Journal of the Korean Chemical Society
1998. *Vol. 42, No. 5*
Printed in the Republic of Korea

단 신

이온선택성 전극용 리튬이온수송체, 시스-시클로헥산 디아미드의 개량 합성

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(1998. 6. 30 접수)

Improved Syntheses of *cis*-Cyclohexane Diamides, Lithium Ion Carriers for Ion-Selective Electrodes

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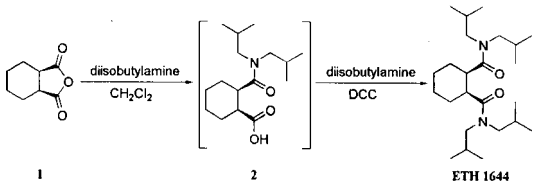
(Received June 30, 1998)

Selective ion carriers have been of considerable interest as tools for the analysis and separation of metal ions as well as for many biological applications. Lithium ion carriers could have a wide range of applications. One potential pharmacological application for such carriers would be, for instance, the enhancement of the uptake of lithium ion into the brain and other tissues.[1-3] Another application is continuous monitoring of lithium ion activity by polymer membrane ion-selective electrodes (ISEs)[4,5] during the lithium therapy of patients suffering from manic-depressive psychosis and some other neurological and psychiatric disorders.[6,7]

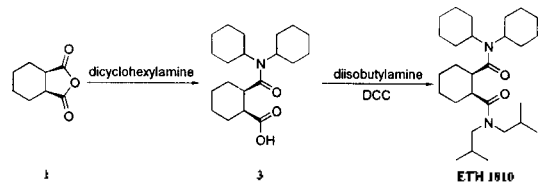
Because of stringent requirements with respect to the Li^+/Na^+ selectivity and electrode potential stability,[8] so far few carriers specific for lithium ion have been described. Bidendate diamides such as ETH 1644 and ETH 1810 derived from *cis*-1,2-cyclohexanedicarboxylic acid have been most widely used as the standard lithium ion carriers for lithium ion selective electrodes because of the easy preparation and relatively high selectivity coefficient of lithium ion over sodium ion *i.e.*, $\log K_{Li,Na} = -2.5$ and -2.1 respectively.[9,10]

This highly lithium selective ionophores have been synthesized by Simon *et al.*[9h] With purification of all the synthetic intermediates the diamide, ETH 1644 was synthesized in 25% overall yield after distillation, as follows: *Cis*-1,2-cyclohexanedicarboxylic anhydride (**1**) was reacted with diisobutylamine in toluene at room temperature to afford *cis*-2-(*N,N*-diisobutylcarbamoyl) cyclohexane carboxylic acid (**2**) in 75% yield. The corresponding *p*-nitrophenol ester was synthesized from the amido acid **2** and *p*-nitrophenol in the presence of dicyclohexylcarbodiimide (DCC) in ethyl acetate at room temperature in 99% yield. The *p*-nitrophenol ester was reacted with diisobutylamine in refluxing benzene. The diamide ETH 1644 was isolated by chromatography in 88% yield and further purified by distillation in 66% yield.

The other diamide, ETH 1810 has been also synthesized from *cis*-2-(*N,N*-dicyclohexylcarbamoyl)cyclohexanecarboxylic acid (**3**) and diisobutylamine with DCC as coupling reagent in 20% overall yield from the anhydride **1**.[9e] The *cis*-amido acid **3** was prepared from the anhydride **1** and dicyclohexylamine in toluene.



Scheme 1.



Scheme 2.

We could easily synthesize the diamide, ETH 1644 by one pot reaction in the presence of DCC. The anhydride **1** was reacted with 2.2 equivalents of diisobutylamine in methylene chloride at room temperature for 30 min, and then a slight excess of DCC was added to the stirred reaction mixture. The diamide, ETH 1644 was isolated by chromatography and purified by distillation in 88% yield (Scheme 1).

The structure of distilled product **ETH** 1644 was confirmed by comparing ^{1}**H**, ^{13}C NMR and melting point of the authentic sample. Furthermore the ion selectivity behavior of the synthesized product was checked by measuring the ion selectivity coefficient of PVC membrane electrode composed of 1 to 1.4 wt% of the carrier, 0.4 wt% of tetrakis(*p*-chlorophenyl)borate and 65.6 wt% of *o*-nitrophenyloctyl ether as a plasticizer.[9c] Ion carrier ETH 1644 gave reproducible results with the selectivity factors, log $K_{Li,Na}$ −2.1 reported by Simom *et al.*[9c,9e,10]

We could also synthesize the diamide, ETH 1810 under the improved reaction conditions, and isolate unusual reaction intermediate derived from DCC. Due to the unsymmetrical diamide structure of ETH 1810, one pot synthesis could not be applicable. The literature procedure[9e] was followed to synthesize **ETH** 1810 by refluxing a mixture of the anhydride **1** and dicyclohexylamine in toluene, followed by treating with diisobutylamine and DCC (Scheme 2).

