^{4,5,6} but it has not yet been fully elucidated. For instance, it is known that phospholene oxides are very efficient catalysts, but the mechanism of catalysis has not been investigated until the present study.

The mechanism of the reaction^{4,5,6} between isocyanates and acids is presented in Scheme 1. The first step of the reaction



Scheme 1

is the equilibrium formation of a mixed anhydride 3 by addition of isocyanates 1 to acids 2. 3 can react with a second molecule 2 to give formation of the acid anhydride 4 and the unstable carbamic acid 5. The latter compound decomposes, with elimination of CO_2 , into the amine 6. Reaction of 6 with 4 leads to amides 7. In a side reaction, 6 may also react with 1 to form 1,3-disubstituted ureas 8. At sufficiently high temperatures, 8 is assumed to dissociate into 6 and 1, whereupon 7 can be formed again. In addition to these reactions, 3 can decompose directly into 7 and CO_2 . Moreover, 6 can also react with 3, leading to formation of 7 and 5.

It is not clear how phospholene oxides 9 could play a role in the kinetics of these reactions. However, the compounds are known to be efficient catalysts for the conversion of isocyanates into carbodiimides^{7.8} and this may be the basis of their catalytic action. The series of reactions leading to the carbodiimide 10 is shown in Scheme 2.

Scheme 2

Recently, we have studied⁹ the kinetics of the reaction of aromatic carbodiimides with carboxylic acids. We found that, above 60° C and through *N*-acylurea 11 as intermediate, amide and isocyanate are the end products (Scheme 3).

The role of phospholene oxides in the reaction of 1 with 2 may be formation of 10 according to Scheme 2, followed by reaction of 10 with 2 under formation of 7 and 1 as shown in Scheme 3.

To test this hypothesis, we followed the course of reactions of phenyl isocyanate (1a) with benzoic acid (2a) in the presence and absence of 4,5-dihydro-3-methyl-1-phenyl-1H-



Scheme 3

-phospholene 1-oxide (9a). If our hypothesis is correct, 1,3diphenylcarbodiimide (10a) and 1-benzoyl-1,3-diphenylurea (11a) must be intermediates, with 9a as a catalyst. N-Phenylbenzamide (7a) is the ultimate product of the catalyzed reaction. In the uncatalyzed reaction, additional products are benzoic acid anhydride (4a) and 1,3-diphenylurea (8a). Tetrahydrothiophene 1,1-dioxide (THTDO) and 1-methyl--2-pyrrolidinone (NMP) were used as solvents; the reaction temperature was varied from room temperature to 140°C. To examine the influence of the isocyanate structure, we also performed reactions with cyclohexyl isocyanate (1b) with 2a.

In order to determine quantitatively the course of the reaction, a high-pressure liquid chromatography method was developed to monitor the concentration of the intermediate products.

Results and discussion

Reactions in tetrahydrothiophene 1,1-dioxide (THTDO)

Because of its inertness towards isocyanates and its high boiling point, THTDO is used a great deal as a solvent for the syntheses of polyamides^{1,2,4} from isocyanates and carboxylic acids. These syntheses in THTDO are mostly carried out at about 200°C. At this temperature, the reaction rate of formation and decomposition of intermediate 11 is so high⁹ that the concentration will be too low to be detected. However, at lower temperatures (about 50° C), 11 is more stable.

Reactions between 1a and 2a were run at various temperatures in the presence and absence of 9a at various temperatures in the hope of detecting 11a in the presence of 9a. The course of a reaction conducted at 32° C is shown in Figure 1. Under these conditions, *N*-acylurea 11a is found



Figure 1. Course of the reaction of 1a (1 mole/l) and 2a (0.5 mole/l) in the presence of 9a (0.02 mole/l) in TMS at $32^{\circ}C$.

as an intermediate. **10a** can be detected, which is in agreement with the relatively low reaction rate for the reaction of **2a** with **10a** under these conditions⁹. At 100°C, **10a** cannot be detected because it reacts away more quickly than it is formed.

Based on these observations, we propose a new Scheme for the reaction of carboxylic acids with isocyanates (Scheme 4).



Scheme 4

This Scheme shows all intermediates and products. On the left-hand side, the uncatalyzed path can be seen; on the right-hand side the reaction catalyzed by phospholene oxide. Published reports^{4,5,6} propose that the intermediate urea 8 dissociates into isocyanate and amine, followed by reaction of amine with anhydride to amide and acid. We think that this reaction may occur at high temperatures (e.g., 200°C) but that, at lower temperatures, acetylation of the urea 8 to form N-acylurea 11 is more likely. This N-acylurea then dissociates into amide and isocyanate as shown in Scheme 4. We tried to test this by reacting 1,3-diphenylurea (8a) with benzoic anhydride (4a) in THTDO at 120°C using again HPLC monitoring. It turned out that, at this temperature, the reaction between 8a and 4a is very slow (hours) whereas the half-life of 11a is about 100 s⁹. Thus, 11a could not be detected. However, in the reaction of 1,3-dicyclohexylurea with 4a, the corresponding N-acylurea could be identified⁹, because these aliphatic N-acylurea are more thermally stable.

