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Synthesis, Characterization of Zinc Complexes with Neutral α-Diimine Ligands and Application in Ring-opening Polymerization of ε-Caprolactone

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Abstract: A series of neutral α-diimine ligands with diacetyl and acenaphthenequinone skeletons were prepared by the reaction between diacetyl and the corresponding aromatic amine. These ligands reacted with $ZnCl_2$ to generate symmetric α-diimine zinc complexes **C1**–**C10**. Experimental results indicated that the α-diimine zinc complexes with a diacetyl skeleton (**C1**–**C4**) were active in ring-opening polymerization (ROP) of ε-caprolactone (ε-CL). The complexes with an acenaphthenequinone skeleton showed a small steric effect (**C5**, **C8** and **C9**) but the complex substituted with an electron-withdrawing group (**C10**) showed high activity in the monomer conversion rate during ROP of ε-CL. The ROP catalysts of ε-CL demonstrated the mechanism of monomer activation in the presence of benzyl alcohol.

Keywords: ε-Caprolactone · Catalyst · Neutral ligands · Ring-opening polymerization · Zinc complex

Introduction

Due to specific biodegradability and biocompatibility, aliphatic polyesters, such as polycaprolactone (PCL),[1,2] polylactide[3,4] and their copolymers, are frequently used as surgical sutures, drug delivery devices, and gene carriers in medical settings.[5–7] Given these applications, reducing the toxicity and adverse events induced by the catalysts used in polymerization is of great importance. This objective has accelerated the development, separation, and purification of efficient catalytic systems with low or zero toxicity (*e.g.* zinc, magnesium, calcium, and iron complexes)[2,8–10] to catalyze the ring-opening polymerization (ROP) of ε-CL or the polymerization of lactide. Zinc catalysts with a phenylic amino,[11] or a β-imino group,[12] or with a Schiff base moiety[13] were proven to have high activity and excellent capability of dimensional control. However, these catalysts are unstable, sensitive to the impact of air and moisture, and difficult to store.

In recent years, only a few neutral ligands[14–17] have been developed to stabilize divalent zinc. The research group of Börner[18,19] has designed and synthesized a series of guanidine imine zinc complexes with neutral ligands. These guanidine imine zinc catalysts possess satisfactory stability toward air and moisture at room temperature and show moderate activity in the polymerization of lactide. To synthesize a simple catalyst with low toxicity and high stability to be applied in the medicine field, we designed and synthesized a novel series of neutral α-diimine ligands with diacetyl and acenaphthenequinone skeletons along with the corresponding zinc complexes, which were commercially available, easy to handle and could tolerate air and moisture. The catalytic activity of these Zn-catalysts was analyzed with respect to the electronic and steric influence of the imino ligands on the catalyzed reaction.

Methods and Results

The α-diimine zinc complexes with diacetyl skeletons were obtained *via* a two-step reaction. The ligands were first synthesized and subsequently purified to produce zinc complexes with zinc chloride (Scheme 1). Under acid catalysis, diacetyl reacted with 2,6-dimethylaniline,[20] 3,5-dimethylaniline, or 4-methoxy aniline to produce ligands **L1**, **L3** and **L4**, respectively. **L1** was dissolved in toluene. Zinc chloride and a catalytic amount of glacial acetic acid were added to the solution at room temperature to produce a pale yellow solid complex (**C1**) with a yield of 72.5%.[21] By using the same method, we synthesized complexes **C3** and **C4** with a yield of 66.9% and 80.2%, respectively.

The α-diimine zinc complexes with acenaphthenequinone skeletons were obtained directly *via* one-pot synthesis (Scheme 1). With formic acid as the catalyst, acenaphthenequinone and aniline were refluxed for 2 h. Zinc chloride was added and the mixture refluxed for another 2 h to obtain red-brown crystals (**C5**) with 63.1% yield.[22] Complexes **C7** and **C8** were produced with a yield of 67.5% and 56.7% following the reaction of acenaphthenequinone with 2,6-diisopropylaniline or 3,5-dimethylaniline. Complexes **C2**, **C6**, **C9** and **C10** were synthesized according to the approaches previously described.[23–25]

All the obtained complexes were separated, purified, and characterized by 1H-NMR. The molecular structures of complexes **C1**, **C2**, **C5**, **C7**, and **C8** were confirmed by X-ray structural analysis.

