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A Case of Serendipity: Synthesis, Characterization, and Unique Chemistry of a Stable, Ring-Unsubstituted Aliphatic *p*-Quinone Methide

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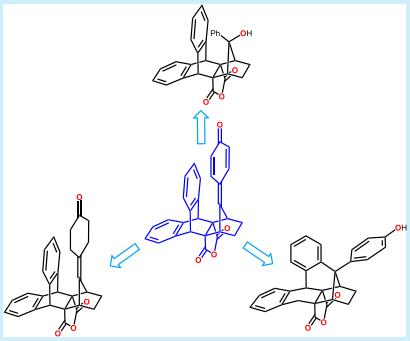
Supporting Information

ABSTRACT: We report the serendipitous synthesis of an indefinitely solution-stable ring-unsubstituted aliphatic *p*-quinone methide (p-QM) and detail its remarkable reaction chemistry through three archetypical chemical transformations: hydrogenation, hydride reduction, and nucleophilic addition. For example, the p-QM hydrogenates in a counterintuitive way; it resists all attempts at aromatization by catalytic reduction. Paradoxically, it does undergo aromatization/rearrangement upon reduction with $LiAlH_4$. Nucleophilic addition of thiol results in an unanticipated rearrangement instead of the expected 1,6-conjugate addition. We hope that this highly stable p-QM and its unique reactivity provide some new insights into the chemistry of this important class of organic molecules.



p-Quinone methides (p-QMs) are remarkable chemical species most often encountered in the biochemical realm. They and their derivatives play an important role in DNA alkylation and cross-linking,[1] in addition to serving as intermediates in organic synthesis.[2−4] Due to their importance in both biological as well as chemical processes, p-QMs have been subjected to intensive study, although they are usually unstable and exist mainly as reactive intermediates.[5] Simple aliphatic p-QMs prove to be especially unstable,[6] which means that they react quickly with just about anything in the reaction medium. Imagine instead a stable, isolable aliphatic p-QM in hand—the chemist could thus investigate interesting chemical reactivity on his own terms and his reactions of choice.

Previous attempts at the synthesis and isolation of simple p-QMs suggest that certain substitutions at the 2, 6, and 7 positions on the quinone ring are important for enhancement of stability (the simplest p-QM is naturally highly unstable) (Scheme 1). A few very select substituted forms have been synthesized and studied for their physical and chemical properties. For example, Chitwood et al. have synthesized the highly resonance-stabilized 7,7-diphenyl p-QM.[7] Hyatt synthesized and studied the chemistry of the likewise stable 7,7-dicyano p-QM.[8] Four different versions of 7-cyano-7-carboxy ester p-QMs have successfully been made and studied as stable molecules.[9] In contrast, Murray et al. observed that 7,7-bis(trifluoromethyl) p-QM is stable only below −196 °C and quickly polymerizes upon warming to room temperature.[10] This particular p-QM motif can only be stabilized by replacing hydrogens at the 2 and 6 positions with alkyl groups.[11] Generally speaking, p-QMs containing alkyl groups at the 7-position are very reactive and dimerize upon attempted isolation unless the 2 and 6 positions have bulky substituents, as observed by Cook and Norcross.[12] Additionally, stabilization of unsubstituted p-QMs using transition metals was first reported by Vigalok et al.;[13] this strategy was followed up by several other groups.[14] In general, p-QMs are most often observed as reactive intermediates unless otherwise stabilized by resonance (for example, as part of a polycyclic structure[15] or through attachment of electron-delocalizing functional groups) or transition metals. In fact, the actual "quinone methide" form may be only one of a large family of other competing resonance structures,[16] and it stands to reason that simple unsubstituted aliphatic p-QMs are generally very unstable in solution. To our knowledge, there has been no evidence of a stable aliphatic p-QM unsubstituted at the 2 and 6 positions.

The story began with the attempted synthesis of the corresponding tertiary chloride from alcohol **3**, which was in turn formed through a Grignard reaction on the known ketone **2**.[17,18] To our surprise, treatment of alcohol **3** with $SOCl_2$ and catalytic Et_3N resulted instead in demethanolation to form the quinone methide **1** (Scheme 1) as a lemon yellow solid after purification (56% yield). The downfield shift of the bridge protons near the −OH from 2.96 ppm in alcohol **3** to 3.37 ppm in the product suggested a change in hybridization of the tetrasubstituted carbon from sp^3 to sp^2. Moreover, the disappearance of methyl protons (3.74 ppm) and the hydroxyl proton (0.47 ppm) in ^1H NMR as well as the appearance of a peak around 186.1 ppm in the ^{13}C NMR of the product indicated the formation of the p-QM **1**. The UV−vis spectrum of the product showed two absorbances at 281 and 340 nm

