BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 52 (2), 533—535 (1979)

Syntheses of Polymerizable Carbodiimides Bearing a Terminal Vinyl Group

Hiroyoshi KAMOGAWA,* Masato NANASAWA, Shigeki UEHARA, and Keisuke OSAWA
Department of Applied Chemistry, Yamanashi University, Takeda 4, Kofu, Yamanashi 400

(Received July 22, 1978)

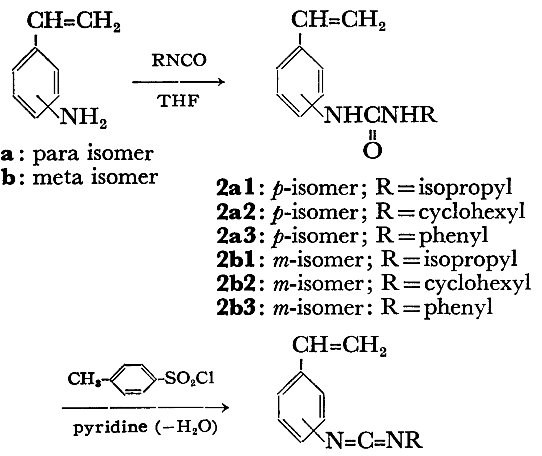
N-(*p*- or *m*-Vinylphenyl)-*N'*-isopropyl- and cyclohexylcarbodiimides (**3**) have been synthesized in reasonable yields by first synthesizing the substituted ureas by the reactions of *p*- or *m*-vinylaniline with isopropyl or cyclohexyl isocyanate in THF and the subsequent dehydration with *p*-toluenesulfonyl chloride in pyridine. The monomers **3** were found to polymerize smoothly with AIBN to afford vinyl polymers bearing the corresponding carbodiimide units as pendants in more or less cross-linked forms. The cross-linked insoluble polymers thus obtained can act as a dehydrative coupling agent in reactions such as the formation of peptide linkages.

Carbodiimides are one of the most versatile dehydrative coupling agents, especially for use in peptide syntheses.[1] An attempt to use carbodiimide units as pendants of vinyl polymers prepared by polymer reactions has been reported,[2] thereby assuring ready separation of carbodiimide reagents after reaction.

The authors have been interested in the syntheses of vinyl carbodiimide monomers and the preparation of vinyl polymers bearing carbodiimide units as pendants by the radical polymerization of the monomers thus synthesized. The carbodiimide polymers thus synthesized can act as polymer reagents in dehydration and other reactions characteristic of low molecular weight carbodiimides such as dicyclohexylcarbodiimide.

Results and Discussion

Carbodiimide monomers have been synthesized as follows.



1a: para isomer
1b: meta isomer

2a1: *p*-isomer; R = isopropyl
2a2: *p*-isomer; R = cyclohexyl
2a3: *p*-isomer; R = phenyl
2b1: *m*-isomer; R = isopropyl
2b2: *m*-isomer; R = cyclohexyl
2b3: *m*-isomer: R = phenyl

3a1: *p*-isomer; R = isopropyl
3a2: *p*-isomer; R = cyclohexyl
3b1: *m*-isomer; R = isopropyl
3b2: *m*-isomer; R = cyclohexyl

Substituted ureas (**2**) have been readily synthesized from vinylanilines (**1**) and isocyanates in tetrahydrofuran (THF) in satisfactory yields, as indicated in Table 1. The conversions of ureas to the corresponding carbodiimides (**3**) were however not successful in all cases. Thus, ureas **2a3** and **2b3** did not provide the corresponding carbodiimides in pure forms, presumably due to the poor stability of the products; the yields of other carbodiimides, as indicated in Table 1, were not high. The synthetic route described here however appears to be useful, since it can be easily conducted and, starting from the readily available **1**, the desired products (**3**) are obtained in two steps.