Single crystals of the complexes **C1** and **C8** suitable for X-ray structural analysis were obtained from concentrated methylene chloride and n-hexane solutions. The Oak Ridge Thermal Ellipsoid Plot drawings that depicted the selected bond distance and angle of the molecular structures of **C1**, **C2**, and **C8** are illustrated in Figs 1, 2, and 3, respectively.

The molecular structures show that the central metal zinc is tetrahedrally coordinated and the ligand angle is between 77° and 80°, close to that reported in ref. [26].

The size and structure of the aromatic amine ligands influence zinc coordination.

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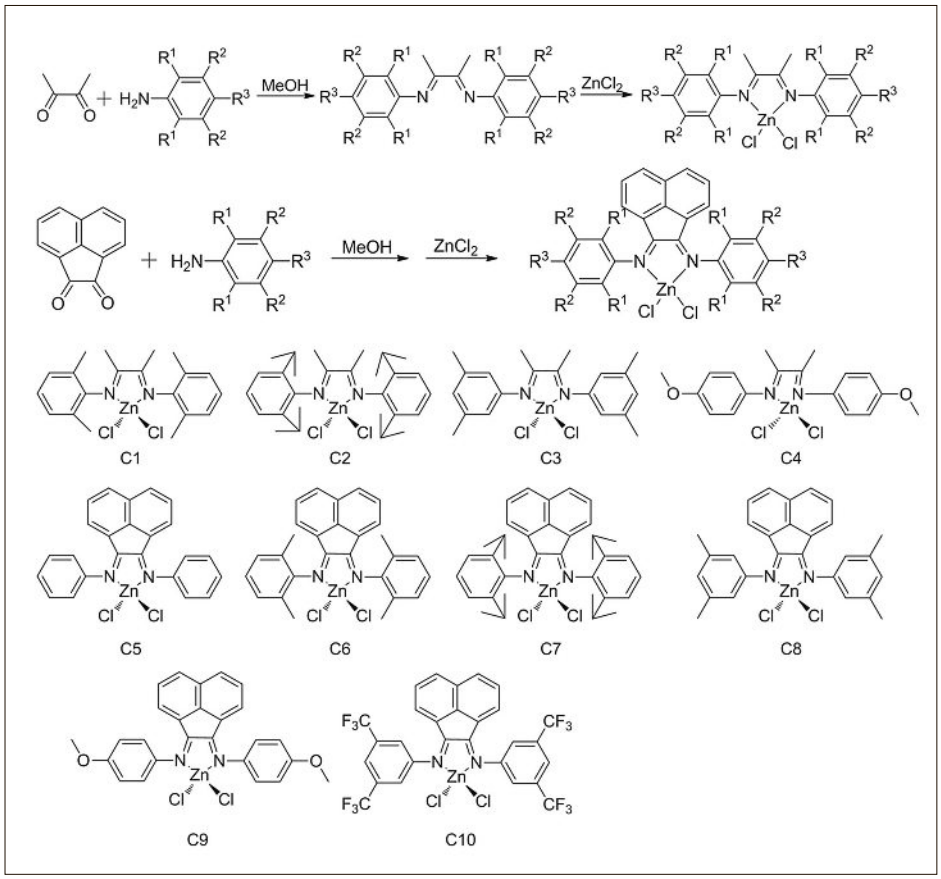


Scheme 1. The synthetic route and chemical structures of the zinc complexes of **C1–C10**.