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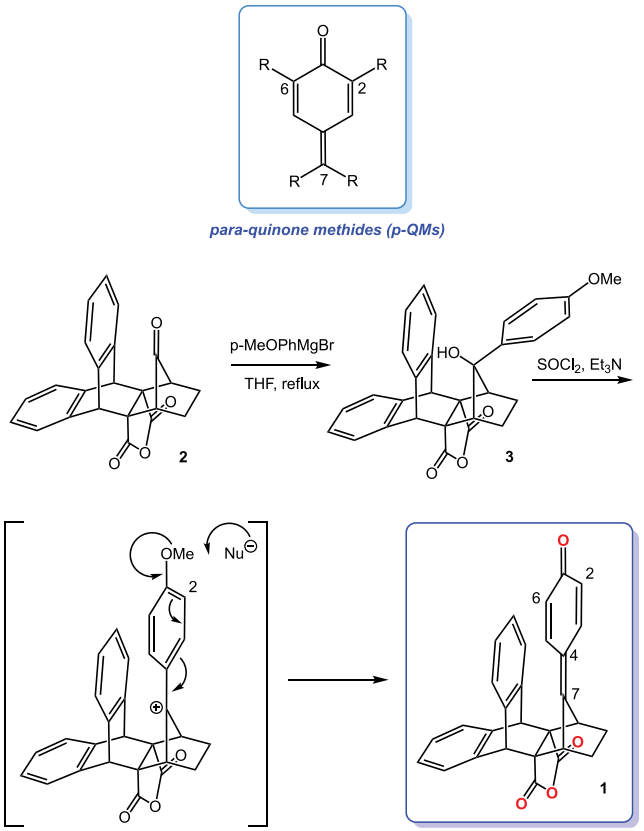
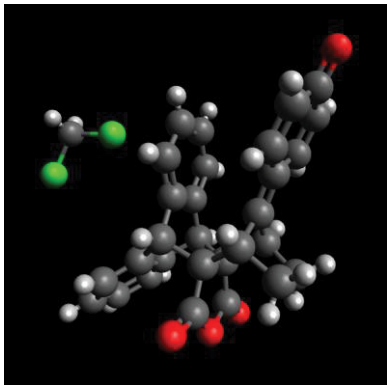
Scheme 1. Synthesis of the Aliphatic *para*-Quinone Methide (p-QM) 1 and Its Crystal Structure (Including a Molecule of the Solvent CH_2Cl_2)





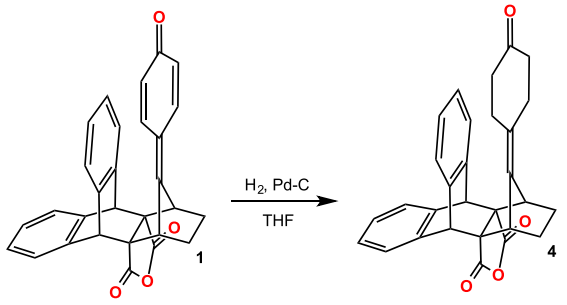
corresponding to orbital transitions on the aromatic rings and the p-QM fragment, respectively.

This demethanolation to form **1** makes sense in retrospect—the sterically hindered carbocation generated by the departure of the −OH leaving group can (for both steric and electronic reasons) only trap chloride from the backside "out" position. This process forces the aromatic rings to clash, thus adding steric strain to the system. Therefore, it is energetically favorable for the molecule to undergo the unexpected demethanolation instead to form p-QM **1**. Any process that involves the retention of aromaticity is liable to be disfavored, affording the p-QM structure stability.

Accordingly, p-QM **1** turned out to be exceptionally kinetically stable and remained intact when dissolved in various solvents such as acetonitrile and THF. Its high stability allowed us to crystallize it from CH_2Cl_2 for an X-ray structure determination (Scheme 1). A side view of the structure shows that, unlike graphene sheets in graphite,[19,20] the QM fragment and neighboring aromatic ring are not perfectly stacked but bent slightly away from each other. For example, whereas carbon 7 is roughly 2.8 Å from the plane of the neighboring aromatic ring, carbon 4 is about 3.1 Å away. Furthermore, the bond angle between the bridge carbons near the QM moiety and carbon 7 has been reduced to 98.18° in **1** which is lower than the same bond angle observed for the p-QM (114.37°) reported by Taljaard and co-workers.[21] In contrast, the bond angle between bridge carbon, carbon 7, and carbon 4 on the QM moiety is 130°, which is larger than the same bond angle in Taljaard's p-QM (122°).[21] These strained bond angles, induced by the Baeyer strain of the norbornyl cage of **1**, might explain some of the unique chemical reactivity associated with the p-QM **1** detailed below. The molecule cocrystallizes with CH_2Cl_2, whose presence is notable by a close approach of Cl to the said aromatic ring (3.62 Å).

