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Crown-annelated *p*-phenylenediamine derivatives as electrochemical and fluorescence responsive chemosensors: synthesis via arene–ruthenium chemistry

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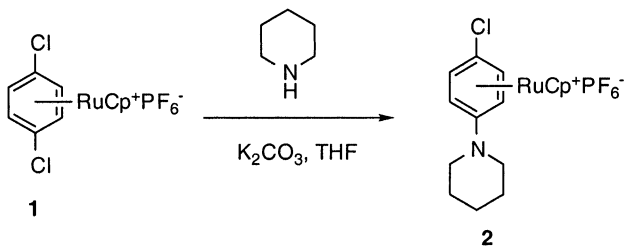
Abstract—The synthesis of two crown annelated tetraalkyl-*p*-phenylenediamine derivatives, via sequential S_NAr reactions on (*p*-dichlorobenzene)RuCp cationic complexes, is described.

1. Introduction

A chemosensor[1] is an abiotic molecule that changes its output signal as a result of its interaction with foreign matter or energy. Such a molecule is composed of a transducer covalently bound to a receptor. Upon interaction with an analyte attached to the receptor, the electronic state of the chemosensor changes, and can be monitored and measured by spectroscopic (e.g. fluorescence and UV–vis absorption) or electrochemical (i.e. voltammetry) techniques. The essentially important features for a practically useful chemosensor are high sensitivity and selectivity. A redox-active[2] or fluorophore[3] molecule can be chosen as the transducer depending on the measurement method chosen. A real challenge for a highly responsive chemosensor is how to selectively (or specifically) and reversibly target the analytes. Nature has given scientists a lesson for molecular recognition in biological systems, such as enzymes and their substrates or antibodies and their antigens. Contemporary research on chemosensors has mostly focused on the use of crown ethers as selective receptors for metal cations—complexation with the cation induces a change in redox potential of the transducer or a change in its fluorescence properties. We have recently described efficient syntheses of a variety of functionalized tetraalkyl-*p*-phenylenediamines, and have shown that these molecules have interesting and potentially useful fluorescence and electrochemical properties.[4] In this and the accompanying papers, we describe the synthesis and some of the properties of two crown-annelated *p*-phenylenediamine derivatives that appear to be of potential value as selective chemosensors for metal cations. Of particular note is the fact that these systems show a dual response capability, as they are both redox active and fluorophores, and these properties are modified upon complexation between the crown ether and metal cations.

2. Synthesis

Complex **2** was prepared in 96% yield from (*p*-dichlorobenzene)$RuCp^+$ complex **1** by S_NAr reaction with piperidine under previously described conditions.[4c] By reaction of complex **2** with aza-crown ethers of different ring sizes, we anticipated that a series of crown-annelated *p*-phenylenediamine–ruthenium complexes could be prepared efficiently from a common precursor, in this case **2**.



1 **2**

Unfortunately, the S_NAr reaction of complex **2** with 1-aza-18-crown-6 or 1-aza-15-crown-5 in THF, in the presence of K_2CO_3 as base, proceeded very slowly and with formation of significant amounts of side products. Similar results were observed by using other bases, e.g. Na_2CO_3 and Cs_2CO_3, or increasing the reaction temper-

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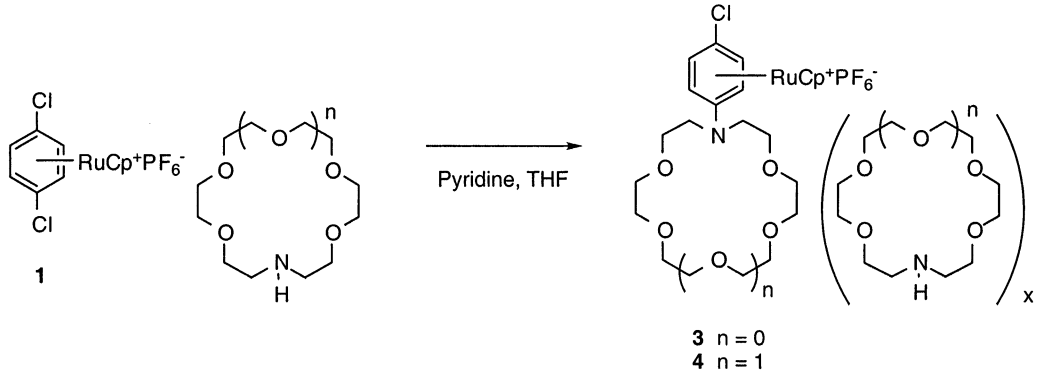
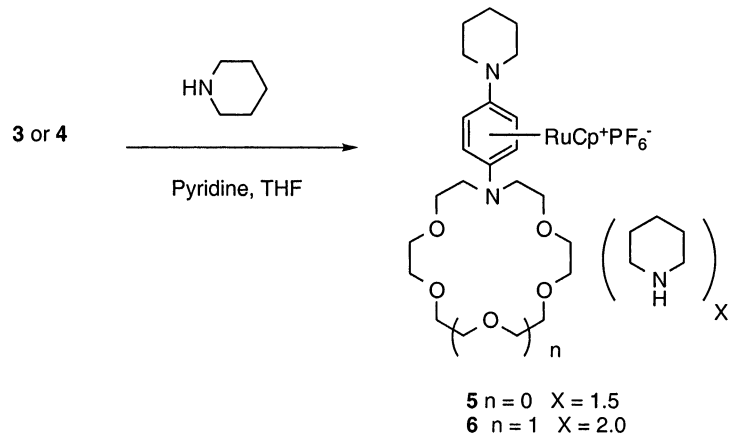
ature to reflux. The product of decomplexation of **2**, together with a significant amount of unreacted starting material, were observed from the ^{1}H NMR spectrum when pyridine was used as base in THF at reflux temperature. This decomplexation is not surprising under these conditions, where the arene ligand is likely to be displaced by pyridine as a donor ligand.[5]

