Polycycloaddition

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Poly(1,2,4-oxadiazolidin-5-one)s Synthesized by Polycycloaddition of Bisoxaziridines and Diisocyanate

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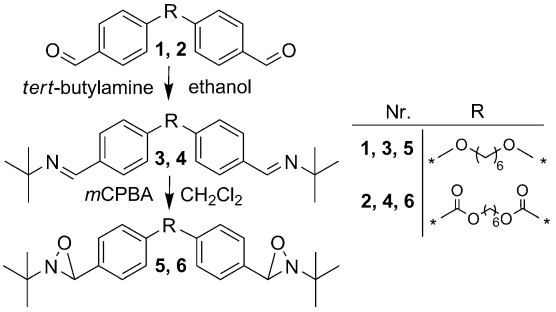
Oxaziridines, featuring a three-membered heterocyclic C,N,O ring, are similar to oxiranes which are an important class of functionality, for example, in polymer chemistry.[1] Owing to the high strain of the three-membered ring, oxaziridines are reactive towards various nucleophilic and unsaturated compounds. Investigations on the cycloaddition of oxaziridines were carried out originally by Agawa et al.[2] in reactions performed with heterocumulenes like diphenylketene, isocyanates, isothiocyanates, carbodiimide, ketenimines, and carbon disulfide. Recently Troisi et al. described the synthesis of various types of heterocyclic compounds by the [3+2] cycloaddition of 2-alkyl-3-aryloxaziridines with aryl alkenes,[3] aryl alkynes,[4] aliphatic alkynes,[5] and nitriles.[6] Isocyanates in particular are commonly used in polymer synthesis.[7] One of the most important diisocyanates is 4,4′-methylene diphenyl diisocyanate (MDI),[8] which has not been used previously in cycloadditions with bisoxaziridines. To our knowledge, cycloaddition reactions of oxaziridines with isocyanates have been employed only for the synthesis of low-molecular-weight five-membered heterocyclic ring systems. In general, 1,2,4-oxadiazolidin-5-ones have tremendous potential as pharmaceutical and otherwise biologically relevant substances, because the 1,2,4-oxadiazolidin-5-one ring is a configurationally stable building block. This unit is found in alkaloids and combines the structural features of barbituric acid and hydantoin derivatives, compounds with broad medical applications.[9]

To study the polycycloaddition we prepared two new bisoxaziridines, 1,6-bis[4-(2-*tert*-butyl-1,2-oxaziridin-3-yl)-phenoxy]hexane (**5**) and 1,6-bis[4-(2-*tert*-butyl-1,2-oxaziridin-3-yl)benzoyloxy]hexane (**6**), in a three-step synthesis (Scheme 1). First the bisaldehydes **1** and **2**, which contain a flexible aliphatic spacer, were synthesized according to literature procedures.[10] Then **1** and **2** were condensed with *tert*-butylamine (used in excess) in ethanol to yield the corresponding bisimines **3** and **4**, which were oxidized to give the desired bisoxaziridines **5** and **6** according to a method described in the literature (addition of *meta*-chloroperoxybenzoic acid (*m*CPBA) in CH_2Cl_2 at 0 °C).[11]

The bisaldehydes **1** and **2**, bisimines **3** and **4,** and bisoxaziridines **5** and **6** were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy and mass spectrometry. In the

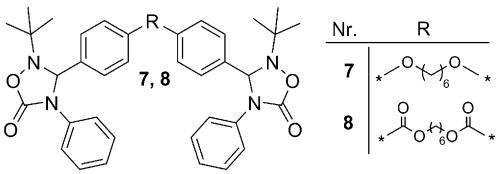


Scheme 1. Synthesis of (*E*)-*bis*oxaziridines **5** and **6.**

^{1}H NMR spectra of the bisimines **3** and **4** the signal of the CH=N group is a singlet at $\delta = 8.12$ ppm and $\delta = 8.21$ ppm, respectively. The bisoxaziridines **5** and **6** were isolated exclusively in the *E* isomeric form; the *Z* configuration is unfavorable as a result of the steric hindrance of the two bulky substituents.[11] The methine proton of the *E*-oxaziridines **5** and **6** gives rise to a signal at $\delta = 4.56$ ppm and $\delta = 4.65$ ppm, respectively. Moreover the IR spectra of the bisimines **3** and **4** exhibit a strong absorption band $\nu_{C=N}$ at about 1640 cm^{-1}, which is not observed in the spectra of the bisoxaziridines **5** and **6**.

