Palladium(II) Cage Compounds Based on Diphenylglycoluril

Frank G. M. Niele and Roeland J. M. Nolte

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Abstract: A four-armed tetra-l-imidazolyl ligand (Lig) equipped with the concave framework of diphenylglycoluril (tetra-hydro-3a,6a-diphenylimidazo[4,5-d]imidazole-2,5(1H,3H)-dione) has been designed to construct a host that contains a potentially catalytically active metal center in or close to a cavity. Reaction of Lig (arm = CH₂(OCH₂CH₂)₂Im) with Pd(CH₃CN)₂Cl₂ results in the formation of a complex with the general formula [Pd(Lig)]Cl₂. This complex has a cage structure that is unstable and collapses. The collapsed structure has either a left or a right twisted configuration. These conformations interconvert rapidly, the activation free energy of the process being 30 ± 2 kJ-mol⁻¹. Ligands without oxygen atoms or only one oxygen atom per arm react with Pd(CH₃CN)₂Cl₂ to afford cage complexes with the molecular formula [Pd(Lig)Cl]Cl. The cages of these complexes do not collapse. The imidazolyl groups and the chloride ions are involved in a scrambling process in such a way that at any moment the Pd(II) ion is surrounded by three imidazolyl groups and one chloride ion. Data are presented suggesting that intramolecular H bonding is a driving force for cage collapse.

When catalytic systems are designed, it is particularly intriguing to mimic nature. In this respect, we are interested in synthesizing systems to imitate the behavior of metalloenzymes, which are involved in substrate activation processes. Simplification of the very special three-dimensional structure of a metalloenzyme shows a cavity-containing molecule with binding sites (B) and one or more metal centers (M) in or close to the cavity. The metalloenzyme acts as a metallohost, and because of the special structure of the cavity, it is quite selective in binding a substrate (S); see Figure 1.

In 1970 Breslow and Overman were the first to report a man-made system based on this MSB concept. They combined a naturally occurring α-cyclodextrine with a nickel(II) ion and obtained a metallohost that shows metalloenzyme features. Tabushi's team reported a carbonic anhydrase model in which they also used this cyclodextrine as a host molecule. At this moment examples of fully synthetic metallohosts are scarce.

Study of metallohosts shows that the organic part is a polydentate macroligand that must be able to furnish substrate-binding sites and the framework for a cavity. In this paper we report the design and synthesis of a new family of ligands having these properties. Several Pd(II) cage compounds based on the new macroligands have been prepared, and features of their solution dynamic behavior are described.

Results and Discussion

Strategy. Cram realized that in the design of cavity-containing molecules it is preferable to start from a concave building block. Our design for a ligand, which has to supply the framework for a cavity-containing molecule, starts from such a block, viz. glycoluril (tetra-hydro-3a,6a-diphenylimidazo[4,5-d]imidazole-2,5(1H,3H)-dione (1a); Chart 1) that has its convex side sterically shielded by two phenyl groups (1c). To the ureylene nitrogen atoms can then be attached four chains as spacer units (A), which are furnished with potential substrate-binding sites and terminated with metal-binding groups (L). In this way what may be called a heterotopic tetrapodal ligand or simply a tetrapodand is formed.

Coordination of the four ligating groups to a metal center M results in the creation of a metalloaggregate (Figure 2). Thus, in this design the metal center has a dual function. First, it acts as a template facilitating the formation of the desired cavity. Second, it is a potentially reactive site, e.g. a catalytic center.

We have chosen ethylene glycol ether chains, which are known to possess binding properties, as spacer units and imidazolyl groups, which are excellent ligands to a variety of metal ions, as the metal-binding groups. For comparative purposes, tetrapodands containing either 2-oxaalkyl chains or n-hexyl chains as spacer units have also been prepared.