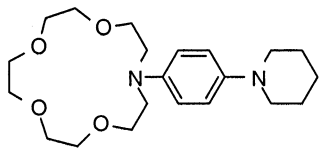
Following these unsuccessful attempts, the sequence of S_NAr reactions was simply reversed by using the aza-crown ether as the first nucleophile. In addition, pyridine was used as base (at room temperature or below to avoid loss of the RuCp moiety) instead of solid bases, e.g. Na_2CO_3, K_2CO_3, and Cs_2CO_3, in order to avoid any complexation effect between metal cations and aza-crown ethers, which might lead to complication of the reactions. According to our earlier studies,[4c] the amount of the first nucleophile can be decreased with the use of excess base to offset any expense or difficult access to the amine nucleophiles.



The S_NAr reaction of (*p*-dichlorobenzene)$RuCp^+$ complex **1** with 1-aza-18-crown-6 (1.2 equiv.) and pyridine (5 equiv.) in THF (0.1 M reaction concentration) proceeded very slowly at room temperature, requiring more than 15 days for completion. No double S_NAr product was detected from the ^{1}H NMR spectrum, indicating that the aza-crown ether is a relatively unre active nucleophile. The first S_NAr reaction was completed in 5 days without any double S_NAr product formation by using 3.3 equiv. of aza-crown ether and 8 equiv. of pyridine in THF. Unreacted crown ether and excess pyridine can usually be removed by washing the product with ether, in which the ruthenium complexes are insoluble. However, in the present case we could only recover about 1.3 equiv. of unreacted aza-crown ether initially. Efforts to recover all unreacted (2.3 equiv.) aza-crown ether without losing considerable amounts of product were unsuccessful. Integrated intensities in the ^{1}H NMR spectrum of the product indicated that approximately 1 equiv. of aza-crown ether still remained, but the spectrum did not reveal the peaks of protons α to the nitrogen in the free aza-crown ethers, which display a triplet at 2.75 ppm. We speculate that there are hydrogen bonding interactions between unreacted aza-crown ethers and complex **4**, resulting in formation of a 1:1 complex, which induces a downfield shift of the α protons. Analogous observations were made for **3**.

Without any further purification, the second S_NAr reaction was carried out with piperidine to examine whether the bound aza-crown adversely affects the reaction. Following this second S_NAr reaction with piperidine (10 equiv.) and pyridine (5 equiv.) as base, TAPD-crown complexes **5** and **6** were obtained. Surprisingly, about 1 equiv. of aza-crown ether, which could not be recovered in the previous step, was collected during the purification. This observation supports the aforementioned assignment of a 1:1 complex for each product **3** and **4**. However, some extra peaks appear in the ^{1}H and ^{13}C NMR spectra of TAPD-crown complexes **5** and **6**, and 2D COSY experiments indicate that these belong to residual piperidine, which is coordinated to TAPD-crown complexes **5** and **6** and is difficult to remove. Based on ^{1}H NMR integration about 1.5 equiv. of piperidine remain coordinated to **5** and 2 equiv. to **6**. We therefore decided to investigate the effect of carrying excess free aza-crown ether through to the second





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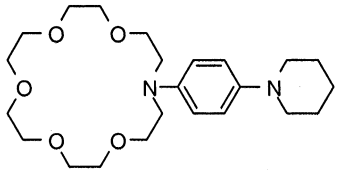

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S_NAr reaction. Using **3** as an example, the reaction with piperidine was performed immediately after the completion of the first S_NAr reaction. Interestingly, the expected amount (about 2.3 equiv.) of 1-aza-15-crown-5 was recovered by ether washing after S_NAr reaction of unpurified **3** with piperidine. Even with an excess of aza-crown ether present, the second S_NAr reaction, i.e. with piperidine, proceeds smoothly without any problems.