It was observed that the expected *cis*-amido acid **3** was not the major product, but *trans*-amido acid. Under these severe reaction conditions the *cis*-1,2-dicarbonyl compound could be isomerized to the more stable trans isomer in the presence of a secondary amine.[11] However, the *cis*-amido acid **3** was synthesized in 30% yield at room temperature with prolonged reaction time. It appears that, probably due to the bulky cyclohexyl groups, attack by dicyclohexylamine might be more difficult as compared to that by diisobutylamine, which reacts rapidly with the anhydride **1** at room temperature. Some other conditions in, *i.e.*, THF, methylene chloride or chloroform at reflux were not satisfactory for this reaction. The *cis*-amido acid **3** was reacted with diisobutylamine in presence of DCC in methylene chloride, giving *cis*-diamide, ETH 1810 in 72% yield. In addition, this reaction produced the unexpected *O*-acylisourea **4** in 14% yield.

DCC is the most often used coupling reagent in peptide synthesis. It is known that the reaction mechanism involves addition of an acid to the reagent to form a reactive intermediate, the *O*-acylisourea corresponding to **4**, and a frequently found byproduct is the *N*-acylurea corresponding to **5**, which can be formed by an *O*- to *N*-acyl migration.[12]

Although two isomers, *O*-acylisourea **4** and *N*-acylurea **5** could not be clearly identified due to the structural similarity, the isolated intermediate was characterized to be *O*-acylisourea **4** by nmr, mass spectrometry and the chemical reaction. When the reactive intermediate **4** was heated in

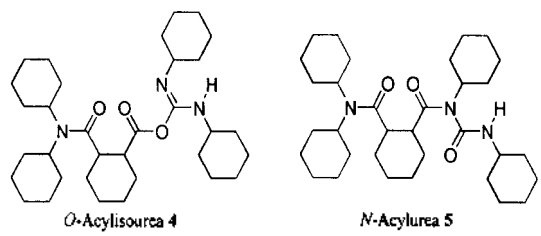
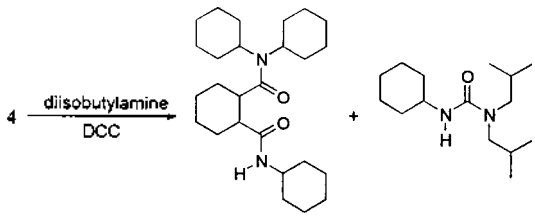


Chart 1.



Scheme 3.

the presence of excess diisobutylamine, two new compounds, *N,N,N'*-tricyclohexylcyclohexane-1,2-dicarboxamide (**6**) and *N*-cyclohexyl-*N',N'*-diisobutylurea (**7**) were isolated (Scheme 3).

The plausible mechanism for the formation of diamide **6** and urea derivative **7** is shown in Figure 1. Whereas *N*-acylureas are unreactive toward amines and do not form amide bonds, at the elevated temperature *O*-acylisourea **4** could rearrange by intramolecular nucleophilic attack of the secondary amino group at the activated electrophilic carbon to form diamide **6** and very reactive cyclohexylisocyanate which could further reacts with diisobutylamine to produce unsymmetrical urea **7**. The isolation of the reactive intermediate, *O*-acylisourea **4** is unusual; its stability might be due to the bulky cyclohexyl groups. The electrophilic carbonyl carbon, the reactive site of the intermediate *O*-acylisourea, is too hindered to be attacked by nucleophiles.

In summary, widely used lithium ion carriers, bidendate diamide ETH 1644 was synthesized in one-pot in improved yield, and ETH 1810 also synthesized under improved reaction conditions. The unusual reactive intermediate, *O*-acylisourea **4** was isolated and characterized, and the reaction mechanism for its reaction with secondary amines has been proposed.

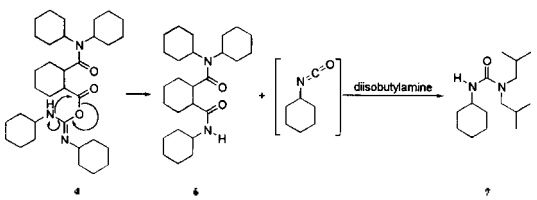


Fig. 1. The plausible mechnism for formation of diamide **6** and urea derivative **7** from *O*-acylisourea **4**.

