Phenylmercury Chloride: Its Single-Crystal X-Ray Structure and Some Aspects of its Biological Chemistry

Michaela Wilhelm, Wolfgang Saak, and Henry Strasdeit

Fachbereich Chemie, Universität Oldenburg, Carl-von-Ossietzky-Straße 9-11, D-26129 Oldenburg, Germany

Reprint requests to Priv.-Doz. Dr. H. Strasdeit. E-mail: henry.strasdeit@uni-oldenburg.de

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A single crystal of phenylmercury chloride (PhHgCl) was obtained by serendipity from a solution of diphenylmercury (HgPh₂) and dihydrolipoic acid in tetrahydrofuran / carbon tetrachloride. The crystal structure of PhHgCl is pseudotetragonal. It is best described in the orthorhombic space group Cmma with \( a = 6.856(1), b = 6.882(1), c = 14.309(2) \) Å (at 193 K), and \( Z = 4 \). The Cl-Hg-C moiety of the PhHgCl molecule is exactly linear. The bond lengths at the Hg atom and HgCl 2.345(2) and Hg-C 2.044(9) Å. In the crystal, the molecules are arranged in double layers parallel to the \( ab \) plane.

In a model medium for the gastric juice (0.1 M DCI in D₂O / [D₈]dioxan, 37 °C), HgPh₂ reacts to form PhHgCl. HgCl₂, which would result from complete dearylation, cannot be isolated from the reaction mixture. However, it appears that a small equilibrium concentration of HgCl₂ may be present, because on addition of 1,4,7-trithiacyclononane (ttcn) and diethyl ether, the dichloride can be trapped as solid [Hg(ttcn)₂][HgCl₄]. We estimate that after oral uptake of HgPh₂ 20 - 90% are transformed into PhHgCl in the stomach after 30 min.

Introduction

Phenylmercury chloride, PhHgCl, which was first mentioned already in 1869 [1] is one of the simplest organomercury compounds. There are convenient methods for its preparation and crystallization [2], but so far it has not been possible to grow single crystals suitable for X-ray diffraction. Two attempts at determining the crystal structure of PhHgCl by powder methods were published [3, 4]. In both cases, however, the space group chosen was not the appropriate one. This will be demonstrated here on the basis of high-quality diffraction data of a serendipitously obtained single crystal of PhHgCl.

Growing interest in the toxicity of organomercury compounds stems from persistent ecological concerns as well as from a recent case of lethal dimethylmercury poisoning [5, 6]. It is well known that the symptoms of poisoning by phenylmercury (PhHg⁺) resemble those of “inorganic” mercury (Hg²⁺) and differ strongly from those of methylmercury (MeHg⁺) [7]. These observations may be explained by the facile intracellular breaking of Hg-phenyl bonds, probably by biological thiols [8]. On oral uptake, phenylmercury compounds are first exposed to the gastric juice before they enter somatic cells. The gastric juice contains ca. 0.1 M hydrochloric acid [9] and therefore might be able to degrade phenylmercury compounds. Results of model reactions are presented in this paper.

Results and Discussion

Crystal structure

PhHgCl has been described in the literature as tetragonal (space group P4/nmm; \( a = 4.76, c = 14.32 \) Å) [3] and as monoclinic (P2/n; \( a = b = 4.89, c = 14.46 \) Å; \( \beta = 90.0^\circ \) ) [4]. In the second work the structure has been solved and refined from powder data \( (R_p = 0.076) \). It is also mentioned there that an appropriate description should be possible in the orthorhombic space group Cmma with cell dimensions \( a = b = 6.92 \) and \( c = 14.46 \) Å.

We unintentionally obtained a diffraction-quality single crystal of PhHgCl from an experiment aiming at the growth of single crystals of [Hg(PhHg)₂(HlipS₂)₂] [10]. A solution of HgPh₂ and dihydrolipoic acid [Hlip(SH)₂] in tetrahydrofuran had been prepared in a test tube. Carbon tetrachloride had been added to form a lower layer.
After several months (initially under a protective atmosphere of N\textsubscript{2}), most of the solvent had evaporated, and a yellow residue remained which contained colourless crystals. At least some of these crystals consisted of PhHgCl. It is not entirely clear how this compound had formed. Razuvaev et al. showed that HgPh\textsubscript{2} reacts with CCl\textsubscript{4} in the presence of tetrahydrofuran already at 100°C, the main product being PhHgCl \cite{11}. Possible organic products, e. g. PhCCl\textsubscript{3}, or products resulting therefrom could not be detected in our reaction system. PhHgCl, on the other hand, was clearly identified by mass spectrometry \cite{12}. This observation is important for the interpretation of the crystallographic results, because it rules out the presence of PhHg(SH) \cite{13, 14}. It is well known that the discrimination between SH and Cl is difficult or even impossible from X-ray diffraction data alone (for a recent example see ref. \cite{15}).