To estimate the possibility of polymer-chain formation by cycloaddition of **5** and **6** with 4,4′-methylene diphenyl diisocyanate (MDI), **5** and **6** were reacted with phenylisocyanate at 110 °C in toluene. The resulting cycloadducts are 1,6-bis[4-(2-*tert*-butyl-4-phenyl-5-oxo-1,2,4-oxadiazolidin-3-yl)-phenoxy]hexane (**7**) and 1,6-bis[4-(2-*tert*-butyl-4-phenyl-5-oxo-1,2,4-oxadiazolidin-3-yl)benzoyloxy]hexane (**8**), respectively. In agreement with literature precedent[2] the cycloaddition reactions yield 1,2,4-oxadiazolidin-5-ones (Scheme 2).

Both bis(1,2,4-oxadiazolidin-5-ones) **7** and **8** were isolated as colorless solids with melting points of 175 °C and 172 °C, respectively. In order to characterize the obtained products, mass spectrometry and ^{1}H NMR, ^{13}C NMR, and IR spectroscopy were employed. The IR spectra of **7** and **8** show a strong broad signal at 1739 cm^{-1} corresponding to the C=O vibration of the 1,2,4-oxadiazolidin-5-one function. The fragmentation in the mass spectra also verifies the structure of **7** and **8**.



Scheme 2. Structures of bis(1,2,4-oxadiazolidin-5-one)s **7** and **8**.

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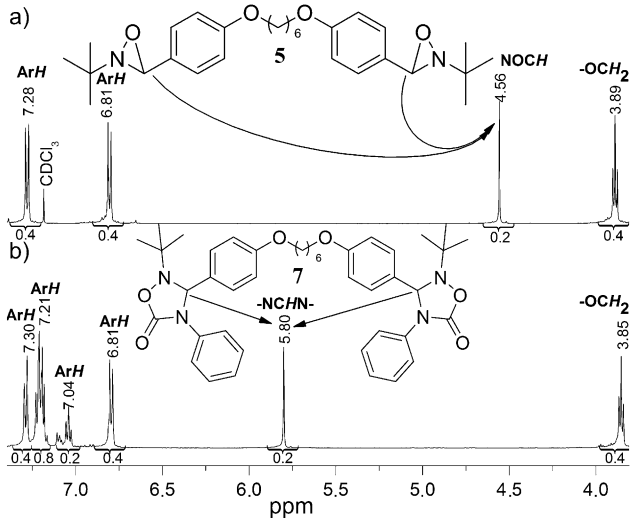
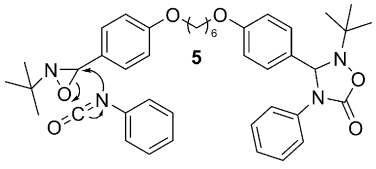


Figure 1. ^{1}H NMR spectrum of **5** and the corresponding cycloadduct **7.**

Further support is given in Figure 1, where a section of the ^{1}H NMR spectrum of **5** is compared with the corresponding section of the spectrum of **7**. The methine proton of the former oxaziridine ring (NOCH) of **5** at $\delta = 4.56$ ppm appears after cycloaddition as the singlet of the 1,2,4-oxadiazolidin-5-one unit in the spectrum of **7** at $\delta = 5.80$ ppm. In accordance with this finding, the resonance of the methine proton of oxaziridine **6** is shifted from $\delta = 4.65$ ppm to $\delta = 5.90$ ppm in cycloadduct **8**.