EXPERIMENTAL

***cis*-N,N,N',N'-Tetraisobutylcyclohexane-1,2-dicarboxamide (ETH 1644).** To a solution of *cis*-1,2-cyclohexanedicarboxylic anhydride (3.08 g, 20 mmol) in 40 mL of methylene chloride at room temperature was added diisobutylamine (5.69 g, 44 mmol), and the reaction mixture was stirred for 30 min. To the resulting clear reaction solution was added dicyclohexylcarbodiimide (4.54 g, 22 mmol), and the mixture was stirred overnight at room temperature. After removing the precipitate by filtration, the filtrate was concentrated. The residue was purified by column chromatography (silica gel, ethylacetate/hexane=1/9) and then distilled under vacuum giving 6.92 g (88%) of a colorless oil: bp 160-170 °C, 1 mmHg (lit.[9b] 120-124 °C, 0.02 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (m, 2H), 3.00 (m, 6H), 2.76 (m, 2H), 2.23 (m, 2H), 1.97 (m, 4H), 1.85 (m, 2H), 1.48 (m, 2H), 1.34 (m, 2H), 0.86 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 56.2, 53.8, 39.5, 28.3, 27.0, 26.5, 23.3; IR (film) 2960 s, 2920 s, 2870, s, 1645 s, 1465 s, 1445 s, 1420 s, 1385 m, 1365 m, 1330 m, 1240 m, 1220 s, 1140 s, 1095 m (cm $^{-1}$).

***cis*-2-(N,N-Dicyclohexylcarbamoyl)cyclohexanecarboxylic Acid (3).** *Cis*-1,2-cyclohexanedicarboxylic anhydride (2.32 g, 15 mmol) and dicyclohexylamine (2.78 g, 16 mmol) were dissolved in 50 mL of toluene, and the solution was stirred at room temperature for 60 h. After removing the solvent *in vacuo*, the crude product was purified by chromatography (silica gel; ethylacetate/hexane=2/8) to afford 1.1 g (30%) of the *cis*-amido acid **3** as a white solid. This product could be crystallized from ethylacetate/hexane: mp 141-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.4 (m, 1H), 2.4 (m, 2H), 2.0 (m, 3H), 1.0-2.0 (m, 26H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 175 b, 174 b, 59 b, 58.0, 57 b, 56.4, 45.5, 43.5, 31.5, 31-22 (group of peaks): Due to the slow rotation of amide bond or the slow conformational process of *cis*-1,2-substitutedcyclohexane, the peaks could not be assigned reasonably: IR (film) 3300-

2800 b, 2930 s, 2860 s, 1730 m, 1700 s, 1630 s, 1560 m, 1450 s (cm^{-1}).

***trans*-2-(*N*,*N*-Dicyclohexylcarbamoyl)cyclohexanecarboxylic Acid.** *Cis*-1,2-cyclohexanedicarboxylic anhydride (4.63 g, 30 mmol) and dicyclohexylamine (8.34 g, 46 mmol) were dissolved in 100 mL of toluene, and the solution was heated at reflux for 24 h. After removing the solvent *in vacuo*, the residue was dissolved in chloroform, washed with 2 M-HCl to remove the excess amine, with a solution of sodium bicarbonate, and then with brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The product was precipitated from chloroform-hexane. The solid product (7.83 g, 77%) was obtained by filteration: mp 199-200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.6 (b, 1H), 2.9 (m, 2H), 2.8 (m, 1H), 2.4 (b, 2H), 2.1 (b, 1H), 1.0-1.0 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 175.0, 58.0 b, 56.5 b, 45.8, 43.9 b, 31.5 b, 30.9 b, 30.2, 29.5, 29.1, 26.7, 26.6, 26.2, 16.0, 25.5, 25.3; IR (film) 3300-2800 b, 2940 s, 2850 s, 2650 b m, 1735 s, 1700 m, 1625 m, 1585 s, 1440 s (cm^{-1}).

