A first approach to 2,2’-bipyridine thiacrown ethers containing bisamide groups

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Dedicated to the 80th birthday of Professor Henk C. van der Plas

Abstract
Synthesis of thiamacrocyclic bisamides incorporating bipyridine subunit tethered to poly(ethylene glycol) chains has been achieved using sequential S-transalkylation–amidification of 2,2’-bipyridine alkyl sulfides.

Keywords: Bisamides, macrocyclization reaction, [4+2] cycloaddition, S-transalkylation

Introduction

Macrocyclic ligands containing amide functional groups play an important role in coordination- and supramolecular chemistry. The amide functionality exhibits a dual complexating feature (C=O and N or NH), thus meaning that amide-based molecular receptors can bind metal, neutral molecules and organic cations and anions as well. Some of them are used as biologically interacting substrates and their optically active forms are applied to chiral recognition processes. There are a number of macrocycles which in addition to amide functional groups contain other elements and/or heteroaromatic rings. For example, a 14-membered ligand containing two amide and two sulfur donor groups was shown to be selective for Pd(II) and Pt(II) over Co(II), Ni(II) and Cu(II) metals. Incorporating a pyridine ring into the macrocyclic skeleton leads to a more rigid macro-ring and may alter the strength and selectivity of ligand interaction with a cation. Thus an 18-membered pyridine-diamide-diester receptor possessing 2x pyN, and 2x amide NCH₃, transports and extracts silver picrate with remarkably high selectivity over alkali, alkaline earth and Pb²⁺ picrate. The study of similar interactions between 2,2’-bipyridine-based macrocycles containing amide functionality and inorganic or organic cations remains an unexplored area, due to the lack of efficient methods for their synthesis.

We have recently developed a simple route to azathiamacrocycles incorporating the 2,2’-bipyridine subunit. On the basis of this prior experience we have elaborated a synthetic pathway
leading to 2,2’-bipyridine thiacrown ethers 2a,b and 3a,b (Figure 1) containing bisamide functional groups, using as the key steps: (1) S-transalkylation of 6,6’-bis(methylsulfanyl)-2,2’-bipyridines 4a or 1,1’-bis(methylsulfanyl)-6,6’,7,7’-tetrahydro-5H,5H’-3,3’-bicyclopenta[c]pyridine 4b with ethyl bromoacetate and (2) amidification of the resulting 6,6’-bis(ethoxycarbonyl)-methylsulfanyl-2,2’-bipyridines 5a or 1,1’-bis(ethoxycarbonyl)-methylsulfanyl-6,6’,7,7’-tetrahydro-5H,5H’-3,3’-bicyclopenta[c]pyridine 5b with the corresponding diamines 7 and 8 (Scheme 1). The reaction sequence presented in Scheme 1 has not been examined before.

Figure 1. Bipyridines 1a, b and bipyridine macrocycles 2a,b and 3a,b (a denotes monocyclic-, and b annulated- 2,2’-bipyridine derivatives).

Results and Discussion

The synthetic pathway leading to macrocycles 2a,b and 3a,b starts with 2,2’-bipyridine methyl sulfides 4a and 4b readily prepared using literature procedures, namely Diels-Alder/retro- Diels-Alder reaction of easily accessible 3,3’-bis(methylsulfanyl)-5,5’-bi-1,2,4-triazine with norbornadiene\(^8\) or 1-pyrrolidino-1-cyclopentene,\(^9\) respectively. Reactions of 4a and 4b with ethyl bromoacetate under non-basic conditions, without solvent, gave S-transalkylated products 5a and 5b in excellent yield.\(^7\) When the reactions were followed by TLC, it was evident in both cases that intermediates were formed which were slowly converted into 5a,b. With aromatic diesters 5a and 5b in hand, we next evaluated their double-amidification reactions with poly(ethylene glycol)diamines 7 and 8 to the corresponding cyclic bisamides 2a,b and 3a,b. To establish optimal conditions for the amidification process, reactions of compounds 5a and 5b with n-butylamine 6 were first investigated. Treatment of monocyclic diester 5a with n-butylamine in methanol in the presence of ammonium chloride afforded the desired bisamide 1a almost quantitatively. Likewise, amidification of 5b with n-butylamine gave compound 1b in good yield.
within 12 hours. The conversion of 2,2’-bipyridine diesters 5a,b into amides 1a,b proceeded gradually via monoamide intermediates, which was noticeable by TLC.

