293(2) K, θ range: 1.71–25.99°; 3966 independent reflections; full-matrix least-squares refinement; R indices [$I > 2\sigma(I)$]: $R_1 = 0.0408$, $wR_2 = 0.1036$; max. residual electron density: 0.431 e Å^{-3}. **10b**: $C_{20}H_{23}FeNO_6$, $M_r = 429.24$ g mol^{-1}, monoclinic, space group $C2/c$, $\lambda = 0.71073$ Å, $a = 19.630(10)$, $b = 15.928(11)$, $c = 15.375(5)$ Å, $\beta = 124.12(2)°$, $V = 3979.8(37)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.433$ g cm^{-3}, $\mu = 0.773$ mm^{-1}, $T = 293(2)$ K, θ range: 1.79–27.50°; 4473 independent reflections; full-matrix least-squares refinement; R indices [$I > 2\sigma(I)$]: $R_1 = 0.0384$, $wR_2 = 0.1075$; max. residual electron density: 0.372 e Å^{-3}. Programs: G. M. Sheldrick, SHELXS-86, Göttingen, Germany, **1986**; G. M. Sheldrick, SHELXL-93, Göttingen, Germany, **1993**; E. Keller, SCHAKAL-97, Freiburg im Breisgau, Germany, **1997**. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-134504 (**8**), -134505 (**10a**), and -134506 (**10b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Intracellular Degradation of Diorganomercury Compounds by Biological Thiols—Insights from Model Reactions**

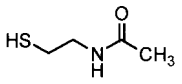
Henry Strasdeit,* Angelika von Döllen, Wolfgang Saak, and Michaela Wilhelm

Dimethylmercury, $HgMe_2$, the simplest diorganomercury compound, is classified as a "super poison"—only a few drops on the skin is fatal for an adult.[1,2] It is noteworthy that several months pass after exposure before the first characteristic symptoms of severe damage to the central nervous system (CNS) appear. In contrast, the onset of the toxic action of diphenylmercury, $HgPh_2$, is rapid and is associated with a different symptomology; it resembles inorganic Hg^{II} salts.[3] At a molecular level these results may only be explained piecemeal, although the extent and rate of degradation of HgR_2 compounds to RHg^+ and finally to Hg^{2+} would appear to play a central role.[4]

We have occupied ourselves with the question as to the possible nature of the degradation reactions in humans from the viewpoint of complexation chemistry. The polar character of Hg–C bonds ($Hg^{\delta+}$–$C^{\delta-}$), which has been confirmed inter alia by quantum-mechanical calculations on $HgMe_2$ and $HgPh_2$,[5] and the protic conditions of most biological compartments suggest that reactions with Brønsted acids are likely. Because of their acidity, their frequent intracellular occurrence, and in particular because of the high thermodynamic stability of the Hg–S bond ("thiophilia" of Hg^{II}), biological thiols have been assumed to be the most important reaction partners [Eq. (1)].

$$HgR_2 \xrightarrow[-RH]{+R'SH} RHg(SR') \xrightarrow[-RH]{+R'SH} Hg(SR')_2 \quad (1)$$

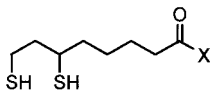
Indeed, we have been able to isolate sequentially the two dearylation stages as $PhHgL^1$ and HgL_2^1 from reactions of $HgPh_2$ with the thiol *N*-acetylcysteamine HL^1 ($HgPh_2$:HL^1 = 1:2, room temperature, tetrahydrofuran (THF), see the Experimental Section), a model for the biological monothiols glutathione and coenzyme A. Moreover, it was also possible to detect the symmetrization of $PhHgL^1$ by NMR spectroscopy in [D_7]*N*,*N*-dimethylformamide [Eq. (2)].



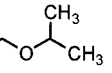
HL^1

$$2\,PhHgL^1 \rightleftharpoons HgPh_2 + HgL_2^1 \quad (2)$$

Accordingly, HgL_2^1 need not necessarily be formed by the direct attack of HL^1 on $PhHgL^1$. Alternatively HL^1 could react solely with $HgPh_2$, first with that initially available and later with that provided by symmetrization. These results show that $HgPh_2$ can be completely dearylated by a suitable thiol under mild conditions.[6]



H_3L^2: X = OH

H_2L^3: X = 

An analogous reaction of $HgPh_2$ with the coenzyme dihydrolipoic acid H_3L^2 also led to the two dearylation stages. However, in this case they appeared unexpectedly as components of the same complex. This complex, $[Hg(PhHg)_2(HL^2)_2]$ (**1**) was isolated in good yield as the poorly soluble THF adduct. [Eq (3), see the Experimental Section].