Apart from these qualitative considerations, we have also simulated reaction kinetics of the catalyzed carboxylicacid/isocyanate reaction to amide, based on reaction rates of the intermediate steps of the right-hand part of Scheme 4. The rate of carbodiimide formation from isocyanate ($1a \rightarrow 10a$) was determined in THTDO at 100°C at a catalyst concentration of 0.002 (mole 9a)/l. The reaction was second order in isocyanate; the reaction rate was 0.00078 $1 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$. The rate constants of the second step (formation of *N*-acylurea 11a) and third step (dissociation of 11a in THTDO) at 100°C are 0.31 $1 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ and 0.0031 s⁻¹, respectively⁹. The catalyst was shown to have no effect on the last two steps.

Using the program GEAR¹⁰, the concentrations of intermediates and products of the reaction of 1a and 2a were simulated using the above mentioned reaction rate values



Figure 2. Observed (——) and predicted (–––) course of the reaction of 1a with 2a (both 0.5 mole/l) at 100°C in TMS, in the presence of 9a (0.002 mole/l).

and compared with experimental values (Figure 2). The fit is not very good: the observed rate of formation of N-acylurea and amide is lower than calculated. A lower rate is surprising because a higher rate could be expected on account of the uncatalyzed reaction, taking place additionally. Evidence for this reaction is also found from the presence of urea and anhydride in the reaction mixture (not shown) and the relatively fast decrease of isocyanate at the beginning of the reaction. The disagreement between the calculated and observed course of the reaction suggests decreased activity of the catalyst in the presence of acid¹¹. To test this suggestion, the increase of the carbodiimide concentration was followed as a function of time, in the presence and absence of acid. It was found that, in the presence of acid, the rate of conversion of 1a into 10a decreases. An equimolar amount of perchloric acid completely blocks the catalyst (Table I).

Table I Influence of acids on conversion of 1a (1.0 mole/l in THTDO) into 10a at $32^{\circ}C$ in the presence 9a (0.02 mole/l) after 3 hours.

Acid	Concr. (mole/l)	10a found (mole%)	
_	_	67	
benzoic	0.5	14 ^a	
perchloric	0.02	< 0.05	

^a As part of **10a** reacts away with **2a** to form **11a**; the sum of **10a** and **11a** is determined in this case.

The observed inhibition of the catalyst by acids can be interpreted as a simple acid/base reaction. Protonation of the oxygen of **9a** was proven by ³¹P NMR. Addition of dichloroacetic acid causes a downfield shift of 6 ppm of the ³¹P signal of **9a**, as is expected¹² when phospholium ions are formed. Reversibility of the process can be proven by addition of propylamine, which causes an upfield shift. From Scheme 2, it is understandable that the protonated phospholene oxide is not active as a catalyst.

The conclusion is that the reaction of isocyanates with carboxylic acids to amides is catalyzed by phospholene oxides. However, the rate enhancement is less than expected from the rate of carbodiimide formation from isocyanate with phospholene catalyst without acid. Reactions in 1-methyl-2-pyrrolidinone (NMP)

THTDO is not such a good solvent for polyamides as, for example, NMP, dimethyl sulfoxide, dimethylformamide, with their higher H-bonding capacity. These solvents, however, react to a certain extent with isocyanates¹³. NMP is said to be relatively inert to isocyanates and has a much lower boiling point (202°C) than THTDO, enabling better solvent removal from polyamides using the isocyanate carboxylic acid reaction. Hence, reactions were also carried out in NMP. Table II shows the composition after a 1-hour reaction under various conditions.

Table II Composition (in mole $\frac{2}{3}$) of reaction mixture after 1 hour reaction at 100°C of 1a with 2a (both 0.5 mole/l).

Component	Catalyzed reaction [0.002 (mole 9a)/l]		Uncatalyzed reaction	
	THTDO	NMP	THTDO	NMP
isocyanate (1a) amide (7a) urea (8a) carbodiimide (10a) N-acylurca (11a)	43 14 14 < 0.05 6	18 70 7.4 0.1 1.4	79 2 16 < 0.05 < 0.05	256010< 0.05< 0.05

The following conclusions can be drawn from Table II:

- Both catalyzed and uncatalyzed reactions to amide are faster in NMP than in THTDO.
- Catalysis in NMP has less effect than in THTDO.
- 10a and 11a are both intermediates in the catalyzed reaction in NMP as well as in THTDO. It is remarkable that 10a can be detected in NMP at much higher concentrations than in THTDO. After 2 minutes reaction at 100°C, the concentration of 10a reached a maximum and amounted to 4.2 mole%. When a reaction at 100°C is carried out in THTDO, 10a is not detectable. This is caused by the fact that reaction of 10a with 2a is much slower in NMP than in THTDO⁹.