TABLE 1. SUBSTITUTED UREAS AND CARBODIIMIDE MONOMERS SYNTHESIZED

Compound	Yield, %	Mp, °C	Bp, °C/mmHg
2a1	88.2	148—150	—
2a2	73.8	178—180	—
2a3	80.3	203—204	—
2b1	81.2	118—120	—
2b2	87.3	149—150	—
2b3	90.9	162—163	—
3a1	62.8	—	97/0.7
3a2	29.0	—	105/3.0
3b1	48.1	—	98/1.0
3b2	40.7	—	128/1.0

As indicated in Table 2, the solution polymerization of the monomer **3**, alone and in the presence of styrene, proceeded smoothly to give homogeneous polymer solutions. Monomers **3a1** and **3a2** were exceptional in that the solutions gave gels. The homopolymers of **3b** became insoluble in THF once precipitated into methanol, indicating that the N=C bonds of the carbodiimide portions in the monomers and polymers participated, more or less, in the polymerizations. The IR spectra of the **3a** polymers indicated a decrease in the intensities of the –N=C=N– absorptions at 2100 cm^{-1} compared with those of the corresponding monomers, together with characteristic absorptions for vinyl polymers containing carbodiimide units as pendant. Copolymerizations with styrene overcame the poor solubility characteristic: copolymers Nos. 4 and 7 in Table 2 are completely soluble in organic solvents, although the contents of the carbodiimide units are considerably lower than those calculated for the monomers employed. It appears, however, that the practical merits of the carbodiimide polymers are displayed when they are employed in the cross-linked insoluble forms and compensate for this fault.

The dehydrative coupling functions of the carbodiimide polymers have been investigated especially for the following amino acid combination:

TABLE 2. SOLUTION POLYMERIZATION OF **3** MONOMERS[a)]

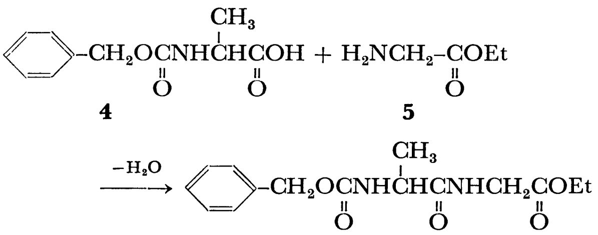
No.	Monomer	Conversion %	3-Content[c)] in polymer, %	[η][d)] dl/g	Remark on polymer
1	**3a2**	52.2	100	—	Homogeneous polymerization but converted to an insoluble gel
2	**3b1**	52.0	100	0.22	Soluble in hot pyridine
3	**3b1**-St (50)[b)]	64.8	44	0.18	Soluble in pyridine
4	**3b1**-St (33)[b)]	44.2	15	0.23	Soluble in organic solvents
5	**3b2**	30.2	100	0.22	Soluble in hot pyridine
6	**3b2**-St (50)[b)]	55.2	48	0.22	Soluble in hot pyridine
7	**3b2**-St (33)[b)]	49.9	19	0.20	Soluble in organic solvents

a) 30% Total monomers and 1% AIBN/monomers in THF; 70 °C×24 h. b) 3 mol % in monomers (St=styrene). c) By CHN analyses (mol %). d) In THF at 25 °C.

TABLE 3. FORMATION OF PEPTIDE LINKAGE WITH **3** POLYMER

No.	Polymer	**6** obtained, mol / g-polymer
1	**3b1**-St (1: 1) copolymer[a)]	0.33
2	**3a1** Homopolymer[b)]	0.25
3	**3a1**-St (1: 1) copolymer[b)]	0.22

a) Obtained by solution polymerization. b) Obtained by precipitation polymerization.



4 **5**

6

Table 3 indicates the results obtained which indicate that the cross-linked insoluble polymers of **3** play the role of polymer reagent inducing the desired reaction in a heterogeneous system. As expected, the capacity as a polymer reagent is dependent upon the origin of the **3** polymer. Thus, No. 1 polymer in Table 3 with a gel structure is superior to No. 3 with a somewhat macroreticular structure. A more detailed investigation is however required for a complete evaluation of the effects of both chemical and physical structures.

Experimental

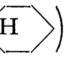
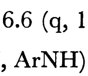
The IR, ^{1}H-NMR, and mass spectra were recorded on a Hitachi 215 spectrophotometer, a JNM-PMX 60 spectrophotmeter, and a Hitachi RMU-6 MG spectrometer, respectively, under standard measurement conditions. Elemental analyses were conducted using a Perkin-Elmer 250 instrument.