The crystal structure of PhHgCl was solved by direct methods and successfully refined in the orthorhombic space group \textit{Cmma} \cite{16}. The final residuals (for all data) are \(R_1 = 0.0178\) and \(wR_2 = 0.0439\). The PhHgCl molecule lies on a crystallographic \textit{mm} position. Its phenyl group is disordered, adopting two equally populated positions as shown in Fig. 1. The two ring planes intersect at an angle of 86.7(3)°. The lattice parameters \(a\) and \(b\) differ by only 0.4%, which is, however, significant as judged by their estimated standard deviations. To a good approximation they result from the \(a\) axis of the earlier tetragonal description \cite{3} by multiplication with \(\sqrt{2}\). The orthorhombic cell can be transformed into a tetragonal one having \(a = 4.857(1)\) and \(c = 14.309(2)\) Å, whereby one significant angular deviation, namely \(\gamma = 89.79(2)°\), must be neglected. Refinement in the tetragonal space group \textit{P4/mmm} then leads to very good residuals (\(R_1 = 0.0175, wR_2 = 0.0441, S = 1.110\) for all data). The Hg-Cl and Hg-C bonds lengths agree with those of the orthorhombic model within less than 1\(\sigma\). However, an additional disorder is imposed on the phenyl group as the molecule is now situated on 4\textit{mm}. The fact, that the two ring positions are not exactly perpendicular to each other (see above), results in a twofold splitting of each of them. Taking all this together, the structure must be regarded as pseudotetragonal, and the description in \textit{Cmma} appears more appropriate.

The molecular structure of PhHgCl is unexceptional. The Hg atom is exactly linearly coordinated with the Hg-Cl bond being slightly (0.01 Å) longer than the longest Hg-Cl bonds found in comparable aryl-Hg-Cl compounds \cite{17}. The Hg-Cl bond length is at the lower end of the usual range for Hg-C(aryl). In the crystal, the PhHgCl molecules are arranged as sheets which are parallel to the \(a, b\) plane.
These sheets partly interpenetrate to form double layers (see Fig. 2). Each double layer bears phenyl groups above and below, while its inner part consists of the Hg and Cl atoms. Each Hg atom is surrounded by four Cl atoms of neighboring molecules, and vice versa. The corresponding Hg–Cl distances are 3.43 and 3.45 Å – too long for even weak (“secondary”) covalent interactions, because the sum of the van der Waals radii of Hg and Cl probably falls in the range 3.4 - 3.5 Å [18]. Within each single layer, only edge-to-face arrangements of the phenyl groups, as found in crystals of benzene [19], are possible. The resulting alternating orientations can easily be recognized in the lower part of Fig. 2. Any phenyl group that adopts the “wrong” disorder position would form four intermolecular H⋯H contacts of less than 1.0 Å! Thus, the disorder can occur from one single layer to the next along the c axis, but not within a single layer. There are no indications that this disorder is not statistical.

Protonolysis of HgPh₂ by hydrochloric acid under near-physiological conditions

After oral uptake, HgPh₂ remains in the stomach for a maximum period of 1 - 3 h. During this time, it is in contact with the gastric juice which typically contains ca. 120 mM hydrochloric acid [9]. We have modelled this situation in a HgPh₂ / DCI / D₂O / [D₈]dioxan reaction system (for details see Experimental Part). The use of [D₈]dioxan was necessary to dissolve HgPh₂ which is poorly soluble in water alone. The reaction rate of the formation of PhHgCl according to

\[
\text{HgPh}_2 + \text{HCl} \rightarrow \text{PhHgCl} + \text{C}_6\text{H}_6
\]

is probably no more than one order of magnitude larger in our 80% dioxan system than in purely aqueous solution. This can be inferred from the results of early investigations on the acidolysis of HgPh₂ which, however, did not have any biological background [20, 21]. The substitution of HCl by DCI should have only a small effect on the reaction rate [20]. Thus the conditions in our model system are not very different from the physiological ones, except for the high concentration of HgPh₂ necessary for NMR detection.

The main results from a typical experiment (see Experimental Part) are the following. At 37 °C, 50% of the HgPh₂ are transformed into PhHgCl within 15 min (80% within 60 min, 90% within 120 min). The interpretation of these data must take into account that the concentration of DCI decreases from initially 130 mM to 80 mM (40 mM) when 50% (90%) of the HgPh₂ has reacted. Consequently, the reaction slows down due to a decrease in concentration of both reaction partners. From the starting phase of the reaction the half-time can be roughly estimated at ca. 10 min. This value is very similar to the one obtained for the half-time of the acidolysis of HgPh₂ by perchloric acid (water, pH 1, 25 °C) [22]. In conclusion, we can estimate that in the stomach 20 - 90% of the HgPh₂ are transformed into PhHgCl within the first 30 min.