Influence of isocyanate structure

The reactions described above were all carried out using phenyl isocyanate. The aliphatic cyclohexyl isocyanate was also tested. In this case, even at a temperature of 160° C, no catalytic effect of phospholene oxide could be detected. This behaviour is not in contradiction with Scheme 4; it is known that aliphatic isocyanates are much less reactive than aromatic isocyanates in the first step of Scheme 2¹¹. The reaction of an aliphatic isocyanate with benzoic acid is much slower: only 20% of the isocyanate was converted to amide after a 1-hour reaction at 160° C.

Experimental

NMR

³¹P NMR spectra were obtained in CDCl₃ on a Fourier Transform Bruker AM400 operating at 160 MHz. The chemical shifts were measured versus 85% H₃PO₄. Spectra were recorded of **9a**, **9a** with an equimolar amount of dichloroacetic acid and **9a** with dichloroacetic acid and propylamine.

Materials

Phenyl isocyanate (1a), cyclohexyl (1b), benzoic acid (2a), benzoic anhydride (4a) and 1,3-diphenylurea (8a) were received, in a purity of at least 99%, from Janssen Chimica and used without purification. 4,5-Dihydro-3-methyl-1-phenylphospholene 1-oxide (9a) was obtained from Merck (98%). This material is supplied as the 2,5 isomer, but that material is a liquid¹⁴, whereas the received material was a solid with melting point and ¹H NMR spectrum of the 4,5 isomer¹³. *N*-Phenylbenzamide was supplied by from Merck-Schuchardt (99 $^{\circ}_{0}$). 1,3-Diphenylcarbodiimide (10a), 1-benzoyl-1,3-diphenylurea (11a) were synthesized as described previously⁹.

Tetrahydrothiophene 1,1-dioxide (THTDO, tetramethylene sulfone) was obtained from Fluka (>99.5%), and 1-methyl-2-pyrrolidinone from Janssen Chimica (>99%); both solvents were dried over molecular sieves prior to use.

Reaction conditions

About 14 mmol of carboxylic acid and 1 g of biphenyl (which was used as an internal standard for the HPLC analysis) and an appropriate amount of catalyst were accurately weighed in a 50-ml threeneck round-bottom flask. The round-bottom flask was equipped with a reflux condensor, a thermometer and a screw-cap septum. To exclude moisture, the whole system was kept under a slight excess pressure of nitrogen during the experiment. After addition of 25.0 ml of solvent, the flask was placed in a silicon oil bath of constant temperature (the variation amounted to 1°C). As soon as the temperature had become constant, the reaction was started by the addition of an equimolar amount of isocyanate with the aid of a syringe via a septum. Most reactions were carried out for about 2 h. At various time intervals, a 50-µl sample was taken from the reaction sample with a syringe. The reaction was quenched by diluting the sample in 15 ml methanol. 1a reacted within 1 minute to form the corresponding urethane; the other components, including 4a, did not react with methanol even after several hours. Just before HPLC analysis, 5 ml of water was added. The samples were analyzed within about 3 h.

The reactions with 1b were quenched in a solution of $50 \,\mu$ l dibutylamine in 1 ml methanol. The reaction of 1b with methanol is not only very slow but the sensitivity of the UV detector to formed methylurethane is much less than that to the urea formed during reaction with dibutylamine.

Reactions between 8a and 4a were carried out using the same equipment and procedures as described above. Internal standard and about 7 mmol of 8a were dissolved in 25.0 ml solvent; as soon as the reaction temperature was reached, the reaction was started by the addition of an equivalent amount of benzoic anhydride.

Chromatography conditions

The GPLC system comprised a Varian Model 5000 chromatograph with UV detection at 254 nm (for reactions with **1b**, use was made of detection at 200 nm). A Waters 712 WISP programmable sample injector was interfaced with the chromatograph. 20 μ l of sample solution was injected into a 12.5-cm RP select B column 91

with an internal diameter of 4 mm and a particle size of 5 μ m. The eluent was a methanol/phosphate-buffer (60/40, v/v). The buffer consisted of 0.02 mole KH₂PO₄ with pH 4. Peak areas were determined with the Nelson Analytical integration system.

Calculations

The course of the reaction in Figure 2 was calculated using the program GEAR¹⁰. This program integrates, by means of the Gear method, the differential equations which result from a reaction model containing an arbitrary set of chemical reactions from the initial conditions and reaction rates. The reaction rate of the conversion of **1a** to **10** was determining using the program GIT⁹.

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