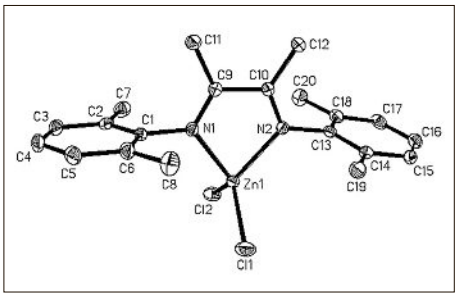


Fig. 1. Molecular structure of **C1**·3CH_2Cl_2 depicted with 30% thermal ellipsoids. Hydrogen atoms and three uncoordinated dichloromethane molecules were omitted for clarity. Selected bond distances(Å) and angles (°): Zn(1)–N(1) 2.078(3), Zn(1)–N(2) 2.073(3), Zn(1)–Cl(1) 2.204(1), Zn(1)–Cl(2) 2.208(1), N(1)-Zn(1)-N(2) 78.83(11), N(2)-Zn(1)-Cl(1) 116.68(8), N(1)-Zn(1)-Cl(1) 113.67(8), N(2)-Zn(1)-Cl(2) 114.91(8), N(1)-Zn(1)-Cl(2) 115.96(8), Cl(1)-Zn(1)-Cl(2) 115.96(8).

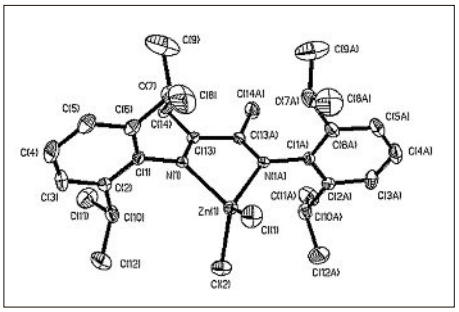


Fig. 2. Molecular structure of **C2** depicted with 30% thermal ellipsoids. Hydrogen atoms were omitted for clarity. Selected bond distances (Å) and angles (°): Zn(1)–N(1) 2.090(4), Zn(1)–N(1A) 2.090(4), Zn(1)–Cl(1) 2.189(2), Zn(1)–Cl(2) 2.201(2), N(1)-Zn(1)-N(1A) 77.7(2), N(1A)-Zn(1)-Cl(1) 117.18(11), N(1)-Zn(1)-Cl(1) 117.18(11), N(2)-Zn(1)-Cl(2) 111.68(11), N(1)-Zn(1)-Cl(2) 111.68(11), Cl(1)-Zn(1)-Cl(2) 115.79(9).

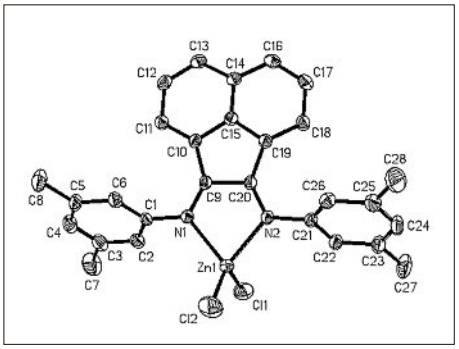


Fig. 3. Molecular structure of **C8**·CH_2Cl_2 depicted with 30% thermal ellipsoids. Hydrogen atoms and one uncoordinated dichloromethane molecule were omitted for clarity. Selected bond distances(Å) and angles (°): Zn(1)–N(1) 2.104(2), Zn(1)–N(2) 2.095(3), Zn(1)–Cl(1) 2.211(1), Zn(1)–Cl(2) 2.170(1), N(1)-Zn(1)-N(2) 80.60(9), N(2)-Zn(1)-Cl(1) 108.69(8), N(1)-Zn(1)-Cl(1) 110.69(8), N(2)-Zn(1)-Cl(2) 114.42(8), N(1)-Zn(1)-Cl(2) 114.43(8), Cl(1)-Zn(1)-Cl(2) 120.94(5).

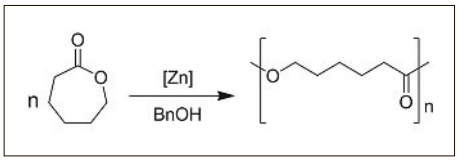
Substituents on the aromatic amines were located above the plane of the metal coordination center. Steric hindrance of these substituents has been proven to affect the catalytic properties of complexes. The steric hindrance of aromatic amines in **C1** was more significant than in **C2** when butanedione served as the skeleton structure. The bond length of Zn–N(1) and Zn–N(2) was 2.078(3) and 2.073(3) Å in **C1** and 2.090(4) Å (both Zn–N bonds) in **C2**. The results indicated that the metal complex capacity of ligands was reduced when the quantity of hindered aromatic amines was increased, which is consistent with the findings in this study. In addition, substituents on the aryl amine were observed above the complex plane of the metal center. Steric hindrances have been known to affect the catalytic properties of complexes. The dihedral angles between the ligand plane of the metal center and the aromatic amine ring of **C1** attached to the amido nitrogen atoms N(1) and N(2) were 87.05° and 85.10°, and 86.62° and 86.65° for **C2**. The introduction of a large, hindered aromatic amine caused the aromatic ring to become approximately perpendicular to the complex plane of the metal center and reduced the coordination ability of the monomer with the metal center, thereby decreasing the catalytic activity of the catalysts.

