Metal-Mediated Generation, Stabilization, and Controlled Release of a Biologically Relevant, Simple Para Quinone Methide: BHT-QM

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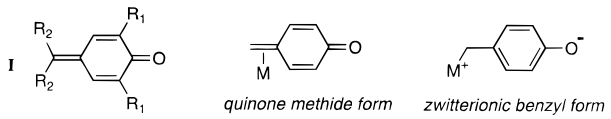
Quinone methides (QMs, **I**) are highly reactive transient compounds involved in many chemical and biological processes.[1] They were proposed as important intermediates in natural products chemistry[2,3] and implicated as the active forms of antitumor drugs.[4] They are highly reactive toward both nucleophiles and electrophiles, and polymerize upon concentration of their dilute solutions, hindering their isolation and characterization. It is also difficult to study their behavior in biological systems due to incompatibility with protic media. This is especially true for simple quinone methides (**I**, R_2=H), i.e. not bearing substituents on the methylene group, which so far have not been isolated, except in very special cases.[5]

Recently, we demonstrated that QMs can be stabilized and isolated by complexation to a late transition metal center.[6,7] The crystal structure of two *p*-QM Rh(I) complexes have been reported. However, in these complexes the QM moiety is part of a specifically designed bis-chelating PCP-type ligand and is therefore very strongly coordinated to the metal and essentially inert.

We now report on (1) a novel synthetic route that leads to the first stable simple *p*-QM complex, in which the QM is coordinated to the metal center only via the exocyclic double bond; (2) the crystal structure of this complex; and (3) the *controlled release* of the coordinated QM into solution. We demonstrate our approach by the stabilization of the biologically relevant 2,6-di-*tert*-butyl-4-methylene-2,5-cyclohexadienone (BHT-QM),[1c,8] a metabolite of the antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT), and the toxicology of which has been extensively studied.[9]

The synthetic strategy presented here is based on the fact that an η^2-methylene-coordinated *p*-QM complex can be viewed as

Scheme 1



an isomeric form of an η^1-methylene-*p*-phenoxy zwitterionic metal complex (Scheme 1). The benzyl bromide **1**[10] was synthesized by silylation of 2,6-di-*tert*-butyl-4-methylphenol (BHT) with $(Me_3Si)_2NH$[11] and bromination of the resulting silyl ether by *N*-bromosuccinimide (NBS). Serving as a BHT-QM precursor, **1** contains a benzyl bromide moiety as an anchoring point to metal centers, whereas the protecting silyl ether prevents the base-catalyzed conversion of **1** into BHT-QM.[12]

Electron-rich chelating bisphosphine palladium and platinum centers can form stable olefin complexes due to substantial back-bonding to the olefin[13] and are, therefore, good candidates for QM stabilization. Unfortunately, oxidative addition of **1** to 3- and 4-coordinated bisphosphine palladium(0) complexes proceeded with very low yields and resulted in mixtures. Therefore, we have utilized (tmeda)$PdMe_2$ (tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) which can oxidatively add benzyl bromide with elimination of C_2H_6.[14] Upon mixing (tmeda)$PdMe_2$ and **1** in cold acetone, the benzyl complex **2** was formed in 79% yield. Addition of 1,2-bis(diphenylphosphino)ethane (dppe) led to the displacement of tmeda and the bisphosphine benzyl complex **3** was quantitatively formed.

Interestingly, when **3** was treated with 1 equiv of $(n\text{-Bu})_4NF\cdot 3H_2O$ in THF, (dppe)Pd(BHT−QM) **4** was obtained in 91% yield. As shown in Scheme 2, the unobserved ammonium phenoxy intermediate formed by the Si−O bond cleavage spontaneously eliminated $(n\text{-Bu})_4NBr$ to give **4**.

The BHT-QM complex **4** was fully characterized by IR and multinuclear NMR spectroscopy, elemental analysis and X-ray crystallography. The ^{31}P NMR spectrum of **4** in C_6D_6 consists of two sharp doublets at 29.07 and 37.49 ppm (J_{PP} = 14.2 Hz), indicative of two inequivalent phosphorus nuclei in a mutual cis configuration. The upfield ^{13}C chemical shift of the two exocyclic double-bond carbons and their *J*-coupling to the two inequivalent phosphorus atoms, $\delta(CH_2)$ = 51.34 ppm (d, J_{PC} = 30.7 Hz) and $\delta(CR_2)$ = 82.28 ppm (dd, J_{PC} = 12.5 and 4.8 Hz), as well as the doublet of doublets originating from the benzylic protons in the ^1H NMR spectrum at δ_H = 3.40 ppm (J_{PH} = 7.1 and 3.8 Hz), strongly suggest that coordination takes place through the exocyclic $R_2C{=}CH_2$ group. The carbonyl carbon gives rise to a signal in the ^{13}C NMR spectrum at 183.96 ppm (br d, J_{PC} = 3.7 Hz), in the region observed for other 2,5-cyclohexadienones and quinones.[15] The carbonyl moiety exhibits a characteristic, strong IR absorption band at 1598 cm^{-1}.[1c]