*N-(p-Vinylphenyl)-N′-isopropylurea (**2a1**).* To a solution of *p*-vinylaniline (2.0 g, 17 mmol), prepared by the alkaline dehydration of 2-(*p*-aminophenyl)ethanol,[3)] in anhydrous THF (20 ml), isopropyl isocyanate (1.5 g, 17 mmol) was added gradually at room temperature with stirring, the resulting solution being allowed to stand overnight at room temperature. The solvent was then removed by evaporation *in vacuo* at 50 °C, followed by recrystallizations from THF–petroleum ether which gave white needles.

Found: C 70.54; H, 7.78; N, 13.24%. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71%. IR(KBr) 3300 (NH), 2860—3000 (alkyl), 1620 (C=O), 1580 (phenyl), 990, 900 (vinyl) cm^{-1}; NMR ($CDCl_3$) δ 1.1 (d, 6 H, Me), 3.8 (m, 1 H, CH), 5.1 (d, 1 H, $C\underline{H}_2$=CH–), 5.5 (d, 1 H, $C\underline{H}_2$=CH–), 5.7 (s, 1 H, $N\underline{H}CHMe_2$), 6.6 (q, 1 H, CH_2=C$\underline{H}$–), 7.2 (s, 4 H, ArH), 7.8 (s, 1 H, NHAr) ppm; Mass (*m*/*e*) 207 (M$^+$, 67), 118, 119 (100).

N-(*p*-Vinyl-phenyl)-*N′*-cyclohexylurea (**2a2**) and *N*-(*p*-vinylphenyl)-*N′*-phenylurea (**2a3**) were synthesized in the same manner to afford fine colorless needles and a colorless powder, respectively, their analytical data being also satisfactory.

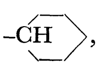
*N-(m-Vinylphenyl)-N′-cyclohexylurea (**2b2**).* By applying the same reaction procedure as that for the synthesis of **2a1**, cyclohexyl isocyanate (5.2 g, 42 mmol) and *m*-vinylaniline (**1b**: 5.0 g, 42 mmol), prepared by the Al_2O_3 dehydration of 1-(*m*-aminophenyl)ethanol,[4)] produced a white powder (**2b2**) which was recrystallized from THF–petroleum ether.

Found: C, 73.25; H, 8.39; N, 11.50%. Calcd for $C_{15}H_{20}N_2O$: C, 73.37; H, 8.52; N, 11.48%. IR(KBr) 3350 (NH), 2860, 2940 (cyclohexyl), 1620 (C=O), 1560 (phenyl), 995, 910 (vinyl) cm^{-1}; NMR (DMSO-d_6+$CDCl_3$) δ 1.1—1.9 (m, 10 H, 5 CH_2), 2.8 (s, 1 H, –CH ), 5.2 (d, 1 H, $C\underline{H}_2$=CH–), 5.7 (d, 1 H, $C\underline{H}_2$=CH–), 5.7 (s, 1 H, –NH– ), 6.6 (q, 1 H, CH_2=C$\underline{H}$–), 6.8—7.6 (m, 4 H, ArH), 8.0 (s, 1 H, ArNH) ppm; Mass (*m*/*e*) 244 (M$^+$, 18), 119 (100). *N*-(*m*-Vinylphenyl)-*N′*-isopropylurea (**2b1**) and *N*-(*m*-vinylphenyl)-*N′*-phenylurea (**2b3**) were synthesized in the same manner to afford fine colorless crystals with satisfactory analytical data in both instances.

*N-(p-Vinylphenyl)-N′-isopropylcarbodiimide (**3a1**).* To a solution of **2a1** (1.5 g, 7.4 mmol) and 4-*t*-butylcatechol (0.1 g) in anhydrous pyridine (20 ml) *p*-toluenesulfonyl chloride (2.8 g, 15 mmol) was added dropwise and the resulting solution heated at 70 °C for 2 h. The reaction mixture was then poured into iced water and extracted with ether (200 ml), the organic layer being washed with water and dried over anhydrous sodium sulfate, followed by distillation *in vacuo* to afford a pale brown liquid. Found: C, 77.91; H, 7.50; N, 14.58%. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04%. IR ($CHCl_3$) 2870—2920 (alkyl), 2120 (–N=C=N–), 1600 (phenyl), 990, 900 (vinyl) cm^{-1}; NMR ($CDCl_3$) δ 1.3 (d, 6 H, 2 Me), 3.7 (m, 1 H, CH), 5.2 (d, 1 H, $C\underline{H}_2$=CH–), 5.6 (d, 1 H, $C\underline{H}_2$=CH–), 6.6 (q, 1 H, CH_2=C$\underline{H}$–), 6.8—7.5 (m, 4 H, ArH) ppm; Mass (*m*/*e*) 186 (M$^+$, 100). *N*-(*p*-Vinylphenyl)-*N′*-cyclohexylcarbodiimide (**3a2**) was synthesized in the same manner to afford a colorless liquid.