$$3\,HgPh_2 + 2\,H_3L^2 \xrightarrow{THF} \mathbf{1}\cdot THF\downarrow + 4\,C_6H_6 \quad (3)$$

The formation of **1**·THF is essentially independent of the stoichiometric ratio of the reagents. $HgPh_2$ also formed a complex of analogous composition with the amide H_2L^3, which we synthesized as a sterically equivalent model for the dihydrolipoyl-lysyl side chain (swinging arm) in enzymes. This excludes the possibility that the carboxyl functionality of dihydrolipoic acid is critical for the formation of **1**. The crystal structure analysis[7] showed that **1** is a trinuclear, centrosymmetric complex (Figure 1). Each of the two peripheral mercury atoms Hg1 and Hg1′ is bound to a phenyl group and to a thiolate sulfur atom; the S-Hg-C arrangement

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[**] Coordination Chemistry of Lipoic Acid and Related Compounds, part 3. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 2: ref. [11].

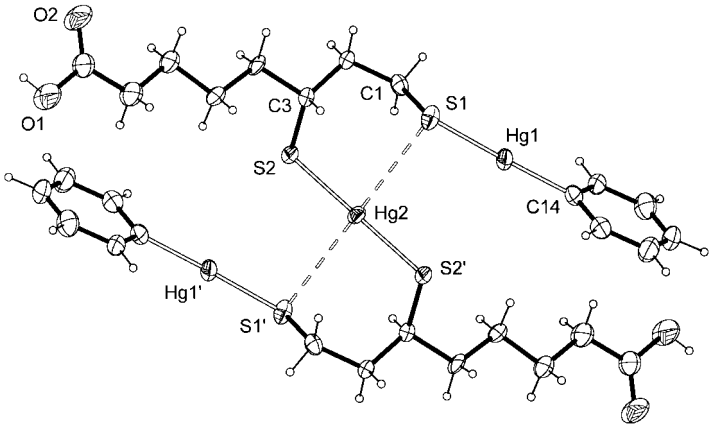

Figure 1. Crystal structure of **1** (thermal ellipsoids at the 50% probability level). Selected distances [Å] and angles [°]: Hg1–S1 2.356(2), Hg1–C14 2.068(7), Hg2–S1 3.259(2), Hg2–S2 2.328(2), S1–C1 1.825(7), S2–C3 1.850(6); S1-Hg1-C14 172.7(2), S1-Hg2-S1′ 180.0, S1-Hg2-S2 89.80(5), S1-Hg2-S2′ 90.20(5), S2-Hg2-S2′ 180.0, Hg1-S1-Hg2 89.88(6), Hg1-S1-C1 103.3(2), Hg2-S1-C1 80.4(2), Hg2-S2-C3 103.1(2).

deviates marginally from linearity. In contrast, the central mercury atom Hg2 is coordinated solely to sulfur atoms. The primary coordination is here exactly linear (S2-Hg2-S2′. In addition there are two secondary bonds to S1 and S1′, each with a length of 3.259(2) Å,[8] so that overall a planar [2+2] coordination is present.

In contrast to $HgPh_2$, $HgMe_2$ reacts extraordinarily slowly with thiols. If $HgMe_2$ and an equivalent amount of the dithiol H_2L^3 are mixed in [D_8]dioxane at 37 °C (physiological temperature), [$MeHg(HL^3)$] is first detectable by ^{1}H NMR spectroscopy after two weeks, and only 2% of the $HgMe_2$ is converted into $MeHg^+$ after seven weeks. Regardless of the thiol used, we were unable to observe cleavage of the second methyl group!

The low solubility of $HgMe_2$ and $HgPh_2$ in water made it necessary to use organic solvents; in addition the concentrations used were comparatively high. Although our results have therefore limited applicability to biological systems, they do support the hypothesis that intracellular degradation of diorganomercury compounds could occur primarily through thiols in the human body. Thus both the first phase of the long latency period in $HgMe_2$ poisoning (degradation to MeHg(SR′)) and the similarity of the toxic action of $HgPh_2$ to that of inorganic Hg(II) salts (more rapid degradation to $Hg(SR')_2$) become understandable. Our findings give no indication of an involvement of biological thiols in the demethylation of $MeHg^+$, for example in the CNS.[4] However, it cannot be excluded on the basis of these results alone that under physiological conditions $MeHg^+$ can also be cleaved slowly by thiols, particularly if the effects of additional donors are taken into consideration.[9]