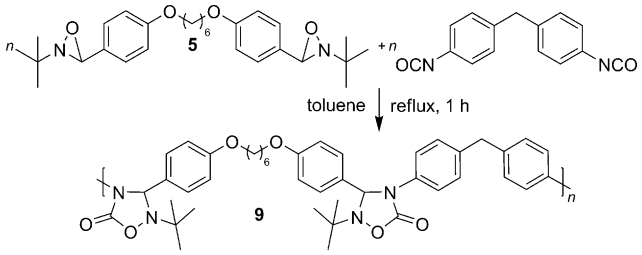
We monitored the reaction by ^{1}H NMR spectroscopy and discovered that the reaction rate strongly depends on the electronic properties of the substituent on the carbon atom of the oxaziridine. We found that the reaction of the electron-rich oxaziridine **5** with phenylisocyanate was relatively fast and proceeded with quantitative conversion to give the corresponding bis(1,2,4-oxadiazolidin-5-one) **7** within thirty minutes. The main product of the cycloaddition of the electron-poor oxaziridine **6** with phenylisocyanate was bis(1,2,4-oxadiazolidin-5-one) **8**. Additional signals were observed in the ^{1}H NMR spectra, which might belong to by-products like aldehydes (e.g. $\delta = 10.03$ ppm) and amides (e.g. $\delta = 6.45$ ppm). It is known that oxaziridines can decompose into aldehydes and hydroxylamines or to imines or alternatively can undergo rearrangement to give amides or nitrones.[12] The electron-donating group makes the oxygen atom of the oxaziridine ring more nucleophilic and promotes the attack of the oxaziridine oxygen atom towards the electron-poor isocyanate group (Scheme 3).

An alternative mechanism via a nitrone can be excluded. Bis(1,2,4-oxadiazolidin-5-one) **7** also resulted after thermal arrangement of bisoxaziridine **5** upon heating at 110 °C in toluene to give the isomeric bisnitrone, which reacted upon addition of phenylisocyanate. It has been previously reported that 1,2,4-oxadiazolidin-5-ones are generated in the reaction between nitrones and isocyanates.[13] This hypothesis is also in accordance with the nucleophilic trend of the oxygen atom in the cycloaddition reaction. However, we did not find any evidence for this alternative mechanism in our ^{1}H NMR spectroscopic investigation of the reaction of **5** with phenylisocyanate. Interestingly in analogous studies on the reaction of the less reactive bisoxaziridine **6** with phenylisocyanate we found that **6** partly rearranges into the corresponding nitrone (CH=N signal at $\delta_H = 7.55$ ppm), which subsequently reacted with phenylisocyanate.



Scheme 3. Mechanism of the reaction of **5** with phenylisocyanate.

As the reactivity of **5** towards isocyanate functions is much higher than that of **6**, we focused on the polycycloaddition of **5** with MDI to afford a linear poly(1,2,4-oxadiazolidin-5-one) architecture. This reaction to build the poly(1,2,4-oxadiazolidin-5-one) **9** was performed using the same method as described for the phenylisocyanate cycloadducts **7** and **8** (Scheme 4).



Scheme 4. Synthesis of poly(1,2,4-oxadiazolidin-5-one) **9**.

The structure of the new polymer product **9** was analyzed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The strong C=O vibration at 1739 cm^{-1} in the IR spectrum and the comparison of the ^{1}H NMR spectrum of polymer **9** with **7** (Figure 1) proved that the polymer main chain contains repeating units of 1,2,4-oxadiazolidin-5-one. In the ^{1}H NMR spectrum of **9** the corresponding broad signal at $\delta = 5.74$ ppm confirmed the five-membered 1,2,4-oxadiazolidin-5-one structure (Figure 2). Some additional signals appeared in the ^{1}H NMR spectrum, which can be explained by side reactions. The small signals in ^{1}H NMR spectrum of **9** might belong to imine (e.g. $\delta = 8.21$ ppm) and aldehyde (e.g. $\delta = 9.81$ ppm) functions. Moreover, the strongest signal at around 1.56 ppm belongs to *tert*-butyl groups of nitrone functions.

Since the signal of an oxaziridine methine proton is missing in the ^{1}H NMR spectrum, we conclude that the polymer sample does not contain residual oxaziridine functions. Furthermore, the lack of an IR absorption for N=C=O (ca. 2300 cm^{-1}) in the spectrum of **9** clearly indicates that all isocyanate functions have reacted.