Similarly, a larger steric hindrance of the aromatic amines decreased the dihedral angle between the ligands and the metal center when acenaphthenequinone served as the skeleton structure. In this study, the dihedral angles for **C7**, **C5**, and **C8** were 88.41°, 60.65°, and 58.78°, respectively. The reduction in the dihedral angle decreased the shielding effect of the aromatic ring on the metal center. The X-ray crystal structural analysis demonstrated that the aromatic ring on the ligand plane approached the axial position with significant hindrance of aromatic amines. Consequently, the open nature of the metal center and the ability to coordinate monomers were thereby reduced. The catalytic activity of the catalyst also declined.

In this investigation, the hindrance and electronic effects on catalytic activity were confirmed when the α-diimine zinc complexes catalyzed ROP of ε-CL[27] (Table 1). As reported in Table 1, the catalytic activity of diacetyl skeletons was significantly higher than that of acenaphthenequinone skeletons with the same substituent on the aromatic ring. Therefore, strengthening the skeleton structure decreased the catalytic activity of the catalysts. Moreover, increasing the steric hindrance of the aryl imines also decreased the catalytic activity of the catalysts. For **C1** and **C2**, the steric hindrance of the *ortho*-substituent on the aromatic ring was increased, which in turn reduced the monomer conversion rate from 86.1% to 78.1% (entry 1 and entry

2), indicating the reduced catalytic activity of the catalysts. The same conclusions could be drawn with acenaphthenequinone as the skeleton structure of the catalysts. In addition, **C6** and **C7** showed no catalytic activity (entry 6 and entry 7).

The highest catalytic activity was observed for **C10** when the monomer conversion rate reached 95.2% (entry 10). This catalyst comprised electron-withdrawing substituents on the aromatic ring. Even with a large steric acenaphthenequinone skeletal structure, the catalysts achieved the maximal catalytic activity. Meanwhile, the monomer conversion rate for **C9** with an electron-donating substituent was only 48.5% (entry 9). The electron-withdrawing group clearly increased the catalytic activity of the catalysts. A potential reason was the introduction of electron-withdrawing substituents, which tended to increase zinc metal Lewis acidity and the electropositive metal center. These substituents were conducive to the formation of bonds between the monomers and the zinc.



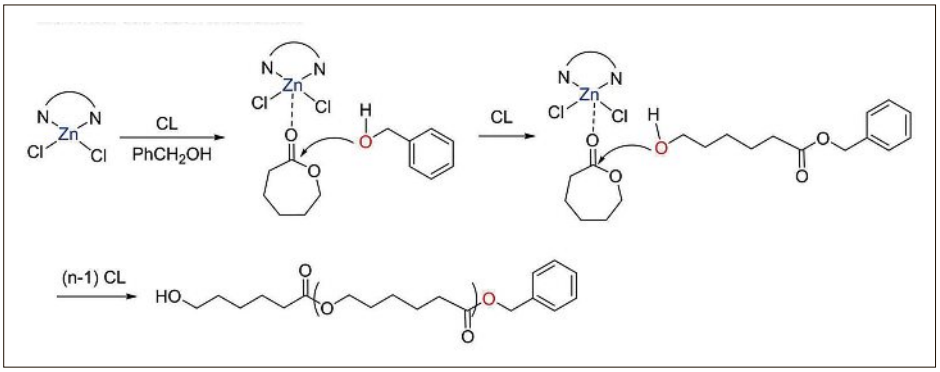
Scheme 2. The synthesis of PCL.