*N-(m-Vinylphenyl)-N′-cyclohexylcarbodiimide (**3b2**).* The same reaction procedure as that for **3a1** was applied to afford a colorless liquid.

Found: C, 79.60; H, 8.18; N, 12.23%. Calcd for $C_{15}H_{18}N_2$:

C, 79.61, H, 8.02, N, 12.38%. IR ($CHCl_3$) 2860—2930 (alkyl), 2120 (-N=C=N-), 1580 (phenyl), 990, 900 (vinyl) cm^{-1}; NMR ($CDCl_3$) δ 1.1—1.9 (m, 10 H, 5 CH_2), 3.5 (m, 1 H, ), 5.3 (d, $C\underline{H}_2$=CH-), 5.8 (d, 1 H, $C\underline{H}_2$=CH-), 6.7 (q, 1 H, CH_2=C$\underline{H}$-), 6.9—7.6 (m, 4 H, ArH) ppm. Mass (*m*/*e*) 226 (M^+, 13), 144 (100).

N-(*m*-Vinylphenyl)-*N'*-isopropylcarbodiimide (**3b1**, a colorless liquid) was synthesized in the same manner.

The analytical data for the synthesized carbodiimide monomers not shown above were satisfactory.

*Solution Polymerization of **3** Monomers.* A solution of the total monomers (1.0 g) and 2,2'-azobisisobutyronitrile (AIBN: 0.01 g) in THF (2.3 ml) was placed in a Pyrex glass ampoule, which was evacuated, flushed with nitrogen, sealed, and allowed to stand for 24 h at 70 °C. Precipitation of the contents into methanol provided the polymer. All polymers of **3** thus synthesized indicated IR absorptions at 2860 and 2930 cm^{-1} attributable to vinyl polymer backbones together with sharp peaks at 2100 cm^{-1} characteristic of -N=C=N- bonds. For the determination of intrinsic viscosities $[\eta]$, 20% of the contents were set aside without precipitation and diluted with THF for use in viscosimetry (Ostwald).

*Precipitation Polymerization of **3** Monomers.* A solution of total monomers (5 g) containing 10% divinylbenzene and AIBN (0.05 g) in heptane (8—15 ml) was stirred at 70 °C for 6—8 h under a nitrogen atmosphere. After 3—4.5 h, heptane (8—10 ml) was further added and stirring continued. The precipitated polymer was washed with petroleum ether and extracted overnight with ether using a Soxhlet extractor. Yields of 60—75% were obtained.

*Formation of Peptide Linkage with **3** Polymer.* Typically, *N*-benzyloxycarbonyl-L-alanine (**4**: 0.8 g, 4 mmol) and glycine ethyl ester (**5**: 0.4 g, 4 mmol) were dissolved in THF (50 ml). The No. 1 copolymer in Table 3, extracted with anhydrous THF, was then added and the mixture stirred at room temperature overnight. The reaction mixture was centrifuged, the supernatant solution evaporated *in vacuo* at 50 °C, the residue dissolved in chloroform, and the resulting solution washed first with aqueous hydrochloric acid, then with aqueous sodium carbonate, followed by evaporation *in vacuo* to give colorless crystals.

References

1) A. C. Cope, *Org. React.*, **12**, 205 (1962).
2) N. M. Weinshenker and C. M. Shen, *Tetrahedron Lett.*, **1972**, 3281, 3283.
3) H. Kamogawa, *J. Polym. Sci.*, *A-1*, **7**, 725 (1969).
4) G. Manecke and G. Kossmehl, *Makromol. Chem.*, **70**, 112 (1964).