Monatshefte für Chemie 116, 217—221 (1985)

Monatshefte für Chemie
Chemical Monthly

New Multidentate Potential Ionophors of Ether-Amide Type

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(Received 10 February 1984. Accepted 27 March 1984)

The syntheses of acyclic compounds featuring ether-amide groups and different terminal substituents are presented. Three series of new multidentate potential ligands were obtained.

(Keywords: Multidentate ligands; Ether-amide ligands; Acyclic ligands)

Neue mehrzähnige potentielle Ionophore des Ether-Amid-Typs

Es wird die Synthese acyclischer Verbindungen mit Ether-Amid-Gruppen und verschiedenen endständigen Substituenten beschrieben. Es wurden drei Verbindungsreihen erhalten, die neue potentielle mehrzähnige Liganden repräsentieren.

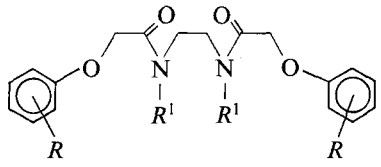
Introduction

One of our research fields is the design and the synthesis of acyclic compounds that are able to coordinate cations in a multidentate manner. Earlier, we have reported the synthesis and cation complexing properties of phenylenedioxydiacetamides and cyclohexanedioxydiacetamides[1,2].

Results and Discussion

For further studies on the influence of the structure on the complexing properties of various derivatives we have now prepared a series of symmetric ligands (**1–3**) containing both amide and ether groups in addition to different substituents on the aromatic ring system.

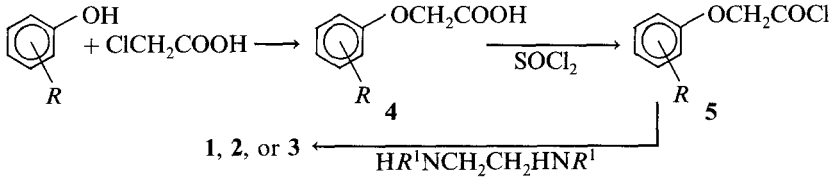
The new symmetric acyclic diether-diamide ligands **1–3** can be prepared by two methods: A. The previously developed reaction of an appropriate phenoxyacetic acid chloride with various amines[1]. All the *o*- and *m*-substituted compounds, except **1c**, **2c**, and **3c**, could be prepared



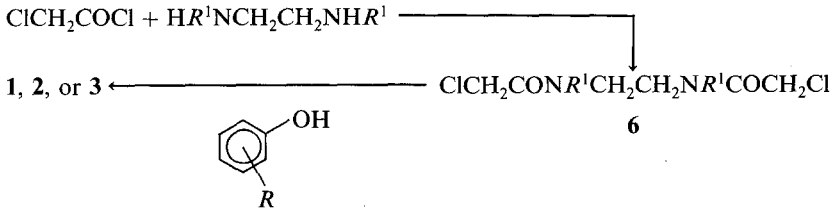
	$-R^1$		$-R$
1:	$-H$	**a:**	*o*-NO_2
2:	$-CH_3$	**b:**	*o*-NHCO*Me*
3:	$-CH_2CH_2-$	**c:**	*o*-CO_2H
		d:	*m*-NHCO*Me*

by using this method in spite of a low yield in the preparation of the phenoxyacetic acid **4**. B. The condensation of chloroacetyl chloride with appropriate diamines yields quantitatively chloroacetamides which then can undergo an alkylation reaction with phenols leading to products **1–3** in good yields. By using this method, compounds containing terminal carboxylic acid groups could be prepared. The alkylation reaction of the appropriate phenol with chloroacetamides is much improved due to the more reactive alkylation agent.

Method A



Method B



The structures for all acyclic diether-diamide compounds are consistent with IR, NMR, and mass spectra data as well as elemental analysis. All amide carbonyls exhibit IR bands at 1 650–1 660 cm^{-1}. In the ^{1}H-NMR spectra all compounds show resonances at δ 5.2 ppm for the $-CH_2-$ group, at 4.0 ppm for the $-NCH_2-$ groups, and at 7–8 ppm for the aromatic protons.

Acknowledgement

We thank the Conselho Nacional de Desenvolvimento Cîentifico (CNPq), Financiador de Estudos e Projetos (FINEP) and Volkswagen Foundation for financial support.

