Blocked Isocyanate Equivalents

Carbonylbiscaprolactam: A Versatile Reagent for Organic Synthesis and Isocyanate-Free Urethane Chemistry

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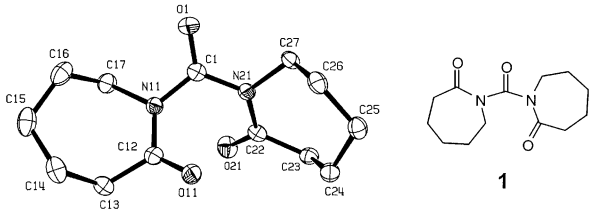
Carbonylbiscaprolactam (CBC, **1**, Figure 1[1]) is a nontoxic (LD_{50} rat (oral) > 2000 mg kg^{-1}, LD_{50} rat (skin) > 2000 mg kg^{-1}) solid derivative of carbonic acid that melts at 118 °C and exhibits unusual selectivity in reactions with amino



1

Figure 1. Crystal structure of **1**.

and hydroxy groups which is very different from that of 1,1′-carbonyldiimidazole (CDI). Compound **1** was first prepared by Meyer in 1956 by reacting phosgene with caprolactam.[2] He first examined its use as a comonomer in polyamide synthesis; however, all early attempts to prepare polymers from **1** failed and only ill-defined oligomeric products were obtained. In 1967 a modified synthesis of **1** was patented by Okuda and Mori.[3] During the 1990s Mateva et al. and researchers at Monsanto employed **1** successfully as an initiator together with the sodium caprolactamate salt in anionic ring-opening polymerization of caprolactam for the production of high-molecular-weight polyamides and copolymers.[4] Müller et al.[5] claimed the use of **1** as an activator for special bleaching agents. The breakthrough in CBC research occurred in 1998 when Lootjens and Plum (DSM)[6] recognized the potential of **1** as a versatile reagent for the conversion of amines into *N*-carbamoyl caprolactam compounds **2**. This development of new chain extenders, which build up molecular weight and improve properties of polyester and polyamide fibers, has led to the renaissance of the CBC chemistry.[7]

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Here we present the first comprehensive studies on the reactions of **1** with nucleophiles such as amines and alcohols. Special attention was paid to the influence of the reaction conditions—for example, choice of catalyst, temperature, and stoichiometry of the reactants—on the selectivity and controllability of the reactions of **1**. Controlling the numerous reaction possibilities of **1** promises manifold new opportunities.

The chemistry of **1** is quite different from reactions of phosgene, diisocyanates, and 1,1′-carbonyldiimidazole (CDI). While CDI[8] is well known as a mild reagent for the conversion of carboxylic acids into the corresponding activated *N*-acyl imidazoles, the reaction of carboxylic acids with **1** to give the corresponding *N*-acyl caprolactams requires prolonged heating at high temperatures. For example, when octanoic acid is heated with an equimolar amount of **1** at 170 °C for 4 h, the corresponding *N*-octanoylcaprolactam is obtained in only 54% yield. Whereas CDI, isocyanate, and phosgene react instantaneously with alcohols and amines to afford carbonates **5** and ureas **4**, respectively, the reactions of **1** depend significantly upon the type of the nucleophile, the reaction conditions, and, in particular, the catalyst.

As illustrated in Scheme 1, two very different reaction pathways are feasible: 1) ring elimination (RE) generating caprolactam, and 2) ring opening (RO) that does not cause caprolactam by-product formation. Model reactions of **1** with a variety of low-molecular-weight monofunctional amines and alcohols were studied by ^{1}H NMR spectroscopy. As is apparent from Table 1, the reaction of **1** with 1-octylamine, performed in bulk with a molar ratio amine/**1** = 2 does not require catalyst and proceeds exclusively by the RE mechanism (Scheme 1). At 70 °C a reaction time of 15 min sufficed for 100% conversion of **1** into 1-octyl-*N*-carbamoylcaprolactam (**2a**) and caprolactam. No side reaction was detected by ^{1}H NMR spectroscopy! In contrast, at higher temperatures (170 °C) **1** was completely consumed but the reaction was not selective; **2a** was obtained in only 13% yield along with *N,N*′-dioctylurea (**4a**) in 87% yield.