Experimental Section

Caution! Organomercury compounds, especially methylmercury compounds are extremely toxic. All direct contact must be strictly avoided by suitable protective measures such as the wearing of special gloves.[1, 2]

For the synthesis of H_2L^3 the imidazolide was first prepared from lipoic acid and *N,N*′-carbonyldiimidazole[10] and then converted into the amide with 3-isopropoxypropylamine. The subsequent reduction to the dithiol was carried out as described for the synthesis of H_3L^2 from lipoic acid.[11] All reactions of Hg compounds with thiols were carried out in an N_2 atmosphere.

Reaction of $HgPh_2$ with *N*-acetylcysteamine: A solution of $HgPh_2$ (355 mg, 1.00 mmol) and HL^1 (238 mg, 2.00 mmol) in THF (30 mL) was allowed to stand for 48 h and then concentrated to 10 mL. After a few days white, feathery needles of $PhHgL^1$ (120 mg, 0.30 mmol) were filtered off. The filtrate was evaporated to dryness in order to remove the benzene formed. The residue was redissolved in THF. The solution was concentrated to 5 mL, and white, microcrystalline HgL^1_2 (80 mg, 0.18 mmol) was isolated after a few days. First precipitation (=$PhHgL^1$): IR (KBr): $\tilde{\nu}$ = 727 (s), 698 (m), 341 cm^{-1} (m), the characteristic band of HgL^1_2 (see below) was absent; $^{13}C\{^1H\}$ NMR (75.5 MHz, [D_7]*N*,*N*-dimethylformamide): δ = 23.03 (CH_3), 27.76 (CH_2S), 45.28 (CH_2N), 128.4 (*p*-C), 129.0 (*m*-C), 137.6 (*o*-C), 164.3 (*ipso*-C), 170.3 (C=O); as a result of symmetrization [Eq. (2)] additional signals of $HgPh_2$ could be observed after a few hours: δ = 127.9 (*p*-C), 128.6 (*m*-C), 138.7 (*o*-C), 171.8 (*ipso*-C). Second precipitation (=HgL^1_2): IR (KBr): $\tilde{\nu}$ = 357 cm^{-1} (m, Hg-S[12]), the characteristic bands of $PhHgL^1$ (see above) were absent. The band at 357 cm^{-1} can be shifted to 366 cm^{-1}. According to the elemental analysis HgL^1_2 was also present in these precipitations, apparently in the form of a second, previously unknown modification: elemental analysis calcd for $C_8H_{16}HgN_2O_2S_2$: C 21.99, H 3.69, Hg 45.91, N 6.41, S 14.68; found: C 22.09, H 3.53, Hg 47.60, N 6.67, S 14.55.

Synthesis of **1** · THF: A stirred solution of $HgPh_2$ (1.06 g, 3.0 mmol) in THF (40 mL) was treated with a solution of H_3L^2 (0.42 mg, 2.0 mmol) in THF (10 mL). After the mixture had been stirred at room temperature for 48 h, most of the solvent was removed under vacuum. The product precipitated as a colorless, finely crystalline powder, which was isolated, washed with THF, and dried briefly under vacuum. A second fraction was isolated after further concentration. Yield: 0.94 g (76%). IR (KBr): $\tilde{\nu}$ = 2926 (m), 1709 (vs), 1427 (m), 1252 (m), 1235 (m), 729 (s), 698 (m), 448 cm^{-1} (m); elemental analysis calcd for $C_{32}H_{46}Hg_3O_5S_4$: C 30.98, H 3.74, Hg 48.50, S 10.34; found: C 31.10, H 3.83, Hg 48.52, S 10.39.