ROP of ε-CL with and without the addition of benzyl alcohol was performed. With **C1** as the catalyst, the catalytic activity in the presence of benzyl alcohol was significantly higher than without benzyl alcohol (entry 1 and entry 11). With **C10** as the catalyst under the same reaction conditions, the reaction rate was the same in both cases (entry 10 and entry 12). Such results may be attributed to the polymerization mechanism.

Table 1. Polymerization of ε-caprolactone with α-diimine zinc catalysts

Entry	Catalyst	[I]:[CL]:BnOH	Conv (%)	Zn[a] (GC)	Zn[b] (Theory)	PDI[c]
1	**C1**	1:200:1	86.1	9916	19739	1.99
2	**C2**	1:200:1	78.1	8024	17915	1.95
3	**C3**	1:200:1	71.4	13622	16387	1.75
4	**C4**	1:200:1	83.4	9074	19123	1.75
5	**C5**	1:200:1	81.2	13479	18622	2.01
6	**C6**	1:200:1	0	–	–	–
7	**C7**	1:200:1	0	–	–	–
8	**C8**	1:200:1	40.3	5313	9296	1.31
9	**C9**	1:200:1	48.5	3621	11166	1.42
10	**C10**	1:200:1	95.2	14209	21814	1.73
11	**C1**	1:200:0	55.9	8477	12853	1.52
12	**C10**	1:200:0	83.9	19640	19238	2.20

[a]Obtained from GC analysis and calibrated by a polystyrene standard; [b]Calculated from the molecular weight of ε-caprolactone×the conversion yield; [c]Polymer dispersity index obtained from GC analysis.



Scheme 3. Monomer activation mechanism.

Discussion

In this experiment, the zinc complexes did not change structurally when they were subjected to 24-h reflux in benzyl alcohol solution, suggesting that the traditional form of zinc metal alkoxide cannot be obtained (Scheme 2).[2] These findings probably result from the characteristics of the Zn-Cl bond, which is significantly stable and unlikely to be cleaved.

Given that α-diimine zinc complexes are extremely stable, their role in the polymerization process was found to be similar to that of Lewis acids in monomer activation. Benzyl alcohol was added as an initiator. The catalytic polymerization exerted both of these combined effects. Therefore, unlike the polymerization mechanism proposed by Herri–Pawlis for biguanide zinc complexes,[28] these catalysts demonstrated that the monomer mechanisms were activated (Scheme 3).

The ratio of ε-CL, the catalyst, and the initiator (benzyl alcohol) was 50:1:1. Thus, ε-CL could be completely converted to a polymer after a 24-h reaction at 100 °C. The resulting PCL was characterized by 1H-NMR. The results are illustrated in Fig. 4. The chain ends of the PCL were benzyl alcohol, which validated the activated monomer mechanism. When benzyl alcohol was added to the catalytic system, it served as the initiator and catalyzed the polymerization with zinc complexes.

In the activated monomer mechanism, the ability of ligands to bind to the metal center was affected by the large steric hindrance of the complex. The catalytic activity of the catalyst was consequently reduced. If the ligand contained electron withdrawing substituents, the electropositivity of the metal center increased, the ability of the ligand to enhance the activation of the monomers increased, and the polymerization reaction proceeded favorably. These outcomes were shown in the crystal structure analysis and the catalytic ROP.

Conclusion

In conclusion, a novel series of neutral α-diimine zinc complexes with diacetyl and acenaphthenequinone skeletons were synthesized and fully characterized. All these complexes were found to be very stable in air and moisture. The complexes were also determined to be capable of catalyzing the ROP of ε-CL. Compared with that of guanidine zinc complexes,[18,19] the