In contrast to the reactions of primary amines, heating secondary amines such as *N,N*-di(1-octyl)amine with **1** did not lead to any reaction even after 60 min at 70 °C. When the reaction mixture was heated to 170 °C or when NaH catalyst was added, only minor amounts of **1** reacted, and complex reaction products were obtained. As a consequence, at temperatures around 100 °C the primary amino groups react selectively and quantitatively in the presence of the secondary amino groups to give the corresponding *N*-carbamoyl caprolactams **2**. This sort of selectivity is not displayed in reactions with phosgene, diisocyanates, and CDI. Recently, special CDI derivatives such as imidazole carboxylic acid esters of secondary and tertiary alcohols were reported to react with similarly high selectivity with primary amino groups in the presence of secondary amino groups.[9]

The *N*-carbamoyl derivatives **2** (Scheme 2) corresponding to caprolactam-blocked isocyanates are also available by reaction of caprolactam with the corresponding isocyanates, which in turn are prepared by phosgenation of the amines. Therefore, reactions of 1 are a very convenient isocyanate-free route to lactam-blocked isocyanates. Upon heating at

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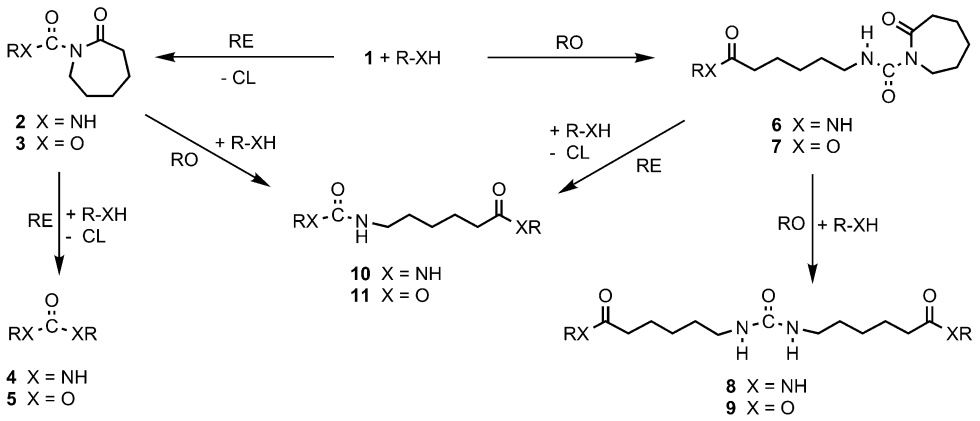
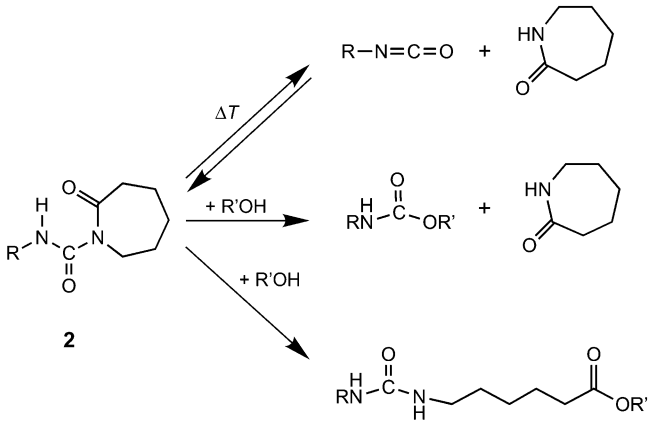


Scheme 1. Reactions of **1** with alcohols and amines: ring elimination (RE) and ring opening (RO) pathways. CL = caprolactam.