Experimental

The nuclear magnetic resonance spectra were recorded in $CDCl_3$ solution with a Hitachi Perkin-Elmer R 20 B spectrometer; *TMS* was used as internal reference. Mass spectra were recorded on a Varian MAT-CH 5 mass spectrometer. The infrared spectra were taken on a Perkin-Elmer Model 180 spectrophotometer in KBr plates. Elemental analyses were obtained on a Perkin-Elmer Model 240 elemental analyzer. The C, H, N values were in good agreement with the theoretical composition of the compounds. All solvents used were distilled and if necessary they were purified by following the procedure mentioned in Ref.[3]. All inorganic salts were reagent grade.

Chloroacetamides (**6**)[4,5]

N,N'-Dichloroacetylethylenediamine (**6 a**)
N,N'-Dichloroacetyl-N,N'-dimethylethylenediamine (**6 b**)
N,N'-Dichloroacetylpiperazine (**6 c**)

Chloroacetyl chloride (2 mol) was dissolved in the same amount of dry chloroform and mixed dropwise with a solution of the diamine (1 mol) (ethylenediamine, dimethylenediamine, or piperazine) in 60 ml of dry chloroform at 0–5 °C. Afterwards the mixture was refluxed for six h. Then the solvent was evaporated and the residue was washed with water several times to yield the product.

Alkylation of Phenols with Chloroacetamide (**6**) – *General Procedure*

The corresponding phenol (2.1 mol) was dissolved in sufficient methanol in the presence of sodium methoxide (2 mol). Compound **6** was added; it only dissolves as long as the mixture is hot. Then the reaction mixture was refluxed for an appropriate period of time. At the end of the reaction the mixture was cooled to 0 °C and the crude product was isolated by filtration.

N,N'-Di(o-nitrophenoxy)acetylethylenediamine (**1 a**)

From *o*-nitrophenol (2.72 g, 0.020 mol) and chloroacetamide (**6 a**) (2 g, 0.0094 mol). Reaction time: 20 h. Yellow crystals from acetic acid (2.29 g, 65% yield), m.p. 230–233 °C; IR: 3 400, 1 685, 1 600, 1 510, 1 335 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 3.95 (broad singlet, 4 H), 5.0 (s, 4 H), 7.13–8.32 (m, 8 H), and 8.45 (m, 2 H) ppm.

N,N'-Di(o-acetamidophenoxy)acetylethylenediamine (**1 b**)

From *o*-acetamidophenol (2.98 g, 0.020 mol) and chloroacetamide (**6 a**) (2 g, 0.0094 mol). Reaction time: 2 h. White crystals from *DMSO* (2.95 g, 95% yield), m.p. 280–282 °C; IR: 3 360, 3 280, 1 680, 1 640, 1 600, 1 460, 1 290 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.55 (s, 6 H), 3.75 (s, 4 H), 4.85 (s, 4 H), 6.9–7.8 (m, 8 H), 8.2 (s, 2 H), and 9.4 (s, 2 H) ppm.

N,N'-Di[o-(hydroxycarbonyl)phenoxy]acetylethylenediamine (**1 c**)

From salicyclic acid (2.49 g, 0.020 mol) and **6 a**. Reaction time: 24 h. White crystals from diglyme (2.57 g, 65.7% yield), m.p. 190–192 °C; IR: 3 300, 1 680, 1 660, 1 610, 1 490, 1 250 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 3.88 (s, 4 H), 5.2 (s, 4 H), and 7.0–8.35 (m, 8 H) ppm.

N,N'-Di(m-acetamidophenoxy)acetylethylenediamine (**1 d**)

From *m*-acetamidophenol (2.84 g, 0.019 mol) and **6 a** (2 g, 0.0094 mol). Reaction time: 5 h. The crude product was a viscous oil which formed a white powder after staying at room temperature for two days. White powder from diglyme (2.83 g, 68.1% yield), m.p. 128–130 °C; IR: 3 500, 3 440, 3 460, 3 400, 1 630, 1 605, 1 598, 1 445, 1 300 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.45 (s, 6 H), 3.95 (s, 4 H), 4.75 (s, 4 H), 6.9–8.7 (m, 8 H), 8.2 (s, 2 H), and 9.5 (s, 2 H) ppm.

N,N'-Dimethyl-N,N'-Di(o-nitrophenoxy)acetylethylenediamine (**2 a**)

From *o*-nitrophenol (2.89 g, 0.021 mol) and **6 b** (2 g, 0.0083 mol) were used. Reaction time: 24 h. Yellow crystals from an acetic acid-water mixture (2.78 g, 75% yield), m.p. 78–80 °C; IR: 1 650, 1 605, 1 440, 1 305, 1 250 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 3.07 (s, 6 H), 3.59 (s, 4 H), 5.8 (s, 4 H), and 7.1–8.5 (m, 8 H) ppm.