Decomplexation of TAPD-crown complexes **5** and **6** in CH_3CN-TMEDA under UV light[4] afforded crown-annelated TAPDs **7** and **8**. Fortunately, no coordinated piperidine remained after chromatographic purification of these materials. Because of the difficulty in calculating accurate yields from each of the two S_NAr reactions, as a result of the binding effects noted above, the isolated yields for **7** and **8** were determined over three steps from the (*p*-dichlorobenzene)$RuCp^+$ complex, and were 37 and 26%, respectively.[6] As far as we are aware, these are the first crown-annelated *p*-phenylenediamines to be reported.

3. Conclusions

Crown annelated *p*-phenylenediamine derivatives have been prepared by sequential displacement of chloride from the *p*-dichlorobenzene–RuCp cation. While aza-crown ethers are not strong enough nucleophiles to effect S_NAr reaction on 4-piperidinochlorobenzene–RuCp, a reverse sequence, which uses piperidine as the nucleophile on crown-substituted chlorobenzene–RuCp, works well.

Acknowledgements

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6. The ruthenium complexes **3–6** were isolated by evaporation of the reaction solvent (THF) and purified by repeated washing with diethyl ether, in which the complexes are insoluble. The TAPDs **7** and **8** were purified by preparative TLC (Merck Al_2O_3 plate, $CHCl_3$ elution). Spectroscopic characterization data: **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.53 (s, 4H), 5.10 (s, 5H), 3.69 (t, $J=5.5$ Hz, 4H), 3.58 (m, 8H), 3.53 (br s, 4H), 3.41 (t, $J=5.5$ Hz, 4H), 3.09 (t, $J=5.6$ Hz, 6H, H from coordinated piperidine), 2.82 (t, $J=5.6$ Hz, 4H), 1.88 (m, 6H, 2H from coordinated piperidine), 1.40–1.60 (br, 8H, 6H from coordinated piperidine); ^{13}C NMR (50 MHz, $CDCl_3$) δ 123.4, 121.7, 77.8, 70.5, 70.4, 69.3, 67.4, 67.2, 64.6, 53.3, 48.7, 44.6, 24.7, 23.4, 22.4, 22.3; FAB HRMS calcd for M–PF_6^--(piperidine) ($C_{26}H_{39}N_2O_4Ru$) 545.1960. Found 545.1950. **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.42 (s, 4H), 4.97 (s, 5H), 3.20–3.65 (24H), 2.94 (br s, 8H, H from coordinated piperidine), 2.71 (br s, 4H), 1.71 (br s, 8H, 4H from coordinated piperidine), 1.30–1.55 (br, 10H, 8H from coordinated piperidine); ^{13}C NMR (50 MHz, $CDCl_3$) δ 123.5, 121.5, 77.5, 70.5, 70.3, 67.6, 67.3, 65.0, 51.4, 48.6, 44.5, 24.6, 23.3, 22.3, 22.2; FAB HRMS calcd for M–PF_6^--2(piperidine) ($C_{28}H_{43}N_2O_5Ru$) 589.2234. Found 589.2231. **7**: ^{1}H NMR (200 MHz, C_6D_6) δ 6.98 (d, $J=9.1$ Hz, 2H), 6.73 (d, $J=9.1$ Hz, 2H), 3.70 (t, $J=5.8$ Hz, 4H), 3.53 (t, $J=5.8$ Hz, 4H), 3.42 (br, 8H), 3.33 (br, 4H), 2.96 (t, $J=5.3$ Hz, 4H), 1.61 (quint. $J=5.6$ Hz, 4H), 1.35 (m, 2H); ^{13}C NMR (50 MHz, C_6D_6) δ 144.6, 143.0, 120.2, 113.3, 71.8, 70.6, 70.5, 69.6, 53.4, 53.4, 26.9, 24.8; EI HRMS calcd for M^+ ($C_{21}H_{34}N_2O_4$) 378.2518. Found 378.2509. **8**: ^{1}H NMR (200 MHz, C_6D_6) δ 6.98 (d, $J=9.0$ Hz, 2H), 6.76 (d, $J=9.0$ Hz, 2H), 3.51–3.65 (12H), 3.50 (br s, 6H), 3.46 (br s, 6H), 2.96 (t, $J=5.3$ Hz, 4H), 1.60 (quint. $J=5.6$ Hz, 4H), 1.36 (m, 2H); ^{13}C NMR (50 MHz, C_6D_6) δ 144.9, 143.3, 120.1, 114.0, 71.4, 71.3 (2C), 71.2, 69.7, 53.2, 52.6, 26.8, 24.8; EI HRMS calcd for M^+ ($C_{23}H_{38}N_2O_5$) 422.2781. Found 422.2780.