Table 1: Reactions of **1** with amines.[a]

Entry	Amine	*T* [°C]	*t* [min]	Conv. **1** [%]	Yield **2** [%]	**4** [%]
1	(1-oct)NH_2	70	15	100	100	0
2	"	170	15	100	13	87
3	$(1\text{-oct})_2NH$	70	60	0	0	0
4	"	170	60	85	n.d.[b]	n.d.[b]

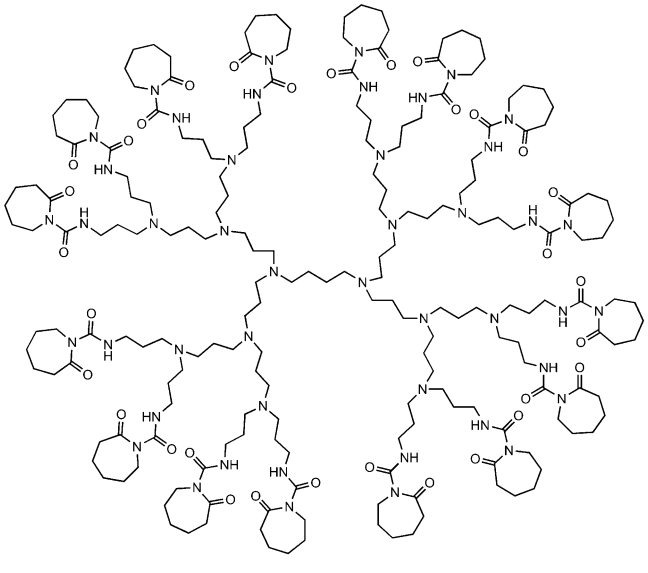
[a] Molar ratio amine/**1** = 2. [b] Not determined (complex mixture of products).



Scheme 2. Reactions of the blocked isocyanate derivative of *N*-carbamoyl caprolactam (**2**).

temperatures between 160 and 180 °C *N*-carbamoyl caprolactams **2** are cleaved to give free isocyanates and caprolactam.[10] Caprolactam-blocked isocyanates are important intermediates in coating applications where blocked isocyanates play a significant role because the presence of free toxic isocyanates is not desirable in industry.[11] Compound **1** reacts with alcohols by ring elimination (RE) and ring opening (RO) (Scheme 2) to afford urethanes without isocyanate intermediates (Scheme 2). Therefore the CBC conversion of amines represents an attractive new key to isocyanate-free urethane chemistry.

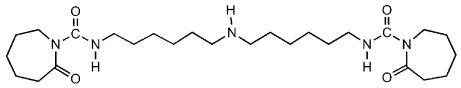
The reaction of **1** with primary amines is stoichiometric and can be performed in bulk at temperatures around 100 °C. Whereas branched polyamines with more than two amino functions crosslink immediately when traces of phosgene or diisocyanates are added due to rapid urea formation, highly branched polyamines react with **1** to give the corresponding polyfunctional *N*-carbamoyl caprolactams without any crosslinking or gel formation. This unusually selective reaction was demonstrated with the polyamine-terminated poly(propylenimine)-hexadecaamine dendrimers (Astramol, generation 3.0 with 16 primary amino groups, from DSM[12]). The dendrimer was heated with 1.05 equiv **1** per NH_2 group in toluene at 100 °C for 2 h to afford the corresponding polyfunctional derivative **2b** with 16 *N*-carbamoyl caprolactam end groups. Derivative **2b** was treated with excess methanol and NaOMe catalyst, and the endgroups underwent ring opening (pathway RO) to afford ester-functionalized urea groups (**9b**) with quantitative conversion and 85 % yield.



2b

The extraordinary selectivity of **1** can be used to prepare a variety of blocked isocyanates with free secondary amino groups. *N,N*-Bis(6-aminohexyl)amine reacts with a stoichio-

metric amount of **1** to produce the novel difunctional caprolactam-blocked isocyanate **2c** (95% yield), which contains a secondary amino group.