**Scheme 1**

The macrocyclization reaction of 5a with diamine 7 was carried out in methanol as solvent under various reaction conditions. In the first case, the reaction was performed under high-dilution conditions to avoid unwanted intermolecular side products. After 14 hours’ stirring at reflux, the diester 5a was only partly consumed and the product 2a was isolated in traces. The cyclization protocol was then investigated using 2 mol. equivalents of sodium methoxide in methanol under the same conditions. The presence of sodium ions was expected to give the optimal template effect on the cyclization process. However, compound 2a was again formed in low yield, which suggests that the template effect of an alkali metal may not be effective in this system. The same procedure was applied for the preparation of compound 3a from 5a and 8. As expected, a similar order of reactivity was observed on treatment of the annulated diester 5b with diamines 7 and 8 under high dilution conditions, giving compounds 2b and 3b in low yields (Scheme 1). The use of sodium methoxide gives better results, and this method for the preparation of compounds 3a,b is recommended. Finally, compound 2b was obtained in 43% yield by heating 5b with diamine 7 at 90°C for 10 hours under solvent free conditions.

Evidence for the structures of compounds 1a,b, 2a,b, and 3a,b was obtained from 1H- and 13C- NMR, HRMS and elemental analysis. Energy minimization calculations on compounds 2 and 3 were determined using the AM1 semiempirical method implemented in the program package HyperChem. The AM1 method was used previously for other molecules containing a 2,2’-bipyridine unit, giving satisfactory results compatible with experimental data.
Figure 2. Heats of formation of thiacrown ethers 2a: -83.22 kcal/mol and 2b: -103.84 kcal/mol.

Calculations of the heats of formation were performed for macrocycles 2a, 2b, 3a, 3b and were found to be: -83.22, -103.84, -136.23 and -162.65 kcal/mol, respectively. According to general rules\textsuperscript{14} the lowest heat of formation indicates that the last compound can easily form complexes with small molecules. The presence of additional methylene groups increases the cavity sizes in macrocycles 3a and 3b. Thus, with regard to size and heat of formation the cavity of macrocycle 3b is the most promising for the complexation process. The twisted structure of 2b (-81.74\textdegree) (Figure 2) is more wrinkled than the macrocycle 2a (-46.25\textdegree) (Figure 2). The same dependence is observed for compounds 3a (+32.16\textdegree) and 3b (-64.59\textdegree) (Figure 3). The reason for the more twisted structures 2b and 3b compared to 2a and 3a is probably the presence of annulated cyclopentene rings.

Figure 3. Heats of formation of thiacrown ethers 3a: -136.23 kcal/mol and 3b: -162.65 kcal/mol.
Conclusions

In conclusion, we have demonstrated the first successful approach to 2,2'-bipyridine thiacrown ethers containing bisamide functional groups. Applications of these systems as chelating ligands are in progress.

Experimental Section

General Procedures. Reactions were monitored by TLC using precoated silica gel or alumina plates containing a fluorescent indicator. Detection was by UV (254 nm). Melting points were determined with a hot-stage microscope and are uncorrected. Column chromatography was performed on silica gel (Merck 60, 70-230 mesh). 1H- NMR spectra were measured on a Varian Gemini (200 MHz) spectrometer using tetramethylsilane as internal standard. Mass-spectra were measured on an AMD 604 spectrometer. The IR spectra were recorded on a Nicolet Impact 400 D spectrometer.

Synthesis of the bisamide N-butyl-6,6'-carbamoylmethylsulfanyl-2,2'-bipyridine (1a). A stirred solution of 5a (392 mg, 1.0 mmol) in n-butylamine (2.5 ml) with catalytic amounts of NH₄Cl was heated under reflux for 10 h. After this time the reaction mixture was cooled and the precipitate 1a was filtered off, and the crude product was crystallized from methanol, to provide 423 mg of 1a (95%). mp 207-217 °C; 1H NMR (CDCl₃) δ: 0.67 (t, 3H, J = 7.5 Hz), 1.1-1.12 (m, 2H), 1.2-1.4 (m, 2H), 3.15 (q, 2H, J = 6.5 Hz), 3.9 (s, 2H), 7.3 (dd, 1H, J=0.8, J = 7.7 Hz); 7.7 (t, 1H, J = 7.7 Hz), 8.2 (dd, 1H, J = 0.8, J = 7.7 Hz). IR (KBr) cm⁻¹: 3298, 1650. Anal. Calcd for C₂₂H₃₀N₄S₂O₂: C, 59.16; H, 6.77; N, 12.54. Found C, 59.29; H, 6.81; N, 12.42%.

