Preliminary Study of Hydrogen Bonding in (3*S*)-3-[(benzyloxycarbonyl)methyl]-morpholine-2,5-dione and Its Effect on Polymerization

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Introduction. Morpholine-2,5-dione derivatives are a family of cyclic monomers that have been reported many times.[1−9] When these monomers are copolymerized with ϵ-caprolactone, lactide, or glycolide, amino acids will be introduced into the synthetic biodegradable polyesters, which will endow the traditional materials with additional properties.

Among these works is the successful synthesis[3,4,6−9] of morpholine-2,5-dione derivatives from multifunctional amino acids (Glu, Asp, Lys, Ser, Cys, etc.). Unfortunately, the homopolymerizations of these monomers were not so successful. Feijen et al.[2] showed that the reactivity of 3- and/or 6-substituted morpholine-2,5-dione derivatives decreases with the increasing number and size of substituents using the same reaction conditions. The decrease in reactivity was attributed to the increase in steric hindrance and stability of the ring structure with the increase in number and size of the substituents. This explanation may also be suitable for the lower reactivity of morpholine-2,5-dione derivatives from multifunctional amino acids.

Recently, we reported the synthesis of (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione (BMD) that is free from any substituent on the 6-position of the morpholine ring.[10] Homopolymerization of this monomer has been successfully carried out. However, comparing with previous reports[4,8] on the polymerization of the same monomer, a large difference in reactivity is observed under almost the same reaction conditions. The maximum $\bar{M}_n$ of the polymers is 13 500, about 4 times higher, as reported previously. This difference in the degree of polymerization cannot be simply attributed to the steric hindrance of substituents. It promoted us to give further consideration to this monomer.

Experimental Section. Material. BMD was prepared as described previously.[10] Chloroform, *n*-hexane, and ethyl acetate were purchased from Beijing Chemical Reagent Co. and purified according to standard methods.

Method. Microscopic FTIR results were collected on a Nicolet NIC-PLAN spectrometer. FTIR results at elevated temperature were collected on a Bruker RFS100/Vector 22 spectrometer. Samples were stored in a drying-gun and dried in vacuo for 6 h before measurement.

Mass spectra were obtained on a VG ZAB-HS mass spectrometer (FAB, fast atom bomb).

DSC results were obtained on Shimadzu DSC-50 and Thermal Analyst 3100 DSC 2010 with a heating rate of 10 °C/min.

Melting points were measured with the *Thiele* apparatus.

Results and Discussion. Hydrogen Bonding in the Monomer and Its Structures. For the recrystallization of BMD, we used ethyl acetate as solvent, while a mixture of chloroform and hexane was used by the other research group. In the FTIR spectrum, the N−H stretch of BMD recrystallized from ethyl acetate was found at 3196 cm^{-1}, which is much lower than that (3358 cm^{-1}) from chloroform/hexane.[4,8] This lower value of the N−H stretch in the amide results from the formation of a strong hydrogen bond.[13]

To obtain BMD with the N−H stretch at 3358 cm^{-1}, the monomer we synthesized was recrystallized with chloroform/hexane twice. The FTIR spectra of the three samples are shown in Figure 1. It is interesting to notice that the main peak of the N−H stretch (3184 cm^{-1}) remains unchanged after the recrystallization processes, while two small new peaks appear at 3286 and 3305 cm^{-1} in the sample of first recrystallization. When the sample was recrystallized again, these two peaks and the very weak peak at 3348 cm^{-1} were changed into a broad platform. The peaks at 3286, 3305 cm^{-1}, and the broad platform indicate the existence of a small amount of weak hydrogen bonding in the resulting monomer.

To fully understand the hydrogen bonding of BMD (recrystallized with ethyl acetate) in the melting state, FTIR spectra of the monomer at elevated temperatures are shown in Figures 2 and 3 (N_2 protected). A slight upshift of the N−H stretch from 3184 to 3206 cm^{-1} was detected when the temperature was raised from 20 to 152 °C. The sample was kept at 152 °C for 30 min before the temperature was elevated to 155 °C. Then, it was kept at this temperature for another 5 min. Surprisingly, the N−H stretch at 3206 cm^{-1}remained unchanged in this process.

According to the FTIR results above, it can be concluded that the hydrogen bonding association form in BMD (recrystallized with ethyl acetate) is rather favorable in recrystallization with chloroform/hexane and it is also stable enough to survive for a certain time in the melting state.

Morpholine-2,5-dione derivatives are lactam and/or lactone. Considering the hydrogen bond association forms of lactam and the chemical structure of BMD,[12−14] two favorable association forms of the hydrogen bond in the crystalline state of BMD (recrystallized with ethyl acetate) are suggested in Chart 1. Among the two structures, (A) is a cyclic dimer representing the intermolecular hydrogen bonding, while (B) represents an intramolecular hydrogen bonding monomer.