2c

The reaction of **1** with primary and secondary alcohols and phenols is affected drastically by the type of hydroxy group and by the catalyst added (Table 2); compound **1** does not react with tertiary alcohols. In the absence of catalysts the reaction of **1** with primary and secondary alcohols (molar ratio alcohol/**1** = 2) proceeds very sluggishly by ring elimination (RE pathway, Scheme 1), as evidenced by the evolution of caprolactam and formation of urethane **10**, carbonate **5**, and *N*-alkoxycarbonyl caprolactam **3**, which is the main product. For example, heating 1-octanol with **1** for 3 h at 120 °C resulted in only 60% conversion of **1** and formation of *N*-octyloxycarbonyl caprolactam **3** as the main product (cf. entry 5 in Table 2). At 170 °C the conversion of **1** was 95% but a complex mixture of reaction products resulted, as expected for a nonselective RE reaction. The reaction of **1** with 2-octanol appeared to favor formation of *N*-alkoxycarbonyl caprolactam **3**.

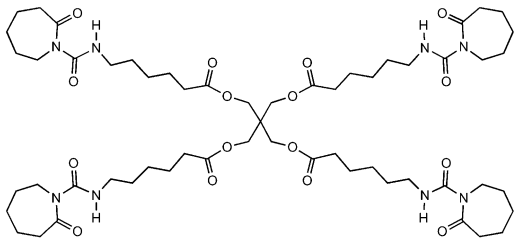
Table 2: Reactions of **1** with alcohols.[a]

Entry	ROH[a]	Catalyst		*T*	*t*	Conv.	Yield				
		Type	mol%	[°C]	[min]	**1** [%]	**3** [%]	**5** [%]	**7** [%]	**9** [%]	**11** [%]
5	1-oct	–	0	120	180	60	39	8	4	0	9
6	1-oct	–	0	170	80	95	20	52	0	0	23
7	2-oct	–	0	170	80	78	62	8	0	0	8
8	1-oct	NaOR	4	30	5	100	0	0	0	84	16
9	2-oct	NaOR	4	30	5	100	0	0	4	40	56
10	1-oct	NaOR	4	120	5	100	0	0	4	4	92
11	2-oct	NaOR	4	120	5	96	0	0	57	7	32
12	1-oct	$Zr(OR)_4$	1	120	5	100	0	8	73	3	16
13	2-oct	$Zr(OR)_4$	1	120	5	100	0	0	79	9	12
14	1-oct	$Zr(OR)_4$	1	170	5	100	0	4	12	9	75
15	2-oct	$Zr(OR)_4$	1	170	5	100	0	0	14	7	79

[a] Molar ratio alcohol/**1** = 2.

The addition of bases and acids as catalysts strongly accelerates the reaction of **1** with alcohols and switches the reaction pathway from ring elimination (RE) to ring opening (RO) with the ester-functionized *N*-carbamoyl caprolactam **7** as the product, which is also equivalent to a caprolactam-blocked isocyanate. The preferred catalysts are metal alcoholates, which are much more effective than Lewis acids. The selectivity of the base-catalyzed reactions depends upon the charge of the cation in the catalyst. Addition of sodium alcoholate, prepared in situ by reacting sodium hydride with the alcohol, promotes formation of urea **9** by twofold ring opening at 30 °C and formation of urethane **10** at elevated temperatures. Besides the temperature, the ratio alcohol/**1** also has an effect on the reaction products (see Supporting Information). If the alcohol/**1** is 2, the formation of urethane **10** by elimination of the remaining ring is favored. On the other hand, a high excess of alcohol causes the formation of urea esters **9** through ring opening. Most likely, formation of **10** results from reaction of the intermediate **7** by ring elimination before nucleophilic attack of the alcohol leads to ring opening. It should be noted that urethane formation can result from either the RO + RE or the RE + RO mechanism (Scheme 1).