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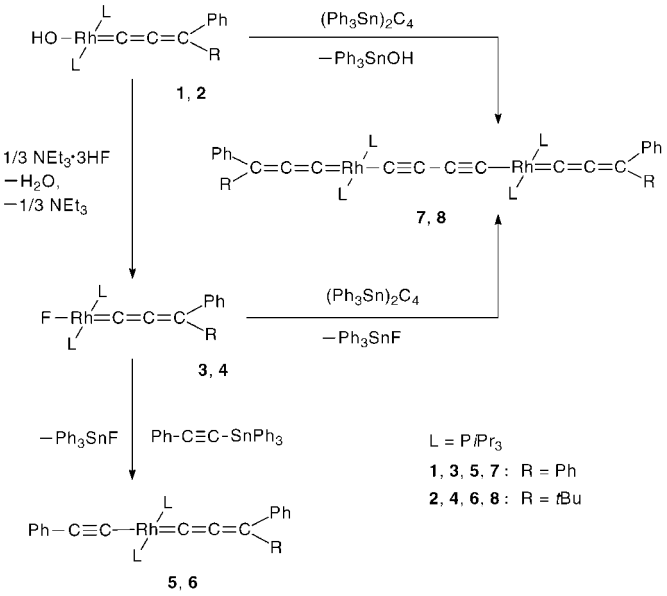
An Unprecedented [C_2+C_1+C_1] Coupling of an Alkynyl, an Allenylidene, and a CO Unit: The Formation of a Highly Unsaturated Cyclobutenone Derivative in the Coordination Sphere of Rhodium(I)**

Juan Gil-Rubio, Birgit Weberndörfer, and Helmut Werner*

Dedicated to Professor Heinrich Vahrenkamp on the occasion of his 60th birthday

Metal-assisted C–C coupling reactions belong to the most important processes in organometallic chemistry.[1] Following our work on the synthesis of metal vinylidene compounds from alkynes, we recently reported that the square-planar rhodium complexes *trans*-[RhR(=C=CR^1R^2)($PiPr_3$)$_2$] (R = methyl, vinyl, phenyl, alkynyl) undergo an intramolecular C–C coupling reaction in the presence of CO to give *trans*-[Rh{C(R)=CR^1R^2}(CO)($PiPr_3$)$_2$].[2] A related reaction occurs between the allenylidene compounds *trans*-[RhX(=C=CR^1R^2)($PiPr_3$)$_2$] (X = OAr, OC(O)Me, N_3) and CO to give the alkynyl complexes *trans*-[Rh(C≡C–CXR^1R^2)(CO)($PiPr_3$)$_2$], resulting from the migration of the group X to the γ-C atom of the allenylidene ligand.[3] While earlier attempts from our laboratory to obtain alkyl, vinyl, or arylrhodium(I) complexes of the general composition *trans*-[RhR(=C=C=CR^1R^2)($PiPr_3$)$_2$] failed,[4] we have now succeeded with the preparation of the corresponding alkynyl(allenylidene) compounds *trans*-[Rh(C≡CPh)(=C=C=CR^1R^2)($PiPr_3$)$_2$], one of which undergoes an unprecedented [C_2+C_1+C_1] coupling reaction with CO to give a highly unsaturated cyclobutenone derivative.

The synthetic route to the new alkynylrhodium(I) complexes **5** and **6** is outlined in Scheme 1. In order to coordinate the C_2 unit to the metal center, the key to success was the use



Scheme 1. Synthesis of mono- and dinuclear rhodium(I) complexes **5**–**8**.

of the mild transmetalating reagent PhC≡$CSnPh_3$[5] and the highly reactive fluoro compounds **3** and **4**. While the latter could not be prepared by salt metathesis from *trans*-[RhCl{=C=C=C(R)Ph}($PiPr_3$)$_2$] and KF or TlF, respectively, they were obtained in excellent yield by treatment of the hydroxo derivatives **1** and **2** with one equivalent of $NEt_3 \cdot 3HF$ in benzene. The fluoro complexes are green-yellow (**3**) and green (**4**) crystalline solids that can be stored at room temperature under argon and are stable for several days in solution in C_6D_6. The ^{19}F NMR spectra of **3** and **4** show the expected pattern of signals with $^{103}Rh-^{19}F$ and $^{31}P-^{19}F$ couplings, the ^2J(P,F) values of about 19 Hz being characteristic for a *cis* disposition of the fluoro and the phosphane ligands.[6]

The reactions of **3** and **4** with PhC≡$CSnPh_3$ resulted in the formation of the alkynyl complexes **5** and **6** together with a white, poorly soluble by-product which was identified as Ph_3SnF by comparison of its IR spectrum with that of an authentic sample prepared from Ph_3SnCl and KF.[7] Although compounds **5** and **6** (which are violet and brown crystalline solids, respectively) are more sensitive than the related fluoro or hydroxo derivatives, they have been fully characterized on the basis of their analytical and spectroscopic data. Besides the single resonance in the ^{31}P NMR spectra with a ^1J(Rh,P) coupling constant that is typical for a *trans* disposition of both phosphorus atoms, the most characteristic features are the

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