N,N'-Dimethyl-N,N'-Di(o-acetamidophenoxy)acetylethylenediamine (**2 b**)

From *o*-acetamidophenol (2.98 g, 0.020 mol) and **6 b** (2 g, 0.0083 mol). Reaction time: 4 h. White crystals from methanol (3.54 g, 80% yield), m.p. 73–75 °C; IR: 3 400, 1 660, 1 630, 1 600, 1 440, 1 290 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.55 (s, 6 H), 3.31 (s, 6 H), 3.93 (s, 4 H), 5.02 (s, 4 H), and 6.8–7.75 (m, 8 H) ppm.

N,N'-Dimethyl-N,N'-Di[o-(Hydroxycarbonyl)phenoxy]acetylethylenediamine (**2 c**)

From salicylic acid (3.86 g, 0.021 mol) and **6 b** (2 g, 0.0083 mol). Reaction time: 12 h. The crude product was an oil which crystallized from ethyleneglycol at low temperature to give white crystals (2.86 g, 65% yield), m.p. 109–110 °C; IR: 3 215, 1 695, 1 660, 1 610, 1 480, 1 330 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 3.35 (s, 6 H), 3.95 (s, 4 H), 5.3 (s, 4 H), and 6.1–8.2 (m, 8 H) ppm.

N,N'-Dimethyl-N,N'-Di(m-acetamidophenoxy)acetylethylenediamine (**2 d**)

From *m*-acetamidophenol (2.63 g, 0.017 mol) and **6 b** (2 g, 0.0083 mol). Reaction time: 4 h. The product was a viscous oil which formed a powder by agitation. White crystals from ethyleneglycol (2.96 g, 76% yield), m.p. 198–200 °C; IR: 3 300, 3 280, 1 650, 1 600, 1 475, 1 300 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.5 (s, 6 H), 3.35 (s, 6 H), 3.5–4.1 (m, 4 H), 4.95 (s, 4 H), 6.9–7.5 (m, 8 H), 9.4 (s, 2 H) ppm.

N,N'-Di(o-nitrophenoxy)acetylpiperazine (**3a**)

From *o*-nitrophenol (2.46 g, 0.018 mol) and **6c** (2 g, 0.0084 mol). Reaction time: 12 h. Yellow crystals from acetic acid (2.56 g, 69% yield), m.p. 244–245 °C; IR: 1650, 1600, 1520, 1440, 1350, 1220 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 3.6 (s, 8 H), 5.2 (s, 4 H), 7.1–8.0 (m, 8 H) ppm.

N,N'-Di(o-acetamidophenoxy)acetylpiperazine (**3b**)

From *o*-acetamidophenol (1.46 g, 0.0097 mol) and **6c** (1.1 g, 0.0046 mol). Reaction time: 2 h. Recrystallized from diglyme (1.61 g, 75% yield), m.p. 219–220 °C; IR: 3260, 3200, 3120, 1690, 1600, 1480, 1260 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.62 (s, 6 H), 4.0 (s, 8 H), 5.2 (s, 4 H), 7.0–7.9 (m, 8 H), and 9.8 (s, 2 H) ppm.

N,N'-Di[o-(Hydroxycarbonyl)phenoxy]acetylpiperazine (**3c**)

From salicylic acid (2.43 g, 0.019 mol) and **6c** (2 g, 0.0084 mol). Reaction time: 16 h. White crystals from ethyleneglycol (2.85 g, 76% yield), m.p. 215–217 °C; IR: 3220, 1690, 1660, 1608, 1420, 1370 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 4.0 (s, 8 H), 5.3 (s, 4 H), 6.98–8.12 (m, 8 H) ppm.

N,N'-Di(m-acetamidophenoxy)acetylpiperazine (**3d**)

From *m*-acetamidophenol (2.78 g, 0.018 mol) and **6c** (2 g, 0.0084 mol). Reaction time: 2 h. White crystals from ethyleneglycol (3.66 g, 93% yield), m.p. 120–122 °C; IR: 3270, 3220, 3150, 1650, 1660, 1440, 1275 cm^{-1}; ^{1}H-NMR (CF_3COOH): δ 2.55 (s, 6 H), 3.95 (s, 8 H), 5.40 (s, 4 H), and 6.90–7.60 (m, 8 H) ppm.

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