In contrast to the reactions with sodium alcoholate catalysts, reactions of **1** in the presence of zirconium alcoholate proceeded mainly by onefold RO to give **7** (ca. 75% yield at full conversion of **1**) accompanied by urethane and carbonate byproduct formation. This represents a very versatile approach for converting both primary and secondary alcohols into blocked isocyanate groups. The selectivity of multivalent metal alcoholates is likely associated with formation of chelate complexes of the metal cation and **1**. Since only one lactam carbonyl group is involved in complex formation, the reactivity of the other carbonyl group can be drastically different. However, further research is required to clarify this hypothesis. Although the selectivity of reactions of **1** with alcohols to give *N*-carbamoyl caprolactams is somewhat lower than that of the reactions with primary amines, the former leads to a wide range of novel blocked isocyanates from readily available polyols. For example, pentaerythritol reacted with four equivalents of **1** to produce the carbamoyl derivative **7a** (with only 7 mol% *N*-acyl caprolactam and 4 mol% carbonate groups).



7a

In conclusion, the reaction of **1** with both primary amines and primary as well as secondary alcohols provides an isocyanate- and phosgene-free route to *N*-carbamoyl caprolactams ("blocked isocyanates"). A variety of other functional groups are tolerated. This offers attractive opportunities for polymer diversification and isocyanate-free polyurethane chemistry.[13] The caprolactam-blocked isocyanates are of interest as nontoxic and low volatile organic compound (VOC) curing agents in the coatings and adhesives industry. End-group conversion of hydroxyl- and amino-terminated oligomers produces new reactive oligomers such as *N*-carbamoyl-caprolactam-functionalized liquid rubbers. Since **1** is nontoxic it can be added during the melt processing of

polymers. As a chain extender it can increase the molecular weights of polyesters and polyamides and improve their yarn properties without tedious solid-phase postcondensation. Due to the clean stoichiometric reactions of **1**, the formation of low volatile and toxic byproducts typically associated with diisocyanate reactions in polyurethane chemistry, can be prevented. This is also of interest for the preparation of polyurethane- and polyurea-based biodegradable polymers used in biomedical applications.

Experimental Section

1-[(2-Oxazepan-1-yl)carbonyl]azepan-2-one (**1**, CBC) was obtained from DSM and used as received (purity >99%). 1-Octylamine (Merck) and *N,N*-di(1-octyl)amine (Merck), 1-octanol (Merck), 2-octanol (Merck), methanol, and toluene were dried over molecular sieves (4 Å) before use. Zirconium tetrapropanolate was obtained from Aldrich (70 wt.% solution in 1-propanol).

Reaction of **1** with amines: Table 1, entry 1: Dry 1-octylamine (11.6 mL, 9.04 g, 70 mmol) was heated under argon to 70°C. Then **1** (8.82 g, 35 mmol) was added and the reaction mixture was stirred for 15 min at 70°C. The composition of the product mixture was determined by ^{1}H and ^{13}C NMR spectroscopy. It consisted of equimolar amounts **2a**, caprolactam, and 1-octylamine.

Reaction of **1** with alcohols: Table 2, entry 12: As a typical example, the reaction of CBC with 1-octanol at 120°C in the presence of zirconium tetraalcoholate as catalyst is described (entry 12). 1-Octanol (22.1 mL, 18.23 g, 0.14 mol) was stirred with $Zr(O\textit{n}\text{-}C_3H_7)_4$ (0.229 g, 0.7 mmol, 1 mol% with respect to **1**) for 1 h at 40°C under vacuum (oil pump). The solution was then heated under argon to 120°C and preheated 1 (17.65 g, 0.07 mol) was added. The reaction mixture was stirred for 5 min before the composition was determined by ^{1}H and ^{13}C NMR spectroscopy to be 73% (based on **1**) **7a**, 16% **10a**, 3% **9a**, and 8% **5a**. Residual **1** and **3a** were not detected.

See the Supporting Information for ^{1}H and ^{13}C NMR data.

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Keywords: carbamates · coupling agents · polyurethane · synthetic methods

[1] CCDC 201802 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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