Synthesis of the bisamide N-butyl-1,1'-carbamoylmethylsulfanyl-6,6',7,7'-tetrahydro-5H, 5H'-3,3'-bicyclopenta[c]pyridine (1b). A stirred solution of 5b (100 mg, 0.2 mmol) in butylamine (2 ml) with catalytic amounts of NH₄Cl was heated under reflux for 23 h. After this time the reaction mixture was cooled and the precipitate 1b was filtered off and the crude product was crystallized from methanol, to provide 1b (61 mg, 55%, of mp 250 °C; 1H NMR (CDCl₃) δ: 0.7 (t, 3H, J = 7.0 Hz), 1.0-1.15 (m, 2H), 1.16-1.30 (m, 2H), 2.20 (quint., 2H, J = 7.5 Hz), 2.87 (t, 2H, J = 7.4 Hz), 3.0 (t, 2H, J = 7.4 Hz); 3.16 (q, 2H, J = 6.2 Hz), 3.9 (s, 2H), 8.02 (s, 1H). IR (KBr) cm⁻¹: 3298, 1655. Anal. Calcd for C₂₈H₃₈N₄S₂O₂: C, 63.84; H, 7.27; N, 10.64. Found: C, 63.80; H, 7.23; N, 10.55%.

13,16-dioxa-7,22-dithia-10,19,27,28-tetraaza-tricyclo[21.3.1.12,6]octacosa-1(27),2(28),35,23,25-hexane-9,20-dione (2a). A stirred solution of 5a (250 mg, 0.64 mmol) and 2,2’-(ethylenedioxy)-bis(ethylamine) 7 (0.09 g, 0.64 mmol) in anhydrous methanol (50 ml) and 0.11 g sodium was heated under reflux for 14 h. The reaction mixture was then cooled and the precipitate 2a was filtered off, and the crude product purified by column chromatography using CH₂Cl₂–acetone (1:1), to provide 2a (52 mg, 19%). Mp 206 °C; 1H NMR (CDCl₃) δ 3.45 (t, 2H,
J = 6.2 Hz), 3.75 (t, 2H, J = 6.2 Hz), 4.10 (t, 2H, J = 7.2 Hz), 5.95 (s, 2H), 7.45 (dd, 1H, J = 0.8, 7.8 Hz), 7.6 (t, 1H, J = 7.6 Hz), 7.8 (d, 1H, J = 0.9, 7.8 Hz). IR (KBr) cm⁻¹: 3327, 1650, 1135. Calcd for C₂₀H₂₄N₄S₂O₄: C, 53.55; H, 5.39, N, 12.49. Found C, 53.64; H, 5.41, N, 12.75%.

16,19-Dioxo-10,25-dithia-13,22,27,28-tetraaza-pentacyclo-[21,6,1,0⁴,₈,₂₆,³¹]-tetraatriaconta-1(33),2(34),3 8,2₆,3₁-hexaene-12,2₃-dione (2b). A stirred solution of 5b (84 mg, 0.18 mmol) in 2,2’-(ethylenedioxy)-bis-(ethylamine) 7 (0.03 g, 0.2 mmol) without any additives was heated at 90°C for 10 h. The reaction mixture was then cooled and the precipitate 2b was filtered off and the crude product crystallized from dichloromethane, to provide 2b (40 mg, 43%). mp 176 °C; ¹H NMR (CF₃COOD) δ: 0.67 (brs, 2H), 2.85 (brs, 2H), 3.10 (brs, 2H), 3.45 (brs, 4H), 3.75 (brs, 2H), 4.15 (s, 2H), 8.10 (s, 1H). ¹³C NMR (CDCl₃) δ: 25.17, 30.91, 33.99, 40.76, 67.46, 70.21, 70.78, 115.82, 139.14, 152.25, 154.35, 157.23, 172.26. IR (KBr) cm⁻¹: 3298, 1650, 1113. HRMS Calcd. for C₂₆H₃₂N₄S₂O₄: 528.1877. Found: 528.1865 [M⁺]. Anal. Calcd for C₂₆H₃₂N₄S₂O₄: C, 59.09; H, 6.06; N, 10.61. Found C, 59.25; H, 5.74; N, 10.03%.

16,19-Dioxo-10,25-dithia-13,22,27,28-tetraaza-pentacyclo-[21,6,1,0⁴,₈,₂₆,³¹]-tetraatriaconta-1(33),2(34),3 8,2₆,3₁-hexaene-12,2₃-dione (2b).

References