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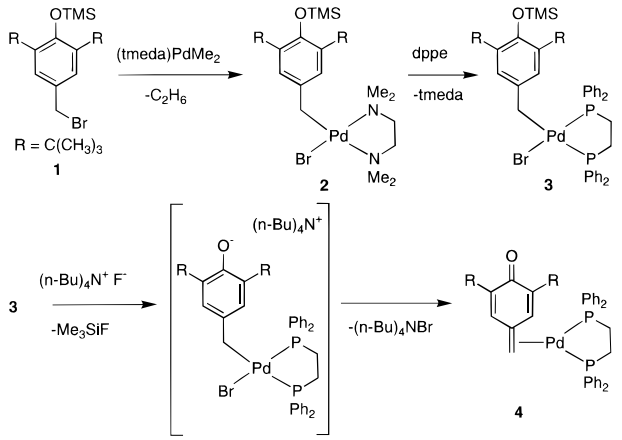
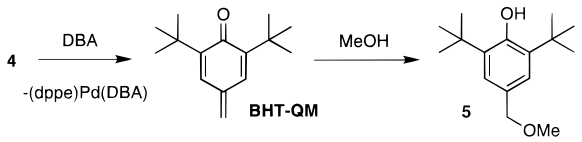
Scheme 2



Scheme 3



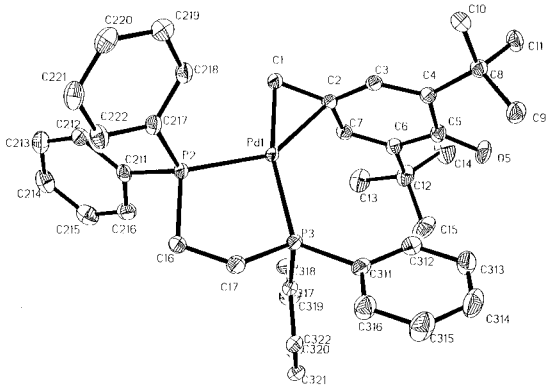


Figure 1. An ORTEP representation of the crystal structure of **4** with the thermal ellipsoids at 50% probability. Selected bond distances (Å) and angles (deg): Pd(1)−C(1), 2.088(2); Pd(1)−C(2), 2.208(2); C(1)−C(2), 1.437(2); C(5)−O(5), 1.251(2); C(2)−C(3), 1.443(3); C(3)−C(4) 1.362(2); C(4)−C(5) 1.474(3); C(5)−C(6) 1.474(3); C(6)−C(7) 1.364(3); C(2)−C(7) 1.441(2); P(2)−Pd(1)−P(3) 86.73(2); Pd(1)−C(1)−C(2) 75.06(10); Pd(1)−C(2)−C(1) 65.97(10).

Orange crystals of **4** suitable for a single-crystal X-ray diffraction study were obtained by slow diffusion of pentane into a solution of **4** in Et_2O.[16] The palladium atom lies in a trigonal planar environment, coordinated to the two phosphorus atoms and the exocyclic double bond (Figure 1).[13a] A practically negligible torsion angle of 2.78° is observed between the P(2)−Pd(1)−P(3) plane and the Pd(1)−C(1)−C(2) plane. There is no interaction between the metal and the QM ring, with the Pd(1)−C(7) distance being 2.923(3) Å. The quinonoid character of the ligand is strongly reflected in the ring bond distances with the C(3)−C(4) and C(6)−C(7) bond lengths being shorter than the rest of the C−C bonds of the ring by at least 0.077 Å. The carbonyl C(5)−O(5) distance of 1.251(2) Å is in the range reported for other quinonoid compounds.[17] The coordinated C(1)−C(2) bond is notably elongated (1.437(2) Å) compared to that of free olefins, as a result of back-donation from the metal. This is also manifested in the loss of planarity around C(2): the exocyclic methylene is bent out of the ring plane by 10.78° away from the palladium atom. Similar structural features were also observed in other P_2Pd conjugated-olefin complexes.[18]

Complex **4** is a thermally stable compound both in solution and in the solid state. No traces of decomposition were observed upon storage of a dry sample of **4** for a month under a dinitrogen atmosphere. Remarkably, **4** is stable even toward nucleophilic attack by water or MeOH and is recovered unchanged after heating in aqueous methanol at 55 °C for 10 h. As free BHT-QM is known to react immediately under these conditions,[8a] *no spontaneous dissociation* of the QM moiety from the P_2Pd fragment takes place.

The reactivity of **4** was tested with respect to ligand exchange reactions. Addition of the hard ligands acetonitrile or pyridine did not result in the release of the BHT-QM. However, when **4** was reacted with 1 equiv of DBA (dibenzylideneacetone) in a C_6D_6 solution at room temperature *instantaneous* dissociation of free BHT-QM took place, as was detected by ^{1}H NMR spectroscopy,[19] with concomitant formation of the known complex (dppe)Pd(DBA).[18c] Similarly, substitution of BHT-QM was achieved by the use of diphenylacetylene, although at a slower rate. When the substitution reactions were performed in methanol, immediate trapping of the free quinone methide by a solvent molecule took place at room temperature to give the 1,6-Michael-type addition product, 2,6-di-*tert*-butyl-4-methoxymethylphenol (**5**), as was detected by ^{1}H NMR spectroscopy and by GC-MS.[20] When CD_3OD was used as solvent, incorporation of the CD_3O group into the organic product took place. Thus, complex **4** allows *controlled release* of free BHT-QM into a solution where it can be effectively trapped by nucleophiles. This together with the high thermal stability of **4** and its compatibility with protic media can make it relevant to selective drug delivery.

In summary, for the first time a simple quinone methide was generated, stabilized, and released with the aid of a metal center. The complex formed was fully characterized (including X-ray structure analysis). It was stable even in protic solvents. A simple chemical stimulus promoted the controlled release of the quinone methide which could be trapped by reaction with nucleophiles. Studies involving other biologically relevant QMs using this approach are currently underway.

Acknowledgment. We thank Dr. L. J. W. Shimon for performing the X-ray structural analysis. This work was supported by the US−Israel Binational Science Foundation, Jerusalem, Israel, and by the MINERVA Foundation, Münich, Germany. D.M. is the holder of the Israel Matz professorial chair of organic chemistry.

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

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