Scheme I

<table>
<thead>
<tr>
<th>Route A:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph₂-GU-H₄</td>
<td>X-A-X</td>
<td>Ph₂-GU-(A-X)₄</td>
</tr>
<tr>
<td>1c</td>
<td></td>
<td>5c, 6a</td>
</tr>
<tr>
<td></td>
<td>X = Cl, Br</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route B:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph₂-GU-H₄</td>
<td></td>
<td>Ph₂-GU-(CH₂OH)₄</td>
</tr>
<tr>
<td>1c</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H⁺</td>
</tr>
<tr>
<td>Ph₂-GU-(CH₂OH)₂</td>
<td></td>
<td>Ph₂-GU-(A-X)₄</td>
</tr>
<tr>
<td>3b</td>
<td>p-TsOH</td>
<td>4a, 4c, 5a</td>
</tr>
<tr>
<td></td>
<td>X = Cl, Br</td>
<td></td>
</tr>
</tbody>
</table>

Scheme II

|          |          |
| Ph₂-GU-(A-X)₄ | Ph₂-GU-(A-Im)₄ |
| X = Cl, Br   | NaNH       |

Synthesis of Tetrapodands. The general synthesis of the tetrapodands begins with the coupling to diphenylglycoluril of four spacer units, each of which is suitably terminated with a halogenide.

Palladium(II) Cage Compounds

Figure 1. MSB concept.

Figure 2. Strategy for preparing a metallocage from diphenylglycoluril.

Chart I

1a, \( R' = H, R'' = H \)
1b, \( R' = H, R'' = CH_3 \)
1c, \( R' = H, R'' = Ph \)
2, \( R'' = CH_2OH, R'' = Ph \)

Short-hand notation:
\((R')_2GU-(R'')_4\)

Figure 3. Crystal structure of compound 4a.

Figure 4. Results of gel permeation chromatography.

Table I. Molar Conductivities of Palladium Complexes

<table>
<thead>
<tr>
<th>compd</th>
<th>( \Lambda_m ) cm² mol⁻¹⁻¹</th>
<th>compd</th>
<th>( \Lambda_m ) cm² mol⁻¹⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{[Pd(4d)]Cl}_2 )</td>
<td>170</td>
<td>( \text{[Pd(6b)]Cl}_2 )</td>
<td>94</td>
</tr>
<tr>
<td>( \text{[Pd(5b)]Cl}_2 )</td>
<td>106</td>
<td>( \text{TEBA}^a )</td>
<td>101</td>
</tr>
<tr>
<td>( \text{[Pd(5d)]Cl}_2 )</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \text{In methanol at 25 °C.} \quad ^b \text{TEBA = triethylbenzylammonium chloride.} \)

as a leaving group for the following synthetic step. Two routes have been used for the spacer coupling (see Scheme I). Route A is the straight-on alkylation of the ureylene nitrogen atoms with a \( \omega \)-dihalogenide to produce the tetrahalogenides 5c and 6a. Route B is a three-step synthesis that starts from 1c with the formation of the unstable tetrol compound 2. In the second step 2 is treated with acid to generate the more stable tetracyclic ether 3. In the final step the strong acid-induced transetherification of 3 with an \( \omega \)-halogeno alcohol under very stringent water-removal conditions affords the tetrahalogenides 4a, 4c, and 5a (see the Experimental Part). In the final stage the resulting tetrahalogenides from these two routes are then reacted with sodium imidazolate to afford the tetrapodands 4b and 4d (containing ethylene glycol spacers), 5b and 5d (containing 2-oxaalkyl spacers), and 6b (containing \( n \)-hexyl spacers); see Scheme II.

During these investigations X-ray structural characterization of a tetracyclic ether (3a) and of a tetrahalogenide (4a) has been carried out.\(^{10}\) The crystal structure of 3a shows a compound with two cis-tied imidazolidon rings and two six-membered ether rings. The latter rings are in the chair conformation. The structure determination of the short-armed tetrabromide 4a not only confirms the primary structure of the compound but also shows the steric shielding by the two phenyl groups on the convex side of the glycoluril unit (see Figure 3).

Palladium Complexes. Reaction of tetrapodand 4d (containing the ethylene glycol spacers) with Pd(\( \text{CH}_2\text{CN} \)) \(_2\) Cl \(_2\) in methanol as a solvent yields a product which, according to elemental analysis, has the molecular formula \( \text{Pd(4d)Cl}_2 \). In the FAB mass spectrum the ion \( \text{[Pd(4d)]}^+ \) was detected with an isotope pattern that perfectly matches the one simulated for \( \text{C}_{48}\text{H}_{62}\text{N}_2\text{O}_6\text{Pd} \).