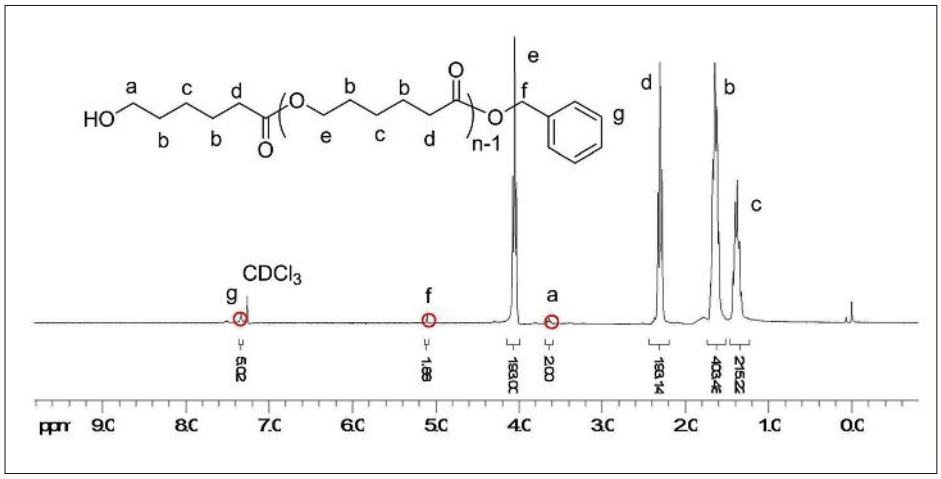


Fig. 4. 1H-NMR spectrum of polycaprolactone.

catalytic activity of the neutral α-diimine zinc complexes increased and the same molecular weight distribution of the polymer was obtained. These catalysts demonstrated activated monomer mechanisms in the presence of benzyl alcohol. Furthermore, the steric and electronic effects of ligands exerted an effect upon the catalytic performance, and catalytic activities were enhanced in the presence of benzyl alcohol.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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[20] Preparation of ligand **L1**: 2,6-dimethylaniline (84 mmol, 2.1 equiv) was added to a solution of butanedione (40 mmol) in 50 ml ethanol. A catalytic amount of formic acid was dropped in. The reaction mixture was stirred for 8 h at 40 °C. After cooling to room temperature and filtered, the crude product was recrystallized with ethanol, affording yellow crystals at a yield of 77.9%.
[21] Preparation of complex **C1**: $ZnCl_2$ (2 mmol) was added to a solution of **L1** (2 mmol) in 20 ml toluene. A catalytic amount of glacial acetic acid was dropped in. The reaction mixture was stirred for 24 h at room temperature and filtration. The crude product was recrystallized with CH_2Cl_2 and hexane, affording yellow crystals at a yield of 73.2%. 1H NMR (300 MHz, DMSO-d6): δ (ppm) 7.02–6.83 (m, 6H, Ar-H), 1.91 (s, 12H, CH3), 1.88 (s, 6H, N=C-CH3). 13C NMR (75 MHz, DMSO-d6): δ (ppm) 167.27, 147.70, 127.54, 123.79, 122.82, 17.29, 15.56.
[22] Preparation of complex **C5**: Aniline (0.6 ml, 6.3 mmol) was added to a solution of acenaphthenequinone (0.5 g, 2.74 mmol) in 50 ml ethanol. A catalytic amount of formic acid was dropped in. The reaction mixture was refluxed for 2 h. $ZnCl_2$ (4.4 mmol) was added and reflux continued for another 2 h. After filtration the crude product was recrystallized with CH_2Cl_2, affording red-brown crystals at a yield of 63.1%. 1H NMR (300 MHz, DMSO-d6): δ (ppm) 8.10 (d, J=7.2 Hz, 2H, Ar-H), 7.54 (m, 6H, Ar-H), 7.31 (m, 2H, Ar-H), 7.10 (m, 4H, Ar-H), 6.73 (d, J=7.2 Hz, 2H, Ar-H). 13C NMR (75 MHz, DMSO-d6): δ (ppm) 163.42, 151.49, 149.87, 129.46, 127.75, 127.13, 123.23, 120.84, 117.41, 116.34.
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[27] Ring opening polymerization of ε-CL: catalyst (0.047 mmol) with benzyl alcohol (0.047 mmol) or without benzyl alcohol added into a 25 ml flask under N_2 atmosphere. ε-CL (9.4 mmol,1.0 ml) was injected quickly to the flask. The flask was then immersed in an oil bath at 140 °C. After 14 h, the polymerization was terminated by addition of a minimum amount of alcohol. The obtained polymers were dissolved in 2 ml CH_2Cl_2 and then poured into alcohol with stirring. The sticky polymers were filtered and collected, then redissolved in CH_2Cl_2 and precipitated by H_2O, and dried in a vacuum oven at 45 °C for 24 h.
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