***cis*-*N*,*N*-Dicyclohexyl-*N*′,*N*′-diisobutylcyclohexane-1,2-dicarboxamide (ETH 1810).** To a solution of *cis*-amido acid **3** (671 mg, 2 mmol) in 30 mL of methylene chloride were added diisobutylamine (285 mg, 2.2 mmol) and DCC (454 mg, 2.2 mmol). The mixture was stirred at room temperature for 12 h. The precipitate was removed by filteration. The filtrate was loaded on a silicagel column, and eluted with ethyl acetate/hexane (1/9). Two major products were isolated, the *cis*-diamide, ETH 1810 (646 mg, 72%) and the reaction intermediate, *O*-acylisourea **4** (155 mg, 14%): **ETH 1810**; mp 104-106.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.4-2.9 (b m, 4H), 2.80 (m, 2H), 2.65 (m, 2H), 2.35 (m, 2H), 2.2-1.0 (b m, 28H), 0.9 (b]s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 173.3, 56.6 b, 55.8 b, 54.6 b, 43.4, 38.0, 32 b, 30 b, 28.2, 26.5 b, 26.3, 25.4, 24.5, 22.3, 20.3 b; IR (film) 2940 s, 2860 s, 1630 s, 1440 s, 1360 m, 1300 m, 1220 m (cm^{-1}).

***O*-Acylisourea 4;** mp 170-171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.6 (b, 1H), 4.12 (m, 1H), 3.88 (m, 1H), 3.52 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.35 (m, 1H), 2.0-1.0 (m, 48H); IR (film) 3250 b, 2935 s, 2860 s, 1705 s, 1650 s, 1540 m, 1450 m (cm^{-1}); MS m/z (relative intensity) 541 (M^+, 0.6), 318 (3), 236 (25), 223 (1), 181 (19), 180 (100), 154 (35), 98 (20), 83 (35), 55 (30).

***N*,*N*,*N*′-Tricyclohexylcyclohexane-1,2-dicarboxamide (6) and *N*-Cyclohexyl-*N*′,*N*′-diisobutyl Urea (7).** The *O*-acylisourea **4** was prepared in situ from the reaction of *cis*-amido acid **3** (4.73 g, 14 mmol) and DCC (3.1 g, 15 mmol) in methylene chloride at room temperature for 3 h and concentrated to dryness *in vacuo*. The crude *O*-acylisourea **4** (7.59 g, 14 mmol) was dissolved in 20 mL of diisobutylamine under nitrogen. The mixture was heated at reflux for 3 h and then the excess amine was removed *in vacuo*. The residue was dissolved in methylene chloride and filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was dissolved in ethyl acetate. Some crystals (2.37 g, 34%, mp 197-198 °C) were formed from ethyl acetate and were collected by filtration. By concentrating the filtrate, more crystals were formed and collected by filtration. The impure second crop of the crystals dissolved in hexane and some insoluble solid was removed by filtration. From the filtrate crystals (2.33 g, 61%, mp 108-109 °C) were formed and obtained by filtration: **6**; mp 197-198 °C; solubility, soluble in ethyl acetate, insoluble in hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (b, 1H), 3.5 (b, 2H), 2.75 (m, 2H), 2.5 (m, 2H), 2.35 (b, 1H), 2.0-1.0 (m, 36H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 174.1, 57.4 b, 55.9 b, 47.7, 46.8, 44.0 b, 32.9, 32.8, 31.5 b, 30.1, 30.0, 28.5, 26.5, 26.5, 26.0, 25.9, 25.5, 25.32, 25.29, 25.19, 24.99, 24.71, 24.66; IR (film) 3300 b, 2940 s, 2860 s, 1650 s, 1615 s, 1550 m, 1450 m, 1370 w (cm^{-1}); MS m/z (relative intensity) 237 (4.7, M^+-dicyclohexylamine), 236 (26.1), 181 (18.8), 180 (100, dicyclohexylamine), 154 (29.3), 98 (25.5, cyclohexylamine), 97 (20), 83 (46.8): **7**; mp 108-109 °C; solubility, soluble in ethyl acetate and hexane, insoluble in diethyl ether; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (b d, 1H), 3.6 (m, 1H), 3.01 (d, J=7.0 Hz, 4H), 1.9 (m, 2H), 1.75-1.45 9m, 4H), 1.4-1.2

(m, 3H), 1.15-0.95 (m, 3H), 0.89 (d, J=7.0 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 55.5, 49.2, 33.9, 27.7, 25.7, 25.0, 20.2; IR (film) 3330 b, 2920 s, 2850 s, 1615 s, 1525 s, 1480 w (cm^{-1}); MS m/z (relative intensity) 255 (0.6), 254 (2.4, M^+), 235 (22), 181 (18), 180 (100), 154 (35), 138 (20), 126 (18), 119 (15), 118 (10), 98 (40), 86 (40.6), 83 (73.6), 55 (99.1).

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