To check that no oligomeric or polymeric networks had been formed, we determined the molecular weight of this new product. The ebulliometric value (in methanol MW 1125 ± 75; cale 1143)

is in agreement with a monomeric palladium-tetrapodal system. In addition, gel permeation chromatography was applied to obtain information on relative molecular sizes. The results (Figure 4) show clearly that Pd(4d)Cl₂ has a molecular size of the same order of magnitude as that of the free tetrapodal 4d. This supports the molecular weight determination, and it is therefore concluded that the complex Pd(4d)Cl₂ is monomeric in solution.

The following step was to identify the ligands comprising the coordination sphere within the Pd(4d)Cl₂ complex. The molar conductivity of this complex determined in methanol solution (Table I) is in the range expected for 2:1 electrolytes¹¹ and suggests that the Cl⁻ anions are not bonded to the palladium center, i.e. [Pd(4d)]Cl₂. Furthermore, the ¹H NMR data for this compound (methanol-d₄, 200 MHz) point to all four imidazolyl groups being coordinated to the palladium; compared to the free tetrapodal 4d. This supports the molecular weight determination, and it is therefore concluded that the complex Pd(4d)Cl₂ is monomeric in solution. The following step was to identify the ligands comprising the coordination sphere within the Pd(4d)Cl₂ complex. The molar conductivity of this complex determined in methanol solution (Table I) is in the range expected for 2:1 electrolytes¹¹ and suggests that the Cl⁻ anions are not bonded to the palladium center, i.e. [Pd(4d)]Cl₂. Furthermore, the ¹H NMR data for this compound (methanol-d₄, 200 MHz) point to all four imidazolyl groups being coordinated to the palladium; compared to the free tetrapodal 4d. This supports the molecular weight determination, and it is therefore concluded that the complex Pd(4d)Cl₂ is monomeric in solution.

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### Table II. NOEDS Results for [Pd(4d)]Cl₂

<table>
<thead>
<tr>
<th>irradiated proton</th>
<th>[Pd(4d)]Cl₂</th>
<th>4d</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(E)</td>
<td>A (3.5)</td>
<td>C (2.9)</td>
</tr>
<tr>
<td>E(D)</td>
<td>A (2.6)</td>
<td>C (2.9)</td>
</tr>
<tr>
<td>I(J)</td>
<td>C (1.0)</td>
<td>K (&lt;0.1)</td>
</tr>
<tr>
<td>A</td>
<td>B (12.5)</td>
<td>C (&lt;0.1)</td>
</tr>
<tr>
<td>B</td>
<td>A (7)</td>
<td>C (2.3)</td>
</tr>
<tr>
<td>C</td>
<td>B (2.7)</td>
<td>B (&lt;0.1)</td>
</tr>
</tbody>
</table>

In a second NOE experiment, the NCH₂Cl₂ methylene protons H¹ and H² were irradiated. The NOE difference spectrum shows a very remarkable NOE enhancement of the H¹ signal, which implies the presence of a spatial connection between H¹H² and H²H¹ (Figure 5b). A CPK model of [Pd(4d)]¹² shows that this spatial connection can arise from a collapse of the metallocage via a twisting motion along the z axis (see Figure 6a). The orientation of the CH¹H² methylene protons must be outward since their irradiation also induced NOE effects on their neighboring methylene protons H¹ and some (likely ortho) phenyl protons H⁵.

Finally, we examined the temperature dependence of the normal ¹H NMR 200-MHz spectrum of [Pd(4d)]Cl₂ in the region 7.5–9.0 ppm. In the range 32–60 °C, the spectrum does not alter noticeably, but lowering the temperature to −95 °C leads to a splitting of the H⁵ signals (Figure 5d). CPK models show that in the twisted compressed conformation two of the imidazolyl groups are situated close to the ureylene carbonyls (Figure 6b, site S), indicating the possibility of a significant anisotropy effect.
on the H\textsuperscript{2} chemical shift. The other two imidazolyl groups are in a different chemical environment (Figure 6b, site T). These variable-temperature \textsuperscript{1}H NMR experiments imply that at room temperature the two sets of imidazolyl protons are involved in a fast exchange process in which the metalloccage alternates between the left and right twisted conformations (Figure 6a). The free energy of activation of this conformational change is 30 \pm 2 kJ/mol.

