Metal-Stabilized Quinone and Thioquinone Methides

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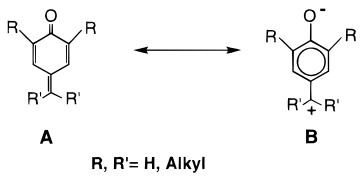
Quinone methides (QMs)—the monomethylene analogues of quinones—have been extensively studied over the last few decades.[1] Both natural and synthetic compounds capable of generating QMs were found to be biologically active, particularly as potential antitumor agents.[2] Being involved in biosynthesis of lignin, they also play an important role in the wood utilization industry.[3] However, despite this wide interest, examples of isolated simple QMs, i.e., not bearing substituents at the methylene group, are scarce.[4] The simplest compound of this series, **A** (Scheme 1, R = R′ = H), has never been characterized. Its 2,6-dimethyl analogue (R = Me, R′ = H) cannot be isolated in pure form,[5] and at room temperature, it undergoes dimerization in solutions more concentrated than 10^{-5} M. The large contribution of the resonance zwitterionic structure **B** (Scheme 1) in the total energy of QMs makes these compounds distinctly different from their parent quinones. Introducing the bulky tertiary butyl groups in the 2 and 6 positions makes the QM somewhat more stable, although again at concentrations higher than 10^{-3} M dimerization occurs.[6] So far, no X-ray structural characterization of these type of compounds has been reported.

We now report the synthesis and crystallographic characterization of the first thermally stable QM, having no substituents at the methylene group ("simple QM"). Stabilization of the QM has been achieved by complexation to a transition metal center.[7] Moreover, the synthetic route to this unprecedented compound includes an unusual sequence of a single carbon−carbon bond activation followed by C−C coupling.

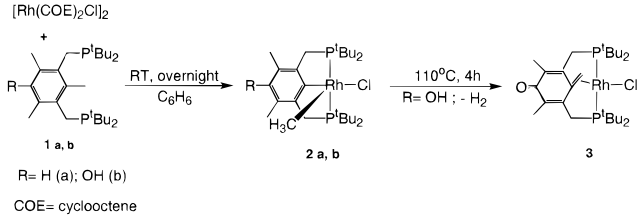
We have recently described the synthesis of the bulky PCP-type ligand **1a** and have demonstrated that it undergoes a room-temperature transition metal insertion into the carbon−carbon bond situated between the two phosphine arms (Scheme 2).[8] This reaction favorably competes with the C−H bond activation, and the C−H activated product is completely converted into the thermodynamically more stable C−C activated one within several hours at room temperature. During the course of our studies of substituent effects on the reactivity of the carbon−carbon bond, we have synthesized the new ligand **1b** bearing an OH group para to the C−C bond to be cleaved.[9] As in the case of an analogous ligand with a MeO group in the para position,[8] reaction of **1b** with $[(COE)_2RhCl]_2$ (COE = cyclooctene) at room temperature overnight results in quantitative formation of the new C−C activated compound **2b**. Remarkably, when a toluene solution of complex **2b** was refluxed for 4 h, quantitative formation of **3**, the first isolated, thermally stable QM took place (Scheme 2). The mechanism for this unprecedentent process might involve a 1,2-methyl shift leading to the conversion of **2b** to an arenonium complex, as observed in a diaminoplatinum system[10] (Scheme 3). Rearrangement of the latter into a hydridoalkyl Rh(III) complex, followed by β-hydrogen elimination and H_2 release, can generate **3**.[11] Alternatively, C−C coupling followed by C−H oxidative addition to give the benzyl hydride complex might take place. The latter can then rearrange into **3** via an inter- or intramolecular protonation of the hydride with the acidic phenolic proton (Scheme 3).[12]

The ^{1}H NMR spectrum of **3** in $CDCl_3$ exhibits a triplet of doublets at 3.13 ppm (J_{RhH} = 2 Hz) due to the methylene group bound to the rhodium atom.[13] The upfield shift of the signal of the methyl groups at the 2 and 6 positions, which appears at