Moreover, matrix-assisted laser desorption-ionization time-of-flight (MALDI-TOF) mass spectrometry indicates the formation of a series of polymeric MDI bisoxaziridine **5** polycycloadducts, which have a molecular mass up to 20000 g mol^{-1}. Gel permeation chromatography (GPC) also confirms the sufficiently high molecular weight for free-standing films of poly(1,2,4-oxadiazolidin-5-one) **9** ($M_w =$

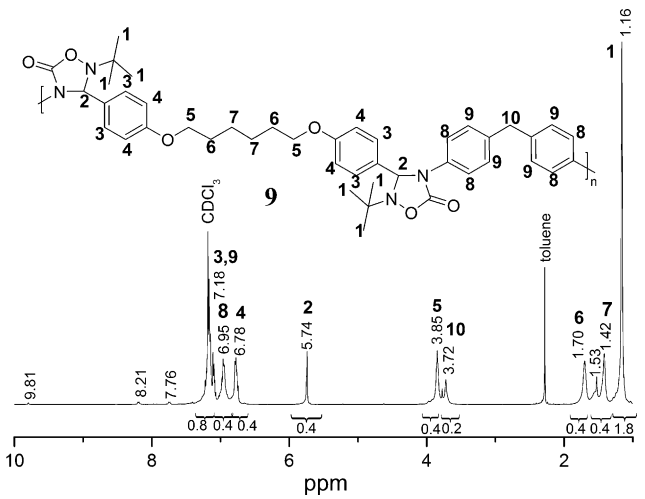


Figure 2. ^{1}H NMR spectrum of the polymer product **9.**

13900 g mol^{-1} and $M_n = 4300$ g mol^{-1}). A higher molecular weight was not achieved presumably because of some side reactions and the solubility of the propagating polymer. Polymer **9** precipitated out of solution during polymer formation. Free-standing films of polymer **9** could be obtained from chloroform.

Thermal properties of polymer **9** were investigated by differential scanning calorimetry (DSC) measurements (Figure 3). The polymer shows a glass transition temperature (T_g) of 156 °C and exhibits a sharp exothermic peak in the region between 200 °C and 240 °C which can be attributed to decomposition at 236 °C. The lack of an IR absorption for C=O (1739 cm^{-1}) after the DSC experiment verified the decomposition. Moreover, a vibration at 1604 cm^{-1} appeared. It might belong to benzamidine functions generated by evolution of CO_2.[2]

It can be concluded that bisoxaziridines can react with diisocyanates to form linear polymer chains. As proof, the polycycloaddition reaction of bisoxaziridine **5** with MDI yields poly(1,2,4-oxadiazolidin-5-one) **9** with a molecular weight of 13900 g mol^{-1} (M_w) and 4300 g mol^{-1} (M_n) according to GPC. The presence of 1,2,4-oxadiazolidin-5-one rings in the main chain was proven by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. DSC experiments confirmed that the thermal stability of the polymer is relatively high (> 200 °C). As shown in the model reaction between bisoxaziridines **5** and **6** with phenylisocyanate, the reaction rate highly depends on the oxaziridine structure and is efficiently promoted by electron-donating groups at the oxaziridine carbon atom. To the best of our knowledge, no polymers containing 1,2,4-oxadiazolidin-5-one rings have been described in literature previously. This opens up a new field for further investigations.

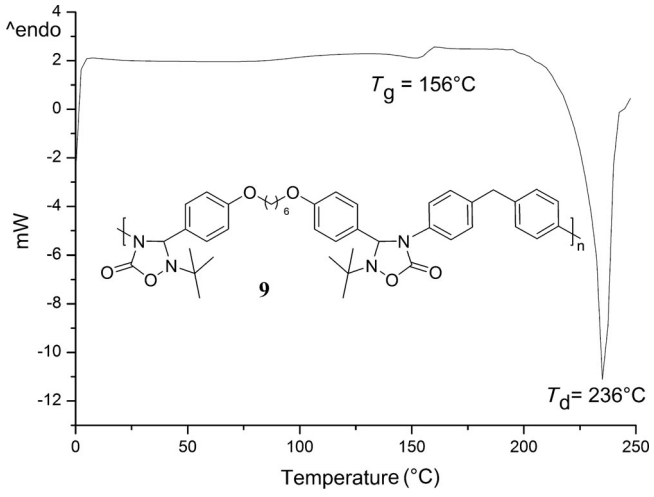


Figure 3. DSC thermogram for **9** with a heating rate of 15 °C min^{-1}.

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