A second phenomenon noted in the \textsuperscript{1}H NMR spectra on lowering the temperature was the downfield shift of the weighted average of the signals of the NCHN protons. This suggests that these protons are participating in a hydrogen bond;\textsuperscript{14} a CPK model of the twisted cage conformation does show that a NCHN hydrogen atom can approach both oxygen atoms of its own spacer unit (Figure 6c).

do discover what would happen when one or both oxygen atoms in the spacer units were omitted, the tetrapodands \textbf{5b}, \textbf{5d}, and \textbf{6b} were reacted with Pd(CH\textsubscript{3}CN)\textsubscript{2}Cl\textsubscript{2}. In all three cases, the elemental analysis of the product corresponded to the molecular formula Pd(tetrapodand)Cl\textsubscript{2}. The molar polarities of solutions of the three Pd(tetrapodand)Cl\textsubscript{2} compounds fall in the range for 1:1 electrolytes (Table I). This means that only one chloride anion is dissociated from the palladium center, whereas the other one is still bonded; i.e., the compounds are more accurately formulated as [Pd(tetrapodand)Cl\textsubscript{2}].

To check whether we dealt with monomeric or oligomeric aggregates, we performed gel permeation chromatography. From the results (Figure 4), we see that the three Pd complexes have sizes of the same order of magnitude as the largest tetrapodand \textbf{5d}. As another reference compound, we used the [Rh(4d)\textsubscript{2}]\textsuperscript{+} metallocage, details of which are published elsewhere.\textsuperscript{15} This compound cannot collapse in the way the [Pd(4d)]\textsuperscript{2+} complex does, because of the presence of a metal-bonded chloride ligand within the cage. Since the sizes of three [Pd(tetrapodand)Cl] systems are also found to be similar to that of this rhodium cage, it is clear that we are dealing with monomeric species.

The \textsuperscript{1}H NMR spectra of the palladium complexes of tetrapodands \textbf{5b}, \textbf{5d}, and \textbf{6b} (methanol-\textit{d}4, 80 MHz) showed very broad signals. Lowering the temperature to -70 °C (200 MHz) in the NMR spectra on lowering the temperature was the downfield shift of the weighted average of the signals of the NCHN protons. This suggests that these protons are participating in a hydrogen bond;\textsuperscript{14} a CPK model of the twisted cage conformation does show that a NCHN hydrogen atom can approach both oxygen atoms of its own spacer unit (Figure 6c).

![Figure 7. Fluxional behavior of the Pd(II) compounds derived from \textbf{5b}, \textbf{5d}, and \textbf{6b}.](image-url)

\textbf{Conclusion}

The above results concerning the palladium complexes clearly show the great importance of the spacer composition of the tetrapodand in determining the type of palladium-tetrapodand complex that is formed. In the case of [Pd(4d)]\textsuperscript{2+}, the metalloccage is unstable and collapses via a twisted motion, most likely as a consequence of intramolecular H bonding between the polar C(2)H bond of the imidazolyl groups and the CH\textsubscript{2}OH functions in the spacers. However, in the three [Pd(tetrapodand)Cl\textsubscript{2}]\textsuperscript{+} cage compounds, where there are fewer ether functions, metal coordination fluxionality is observed.

\textbf{Experimental Part}

\textbf{General Procedures.} \textsuperscript{1}H NMR spectra were recorded on Varian EM-360, Bruker AW-80, and Bruker WP-200 instruments. Chemical shifts (\delta) are reported downfield from internal (CH\textsubscript{3})\textsubscript{2}Si. Abbreviations used are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Infrared and UV-vis spectra were taken on Perkin-Elmer 283 and Perkin-Elmer 555 spectrophotometers, respectively. FAB mass spectra were recorded on a VG ZAB 2F spectrometer (matrix: glycerol, thiglycol). Conductivity measurements were carried out at 25.0 °C with a Philips PW 9501 conductivity meter. Molecular weights were determined with a modified Gelfiltration ebulometer. Elemental analyses were carried out by the Elemental Analytical Section of the Institute of Physical Chemistry, Faculty of Science, Charles University, Prague, Czechoslovakia. Melting points were determined on a Mettler FP5/FP51 photoelectric melting apparatus. Gel permeation chromatography was performed on a Sephadex LH-60 column (length 21.5 cm, diameter 1 cm) with methanol as eluent at a flow rate of 31 mL/h.