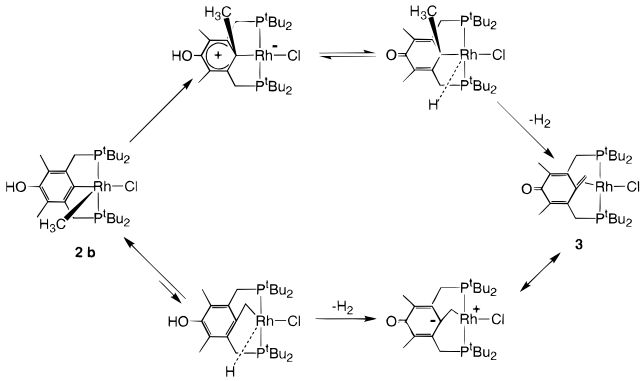
Scheme 1



Scheme 2



Scheme 3



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(2) See, for example: (a) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. For recent reviews, see: (b) Moore, H. W.; Czerniak, R.; Hamdan A. *Drugs Exp. Clin. Res.* **1986**, *12*, 475. (c) Sugumaran, M. *Bioorg. Chem.* **1987**, *15*, 194. (d) Thompson, D. C.; Tompson, J. A.; Sugumaran, M.; Moldeus, P. *Chem. Biol. Interact.* **1992**, *86*, 129.

(3) For a recent review, see: (a) Shevchenko, S. M.; Apushkinskii, A. G. *Russ. Chem. Rev.* **1992**, *61*, 195.

(4) Only two examples of isolable simple QMs, both containing fused aromatics (i.e., with negligible quinonoid character) have been reported: (a) Starnes, W. H., Jr. *J. Org. Chem.* **1970**, *35*, 1974. (b) Boger, D. L.; Nishi, T.; Teegarden, B. R. *J. Org. Chem.* **1994**, *59*, 4943.

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(6) Bauer, R. H.; Coppinger, G. M. *Tetrahedron* **1963**, *19*, 1201.

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(8) Rybtchinski, B.; Vigalok, A.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **1996**, *118*, 12406.

(9) For the synthesis and spectroscopic data of this and other reported compounds, see Supporting Information.

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(11) A facile dihydrogen elimination process to give a rhodium(I) olefin complex in the PCP-type ligand system has been reported: Crocker, C.; Errington, R. J.; McDonald, W. S.; Odell, K. J.; Shaw, B. L.; Goodfellow, R. J. *J. Chem. Soc., Chem. Commun.* **1979**, 498.

(12) While we believe that radical pathways are less likely, they cannot be ruled out at this stage.

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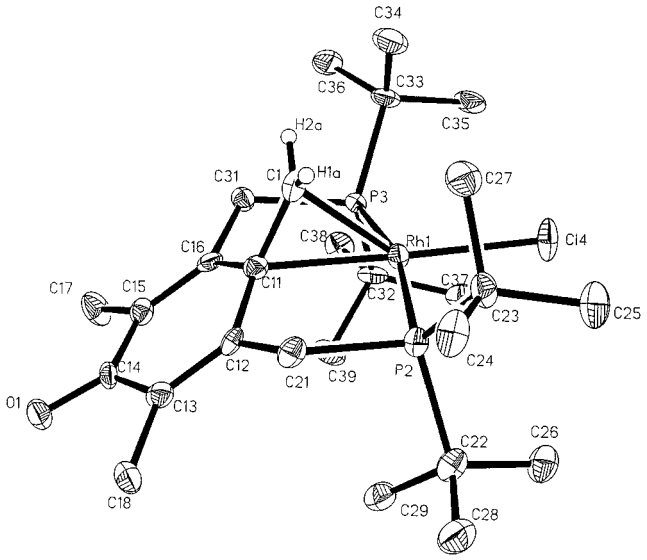


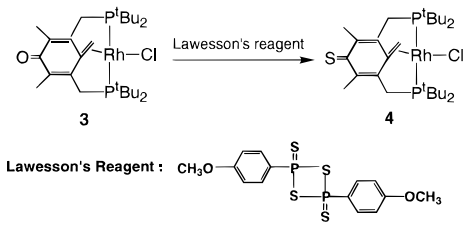
Figure 1. ORTEP view of a molecule of **3** with the thermal ellipsoids at 50% probability. The hydrogen atoms (except H(1a) and H(2a)) are omitted for clarity. Selective bond distances (Å) and angles (deg): Rh(1)−C(1), 2.052(6); Rh(1)−C(11), 2.183(5); C(1)−C(11), 1.441(8); O(1)−C(14), 1.239(6); C(12)−C(13), 1.349(8); C(13)−C(14), 1.477(8); C(16)−C(11)−C(12), 118.7(5).