Incidentally, toluene had been tried in recrystallization of BMD by us. The N−H stretch is found at 3299 cm^{-1} in its FTIR spectrum. Surprisingly, only the 2M + 1 peak (527) is detected in its MS (FAB). Considering the mechanism of FAB, we concluded that the BMD recrystallized from toluene give a crystalline structure, as presented in Chart 1A. In fact, the dimeric structure (A) is the most favorable choice for a six-member ring lactam[14] and the N−H stretch should be found at 3200 cm^{-1}.[12] But it can be seen in structure (A) that the bulky substituent of $CH_2COOBzl$ will prevent the morpholine ring from getting close to each other. This explains the upshift of N−H stretch from 3200 to 3299 cm^{-1}. In addition, the high melting peak

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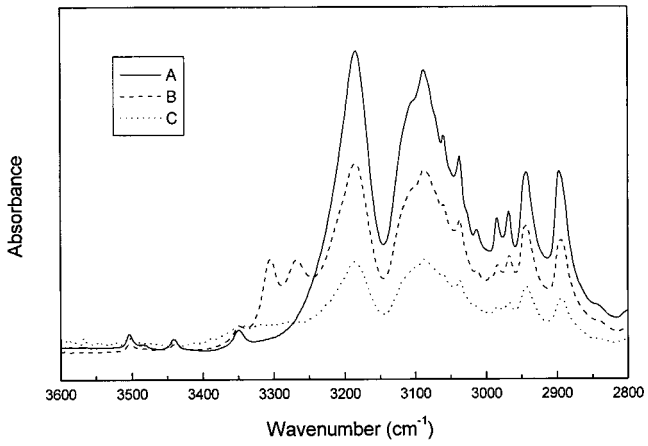


Figure 1. FTIR spectra of (3*S*)-3-[(benzyloxycarbonyl)methyl]-morpholine-2,5-dione recrystallized from different solvents (microscope; A = monomer recrystallized from ethyl acetate; B = recrystallization product of monomer A from chloroform/hexane; C = recrystallization product of monomer B from chloroform/hexane).

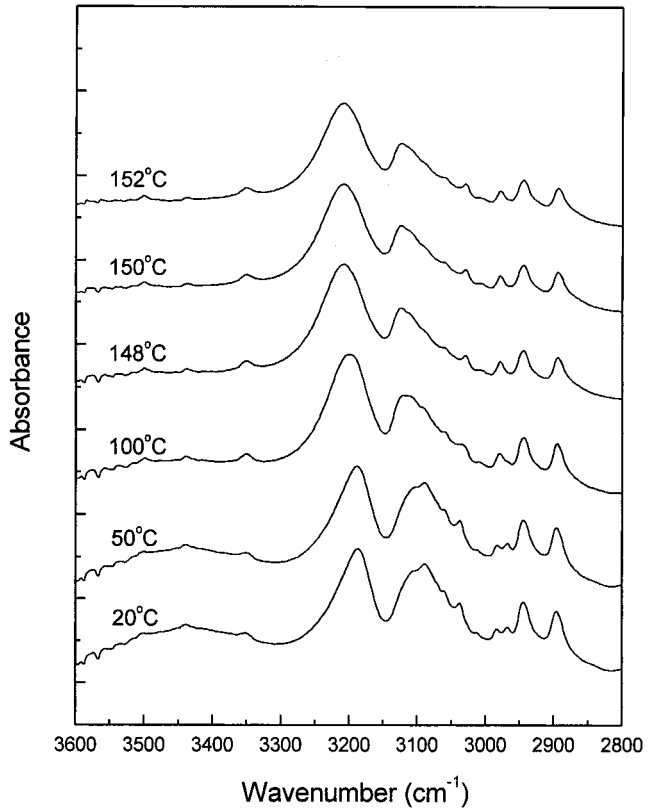


Figure 2. FTIR spectra of (3*S*)-3-[(benzyloxycarbonyl)methyl]-morpholine-2,5-dione at elevated temperatures (KBr; 18−152 °C; N_2 protected).

of the monomer (200.2 °C) strongly supports the dimeric structure as a result of intermolecular hydrogen bonding.[13] However, the BMD recrystallized from toluene was no longer used in polymerization by us, because of its higher melting temperature.

The BMD that we polymerized is recrystallized from ethyl acetate. Its melting point measured with the *Thiele* apparatus is 150−150.2 °C (the melting peak in DSC is 151.95 °C). Compared with the melting peak of BMD recrystallized with toluene, this lower melting point indicates a hydrogen bonding different from that of structure (A). In the FTIR spectrum, the N−H stretch of the monomer is found at 3190 cm^{-1}. In the