Unless otherwise indicated, commercial chemicals were used as received. DMSO, DMF, and THF were distilled over 3-A sieves prior to use. Diethyl ether and chloroform were distilled from benzophenone ketyl and CaCl\textsubscript{2}, respectively.

\textbf{Tetrhydroimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (1a).} This compound was synthesized as described in literature.\textsuperscript{16}

\textbf{Tetraphydro-3a,6a-dimethylimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (1b).} This compound was synthesized according to a literature procedure.\textsuperscript{17}

\textbf{Tetraphydro-3a,6a-diphenylimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (1c).} This compound was synthesized according to a literature procedure.\textsuperscript{18}

1.3.4.6-Tetraphydroimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (2). In a nitrogen atmosphere, compound 1c (1 g, 3.4 mmol) and paraformaldehyde (0.5 g, 16.7 mmol) were mixed in DMSO (5 mL). The mixture was adjusted to pH 9 with 1 M aqueous NaOH. The reaction mixture was stirred at ambient temperature for 16 h, filtered over a fritted glass filter, and then placed in a refrigerator for 20 h. The precipitate was filtered, washed with water and acetone, and dried under vacuum: yield 1.2 g (82%) of white crystals (m.p. 102 (Dec). Anal. Calcd for C\textsubscript{18}H\textsubscript{14}N\textsubscript{2}O: C, 66.6; H, 5.1; N, 13.5; Found: C, 66.5; H, 5.8; N, 13.0. mp > 300 °C dec.

1.3.4.6-Bis(2-exapropylene)tetraphydro-3a,6a-dimethylimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (3a). Compound 1b (1 g, 5.9 mmol) and formaldehyde (37 wt% solution in water; 2.2 g, 26.6 mmol) were mixed in DMSO (5 mL). The mixture was adjusted to pH 9 with 1 M aqueous HCl. The reaction mixture was stirred at ambient temperature for 16 h, filtered over a fritted glass filter, and then placed in a refrigerator for 20 h. The precipitate was filtered, washed with water and diethyl ether, and dried under vacuum: yield 1.4 g (82%) of white crystals with mp = 300 °C dec. FABMS (M + H)+ m/e 415; IR (KBr) 1728, 1700, 1595, 1285, 1126, 1027 (COC) cm\textsuperscript{-1}; 'H NMR (DMSO-d6) 2.70 (m, 10 H, ArH), 6.30 and 6.20 (2 \times J = 6 Hz, 4 H, OH), 5.05 and 4.50 (2 dd, J\textsubscript{1,2} = 12 Hz, 8 H, CH\textsubscript{2}).

1.3.4.6-Bis(2-exapropylene)tetraphydro-3a,6a-dimethylimidazol-4,5-d-jimidazole-2,5-(1H,3H)-dione (3b). In a nitrogen atmosphere, compound 1c (1 g, 3.4 mmol) and paraformaldehyde (0.5 g, 16.7 mmol) were mixed in DMSO (5 mL). The mixture was adjusted to pH 9 with 1 M aqueous NaOH. The reaction mixture was stirred at ambient temperature for 16 h. The pH was brought to 1 with concentrated HCl, and the mixture was concentrated to 100 °C for 2 h. The precipitate was filtered, washed with...
and 4.60 (AB q, 2 H, CH2Br). Anal. Calcd for C28H34Br4N4O6: C, 39.93; H, 4.07; Br, 24.81; N, 6.17; O, 12.56. Evaporation of the solution at 30 °C under vacuum afforded 38.7 g (92%) of white imidazo[4,5-i/]imidazole-2,5(1f/,3f/)-dione (4c).

In a nitrogen atmosphere the tetralogendiol (1 mmol) was mixed with a solution of sodium imidazolate (8 mmol) in 10 mL of DMF and the solution stirred at 80 °C for 16 h. The reaction mixture was treated with 0.2 mL of water and evaporated under water vapor pressure (65 °C). The residue was dissolved in 8 mL of CHCl3, washed (4X) with 8 mL of basic water (adjusted to pH 12 with Na2CO3) and with 8 mL of water (2X), dried (MgSO4), and evaporated under vacuum; yield = 100% of the tetralimidazolyl compound.