Even at an initial DCI-to-HgPh₂ ratio of ca. 2.6:1, no further reaction of PhHgCl to HgCl₂ was observed (see Experimental Part). After 14 d at 37 °C, PhHgCl was isolated as the only product. Addition of 1,4,7-trithiacyclooctane (ttcн) has no effect, i.e. there is no donor activation of PhHgCl by ttcн. Ttcn serves as a model for biological thioethers like methionine which are potential ligands for PhHgCl even in strongly acidic media. However, when diethyl ether is allowed to diffuse via the gas phase into the ttcн containing reaction mixture, the poorly soluble complex salt [Hg(ttcn)₂][HgCl₄] crystallizes. It was identified by X-ray structure determination [23]. This result indicates that a low equilibrium concentration of HgCl₂ may be present also in the ttcн free system.

Experimental Part

Caution! Phenylmercury compounds are highly toxic. Any swallowing, contact to skin or inhalation of dusts must strictly be avoided. When solutions of these compounds are handled, it is recommended to wear the special combination of gloves specified in ref. [5, 6].

Crystal structure determination

A suitable single crystal of PhHgCl was obtained as described in the previous section. It was mounted on the top of a glass capillary on a STOE IPDS area detector diffractometer. MoKα radiation (\(\lambda = 0.71073\) Å) was used for intensity data collection. Crystal data: C₆H₅ClHg, \(M_r = 313.15\), orthorhombic, space group Cmma; \(a = 6.856(1), b = 6.882(1), c = 14.309(2)\) Å; \(V = 675.1(2)\) Å³, \(Z = 4\), \(\rho_{calc} = 3.081\) g cm⁻³, \(\mu(\text{MoKα}) = 230.8\) cm⁻¹, crystal size: 0.44 × 0.38 × 0.03 mm, \(T = 193\) K, 178 exposures, \(\Deltaφ = 1.8°, 5.7 ≤ 2Θ ≤ 52.0°\), completeness to
2\(\Theta\) = 52.0\(^{\circ}\); 97.2%; reflections: 4093 collected, 385 independent; numerical absorption correction, min./max. transmission: 0.0351/0.5444, refinement on \(F^2\); 36 parameters, \(R = 0.0173\) [\(I > 2\sigma(I)\)]; residual electron density: +1.62/−0.61 eÅ\(^{-3}\). All non-hydrogen atoms were anisotropically refined. The hydrogen atoms were included on idealized positions. Programs used were the SHELX-97 program package [16] and DIAMOND [24]. Further details of the structure determination have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk), and may be obtained by quoting the deposition no. CCDC 135477, the authors' names and the literature citation.

**Reaction of diphenylmercury with hydrochloric acid**

A typical experiment, in which the time course of the reaction between HgPh\(_2\) and DCl was studied, was conducted as follows. HgPh\(_2\) (44 mg, 125 \(\mu\)mol) was dissolved in \(\text{D}_2\text{O} / \text{D}_2\text{O}\) : Dioxan (0.20 ml / 1.00 ml) in an NMR sample tube. An initial \(^{13}\)C NMR spectrum (75 MHz) was recorded at 37 °C. After addition of a 20\% solution of DCl in \(\text{D}_2\text{O}\) (24.4 \(\mu\)l, 157 \(\mu\)mol), the sample was kept at 37 °C. The initial concentrations were ca. 130 mM DCl and 100 mM HgPh\(_2\). Starting immediately after the addition of the DCl, a series of \(^{13}\)C NMR spectra was recorded at 37 °C over a period of 3 h. The relative concentrations of HgPh\(_2\) and the reaction product PhHgCl were estimated from the peak heights of the signals of the ortho-C atoms. HgPh\(_2\): \(\delta = 128.36\) (p-C), 128.91 (m-C), 134.44 (o-C), 171.54 (ipso-C); PhHgCl: \(\delta = 129.35\) (p-C), 129.49 (m-C), 137.24 (o-C), 150.74 (ipso-C); [\(\text{D}_8\)] dioxan as internal standard at \(\delta = 66.50\).

In a further experiment, an analogous sample was prepared which contained, however, twice the amount of DCl. Hence, the ratio of DCl to HgPh\(_2\) was sufficiently high to allow the hypothetical transformation of HgPh\(_2\) to HgCl\(_2\) to proceed completely. After the sample had stood at 37 °C for 14 d, HgPh\(_2\) was no longer detectable by NMR spectroscopy. The solvent was evaporated, and the white solid residue was dried in vacuo. CI analysis: calcd for HgCl\(_2\): 26.1\%, for PhHgCl: 11.3\%; found for the residue: 10.9\%.

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[10] The crystal structure of this trinuclear complex is described in [8].
[12] El mass spectra of PhHgCl are available on the Internet via the following URLs:
a) http://webbook.nist.gov/chemistry/name-ser.htm;
b) http://www.aist.go.jp/RIODB/SDBS/menu-e.html.
[13] Dihydrolipoic acid can be regarded as a potential SH− source.