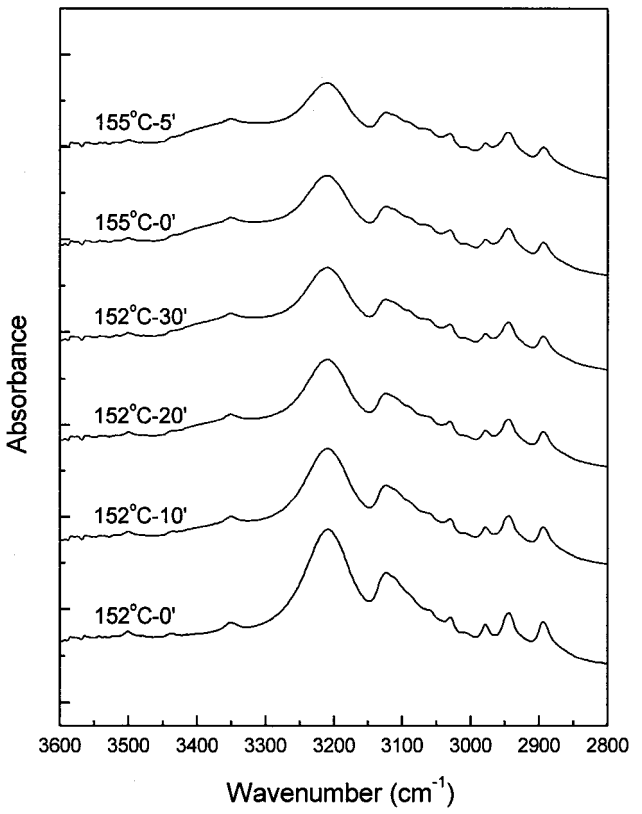
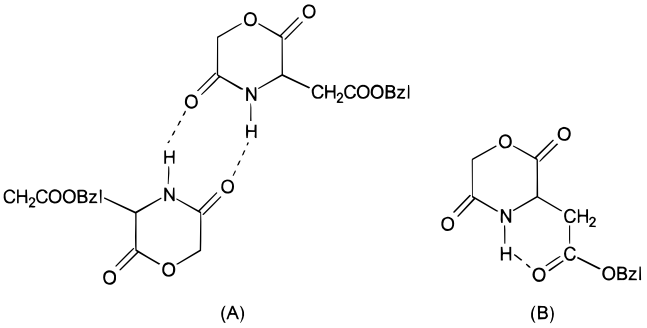


Figure 3. FTIR spectra of (3*S*)-3-[(benzyloxycarbonyl)methyl]-morpholine-2,5-dione at elevated temperatures (KBr; 152 °C for 30 min, then 155 °C; N_2 protected).

Chart 1. Favorable Hydrogen Bond Structures in the Crystalline State of BMD



MS (FAB), the M + 1 peak at 264 is observed accompanied by a very weak 2M + 1 peak. These data suggest that the monomer self-organizes in agreement with a crystal structure (B). The six-member ring containing an intrahydrogen bond is an energetically favorable structure.[13] It is also reasonable to deduce that structure (B) is valid in the melting state, because Figures 2 and 3 showed that its corresponding N−H stretch in the FTIR spectrum could remain unchanged at 152 °C for more than 30 min. Growth of a monomer single crystal from ethyl acetate is now in process to give further support of this theory.

In contrast, the N−H stretch of BMD recrystallized from chloroform/hexane[4,8] was found at 3358 cm^{-1} in its FTIR spectrum, which represents a rather weak hydrogen bonding in the monomer crystal. Its corresponding association form belongs to neither of the two structures in Chart 1.

Hydrogen Bonding in the Monomer and Its Effect on Polymerization. Feijen et al.[2] had reported

that the polymerization of morpholine-2,5-dione derivatives in bulk with stannous octoate as catalyst may proceed via a coordinated mechanism by cleavage of the ester bond. It is likely that the free or weakly associated amide functional group of the morpholine-2,5-dione derivatives interacts with stannous octoate and interferes in the polymerization process. It has been demonstrated that the BMD described here and which was recrystallized from ethyl acetate is stabilized by hydrogen bonding. No matter what kind of association form it is (A or B), the strong hydrogen bond and the resulting steric hindrance will prevent the amide functional group from forming a complex with stannous octoate. This will facilitate the polymerization process. Furthermore, the "self-saturated" amide functional group in this monomer would not favorably coordinate many water molecules. This will also help to get higher molecular weight polymers, because a small amount of water has been proved as an important co-initiator in ring-opening polymerization catalyzed by stannous octoate.[11]

Consequently, the higher reactivity of BMD shown in this research should be attributed to a very stable hydrogen bonding in the monomeric crystals. Different conformations of the monomer result from monomer recrystallization with different solvent systems.

Conclusions. Generally, we concluded that hydrogen bonding in (3*S*)-3-[(benzyloxycarbonyl)methyl]morpholine-2,5-dione (BMD) has a large effect on its polymerization reactivity. Although overall chemical compositions may be the same, quite different polymerization properties due to different ways of hydrogen bonding in the monomer are observed. Selection of a suitable recrystallization solvent system results in different types of monomer crystals in which either intramolecular or intermolecular hydrogen bonds will be formed. This will help to achieve a higher reactivity in the ring-opening polymerization.

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