1,3,4,6-Tetrikis(7-chloro-2,5-dioxo-2-ethylhexyl)tetrahydro-3a,6a-diphenylimidazol-4,5-dimide-2,5(1H,3H)-dione (5a). Compound 4a (20.8 g, 90 mmol) was treated with methylamine (90 °C for 1 h. The DMF was evaporated under water vapor pressure. The mixture was refluxed for 16 h and filtered over infusorial earth. After reduction of the volume to 3-5 mL, the mixture was added dropwise, with vigorous stirring, to 100 mL of diethyl ether. The precipitate was filtered, washed with cold diethyl ether, and dried under vacuum: yield 2.9 g (7%) of white imidazo[4,5-i/]imidazole-2,5(1f/,3f/)-dione (5a).

The undecyl layer was washed first with 10 mL and subsequently with 30 mL of diethyl ether. The solution was stirred at ambient temperature and the mixture was refluxed for 16 h, filtered over infusorial earth, and evaporated under vacuum; yield = 100% of the tetralimidazolyl compound.

1,3,4,6-Tetrikis(7-chloro-2,5-dioxoethyl)tetrahydro-3a,6a-diphenylimidazol-4,5-dimide-2,5(1H,3H)-dione (5b). Compound 4a (5.9 g, 20 mmol) and NaH (from a 80% dispersion of 4 mmol) in 10 mL of DMF and the solution was refluxed for 16 h. The reaction mixture was treated with 0.2 mL of water and evaporated under water vapor pressure (65 °C). The residue was dissolved in 8 mL of CHCl3, washed (4X) with 8 mL of basic water (adjusted to pH 12 with Na2CO3) and with 8 mL of water (2X), dried (MgSO4), and evaporated under vacuum; yield = 100% of the tetralimidazolyl compound.

1,3,4,6-Tetrikis(7-chloro-2,5-dioxo-2-ethylheptyl)tetrahydro-3a,6a-diphenylimidazol-4,5-dimide-2,5(1H,3H)-dione (5c). Compound 4a (9.57 g, 34 mmol) was treated with methylamine and the mixture was refluxed for 16 h, filtered over infusorial earth, and evaporated under vacuum; yield >100% of the tetralimidazolyl compound.

1,3,4,6-Tetrikis(6-chloro-2-oxahexyl)tetrahydro-3a,6a-diphenylimidazol-4,5-dimide-2,5(1H,3H)-dione (5d). Compound 4a (20.8 g, 90 mmol) was treated with methylamine (90 °C for 1 h. The DMF was evaporated under water vapor pressure. The mixture was refluxed for 16 h and filtered over infusorial earth. After reduction of the volume to 3-5 mL, the mixture was added dropwise, with vigorous stirring, to 100 mL of diethyl ether. The precipitate was filtered, washed with cold diethyl ether, and dried under vacuum: yield 2.14 g (78%) of white [(Pd(5d)Cl)2]; mp >90 °C; dec. FABMS (M — PdCl) at m/e 1107, (M — 2Cl)+ at m/e 1072; IR (KBr) 1730 (C =0), 689 (CBr) cm—1; 'H NMR (CD3OD) as for 5a.

Acknowledgment. We thank R. H. Fokkens and Prof. N. M. Nibbering for measuring the FAB mass spectra. R. P. Sybesma for carrying out the NOE experiments, C. J. Witman and Dr. J. W. Zwicker for synthesizing compounds 5, and Dr. M. Grove for assistance.
Selective Molecular Oxygen Oxidation of Thioethers to Sulfoxides Catalyzed by Ce(IV)

D. P. Riley,*† M. R. Smith,* and P. E. Correa†

Contribution from the Monsanto Company, 800 North Lindbergh Boulevard, St. Louis, Missouri 63167, and The Procter and Gamble Company, Miami Valley Laboratories, P.O. Box 39175, Cincinnati, Ohio 45247. Received June 15, 1987

Abstract: The selective molecular oxygen conversion of thioethers to sulfoxides is catalyzed by ceric ammonium nitrate (CAN) with rate enhancements that are at least three orders of magnitude greater than the uncatalyzed autoxidation of thioethers. Mechanistic studies (including spectroscopic, labeling, uptake, mixed reactant, and autocatalysis studies) of this novel reaction reveal that both atoms of dioxygen are incorporated into product sulfoxide, that a novel oxygen-driven Ce(IV)/Ce(III) redox cycle gives rise to the catalysis, and that molecular oxygen efficiently traps a sulfur-centered radical cation of the thioether (produced by Ce(IV) oxidation of thioether) to yield the oxygenated radical cation R₂SO₂⁺ which, it is proposed, reoxidizes Ce(III) to Ce(IV). The zwitterionic R₂S*OO⁺ intermediate (persulfoxide) reacts with thioether to yield two sulfoxide product molecules.