1.89 ppm (compared to 2.34 ppm with **1b**), indicates loss of aromaticity. The coordinated methylene group gives rise to two doublets of triplets in the $^{13}C\{^1H\}$ NMR spectrum at 41.91 ppm (J_{RhC} = 20.4 Hz) (=CH_2) and at 66.97 ppm (J_{RhC} = 14 Hz) (=C), respectively, characteristic of similar Rh(I) complexes containing a rigid PCP chelating core.[14] The IR spectrum of **3** exhibits two bands due to the carbonyl group at 1595 cm^{-1} (s) and at 1625 cm^{-1} (m) similar to what was found for other QMs.[1c]

Crystals of complex **3** suitable for an X-ray single-crystal analysis were obtained by recrystallization of **3** from benzene.[15] The rhodium atom in **3** is situated in the center of a distorted square (Figure 1). It is clearly seen that the aromatic ring does not exist anymore, with the bond lengths C(12)−C(13) and C(15)−C(16) of 1.349(8) and 1.353(7) Å, respectively, being substantially shorter than other bonds of the six-membered ring (cf. 1.352(8) Å for that in duroquinone[16]). The C(14)−O(1) double-bond length of 1.239(6) Å is in the range expected for substituted quinones. It is also noteworthy that coordination of the methylene group to rhodium displaces it from the plane of the six-membered cyclohexadiene ring. The C(1)−C(11)−Rh angle of 65.3(3)° is smaller than the one observed for similar symmetrical alkene rhodium complexes.[14] The rhodium atom is situated unsymmetrically along the double bond (C(1)−C(11) = 1.441(8) Å) with the Rh−C(1) distance of 2.052(6) Å being shorter than Rh−C(11) (2.183(5) Å).

Evidently, the rhodium center is very strongly bound to the quinonoide ligand. Under normal conditions, complex **3** did not react with air, carbon monoxide, or trimethylphosphine. No free ligand (or products of its further reactivity) was observed upon refluxing of a solution of **3** in toluene or in THF for days. It is well established that QMs of structure **A** undergo reactions with both nucleophiles and electrophiles giving products of 1,6-addition. They react smoothly with water or alcohols forming the corresponding phenols.[17] Aromatization is, thus, a major driving force in the reactivity of QMs, resulting in their general instability. In sharp contrast, complex **3** was indefinitely stable toward water and alcohol even upon moderate heating. Notably, coordination of a metal center results in complete blockage of the methylene group as a possible reaction site.

Scheme 4



Interestingly, when a toluene solution of **3** was stirred at room temperature with 1.5 equiv of Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide) for 2 h, quantitative formation of the thioquinone methide **4** was observed (Scheme 4). Complex **4** exhibits spectroscopic data similar to that of **3**. The most significant difference between these complexes can be observed in the $^{13}C\{^1H\}$ NMR spectrum where the signal of the carbon atom attached to sulfur gives rise to a singlet at 211.71 ppm, about 25 ppm downfield from the one in **3** (186.51 ppm). This downfield shift of the thioketone carbon atom in comparison with it's oxo analogue is very characteristic and has been a subject of several investigations.[18] It is noteworthy that, although "simple" QMs could be spectroscopically detected under certain conditions, *their thio analogues are unknown*. Even those having strong electron-withdrawing substituents, such as −CN, in the methylene group undergo rapid oligomerization and, thus, have never been characterized.[19]

In summary, an unprecedented sequence of reactions leading to the formation of the first thermally stable quinone methide is reported. The use of transition metals allows for the first time the full characterization (including X-ray analysis) of this type of compound, which is known to be a key intermediate in various biochemical processes. Even more reactive thioquinonemethides can also be isolated and fully characterized.

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Supporting Information Available: Text describing the synthesis and characterization of compounds **1b**, **2b**, **3,** and **4** and tables of crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and hydrogen atom coordinates for complex **3** (11 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Crystal structure data for **3**: $C_{27}H_{48}P_2ClORh + C_6H_6$, orange plates, monoclinic, $P2(1)/c$, a = 8.505(2) Å, b = 16.552(3) Å, c = 23.295(5) Å, β = 95.35(3), Z = 4, $R_1(I > 2\sigma I)$ = 0.0656.

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