The ability to selectively convert a particular molecule via an oxidation utilizing the abundant and cheap oxidant oxygen often represents a desirable low-cost method for upgrading the value of a raw material. The goal of much of our research in recent years has been directed toward the utilization of oxygen as a cheap and selective oxidant. During our research into better methods of selectively oxidizing waste thioethers (e.g., Me₂S) to their more valuable sulfoxides, we discovered that thioethers are subject to a novel autoxidation process that under high oxygen concentration, elevated temps., and polar solvents yields almost exclusively the sulfoxide product.† The mechanism of this unusual autooxidation most likely involves an initial unfavorable electron transfer step (eq 1), followed by triplet oxygen (in high concentration) trapping of the resultant radical cation (eq 2). Back-}

\[
\begin{align*}
R₂S + \frac{1}{2}O₂ & \rightarrow R₂S⁺ + O₂⁻ \quad (1) \\
R₂S⁺ + \frac{1}{2}O₂ & \rightarrow R₂SO₂⁺ \quad (2)
\end{align*}
\]

donation of an electron from superoxide to the oxygenated radical cation yields the zwitterionic species (eq 3) whose chemistry is known to yield sulfoxide upon exposure to additional thioether (eq 4).†

\[
\begin{align*}
R₂S⁺O⁻⁺ + O₂⁻ & \rightarrow R₂SO⁻⁻ + O₂ \quad (3) \\
R₂SO⁻⁻ + R₂S & \rightarrow 2R₂SO₂⁺ \quad (4)
\end{align*}
\]

Given that the initial unfavorable electron-transfer step is rate-determining in this slow autoxidation reaction, we believed that the use of a suitable one-electron oxidant would possibly be capable of catalyzing or initiating the desired oxygen oxidation of R₂S to sulfoxide. We have communicated our preliminary successful attempts to catalyze this reaction using Ce(IV), and in this paper we present additional examples and mechanistic studies of the novel Ce(IV)-catalyzed molecular oxygen oxidation of thioethers to sulfoxides.

Experimental Section

All of the thioethers used in these studies were purchased from Aldrich Chemical Co. and distilled before use. Sulfoxide standards were prepared by standard procedures with H₂O₂ and (NH₄)₂Ce(NO₃)₆ and Ce(N-O₃)₆·6H₂O and purchased from Alfa-Ventron. HPLC grade acetonitrile was distilled before use and distillate, de-ionized water was used in all cases.

Electronic spectra were monitored by using matched quartz cells in a Hitachi 110A UV-VIS spectrophotometer over the range 200–500 nm. All high-pressure catalytic runs used an apparatus analogous to that reported previously. In general reactions were carried out with a reaction volume of 10 mL in an all-glass/Teflon reactor. This small volume thus, only a small amount of O₂ is present in the reactor at any time. This reduces the possibility of extensive deflagration. Gas uptake measurements were made by utilizing a pressurized external calibrated steel tube connected directly to the reactor. Pressure drop in this calibrated external tube could be correlated to moles of O₂ consumed during the reaction. Reactions were monitored by gas chromatography on a Varian Model 3400 GC with a flame ionization detector and analyzed on a 15 M OV101 capillary column. Yields were determined by utilizing dodecane as an internal standard and by comparison to calibrated solutions. Electrochemical studies were performed on a Bioanalytical Systems CV-1B cyclic voltammograph, and voltammograms were recorded on a Houston Instruments 100 XY recorder. All cyclics were recorded in dry methylene chloride with 0.5 M tetra-n-butylammonium tetrafluoroborate.


(2) Riley, D. P.; Correa, P. E.; Hardy, G. J. Org. Chem., accepted for publication.


†Monsanto Company.

‡The Proctor and Gamble Company.