We turned next to detailing **1**'s reaction chemistry through three archetypical chemical transformations: hydrogenation, hydride reduction, and nucleophilic addition. It did not take long to discover that **1** behaves in ways that contrast with conventional quinone methide chemistry. Typically, stable p-QMs hydrogenate through 1,6-addition in order to facilitate the formation of an aromatic ring. For example, the catalytic hydrogenation of 7,7-dicyano p-QM yields (*p*-hydroxyphenyl)-malononitrile as a result of 1,6-addition.[8] When **1** was subjected to standard catalytic reduction (H_2, Pd/C), the major product revealed regioselective hydrogenation of the two endocyclic double bonds. The reaction, which was done on milligram scales, afforded 77% crude NMR yield and 49% isolated and analytically pure product (Scheme 2, X-ray determination in Supporting Information). Isolated yields for the reactions in general are low due to the difficulty we encountered in working on very small scales.

Scheme 2. Catalytic Hydrogenation of p-QM 1



p-QM **1**'s resistance to aromatization by *catalytic* reduction led us to investigate its behavior with a strong carbonyl reducing agent. Precedent also reveals that more stabilized p-QMs generally aromatize upon $LiAlH_4$ reduction; for example, treatment of the p-QM 2,6-di-*t*-Bu-7,7-dimethyl p-QM yields 2,6-di-*t*-butyl-4-isopropenylphenol as a result of 1,6-addition.[12] Interestingly, we found that the resistance to aromatization can be overcome in this particular case. Treatment of **1** with $LiAlH_4$ resulted in rearranged alcohol **5** as the major product (70% by crude NMR, 34% isolated yield, Scheme 3) which presumably arises in the workup step, wherein water can effect rearrangement, aromatization, and trapping.

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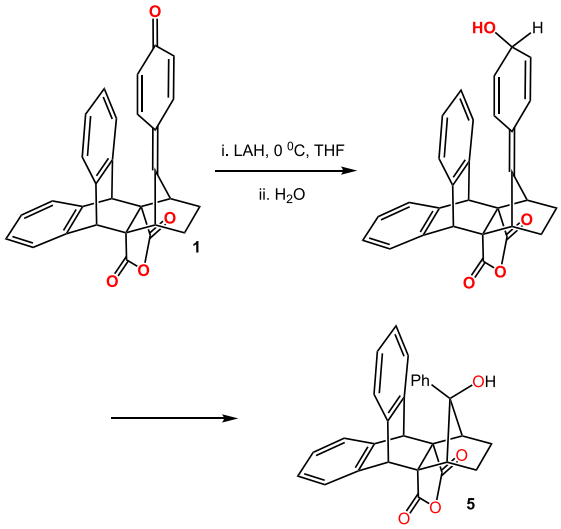
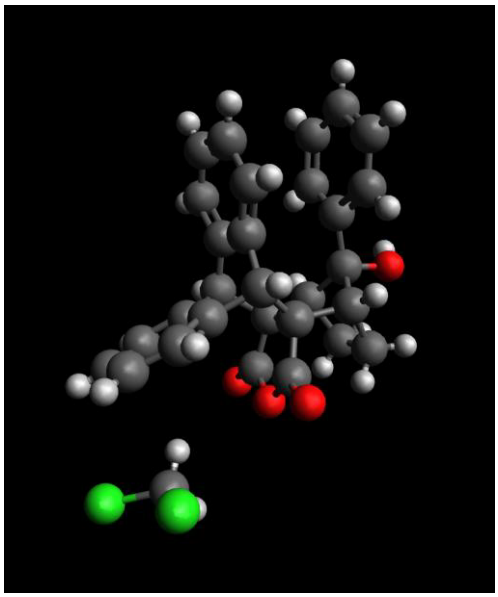
Scheme 3. $LiAlH_4$ Reduction of p-QM 1 to Afford 5[a]





[a]X-ray crystal structure of **5** (solvent molecule removed for clarity).

The appearance of aromatic protons in the range 6.85−7.00 ppm and a singlet peak for the OH proton at 0.67 ppm in the ^{1}H NMR of the product indicated that the aromatic ring is pointing inward (previous works from our group have shown that the proton peak for the OH group appears *downfield* in the negative region of the ^{1}H NMR if the OH group is pointing in).[17] The structure of **5** was also confirmed by X-ray crystallography, most notably confirming the two "pancaked" aromatic rings. In the crystal structure, **5** has lost its plane of symmetry, which is not apparent on the NMR time scale. DFT calculations (ωB97XD/6-311+G**) suggest the in−OH diastereomer to be 5.75 kcal/mol more stable than the observed out−OH (Figure 1). However, the nucleophilic attack of water on the putative cationic intermediate that forms the energetically more stable product is apparently blocked by the "stacked" aromatic ring. The closest approach of the two pancaked aromatic rings in **5** is 3.0 Å which is similar to the mean C−C distance in 2,2-cyclophanes but less than its higher homologues; for example, the distance between the neighboring aromatic rings is almost 4.0 Å for 4,4-cyclophanes.[22] Once again, the crystal incorporates a CH_2Cl_2 molecule in the unit cell; in contrast to **1**, a hydrogen

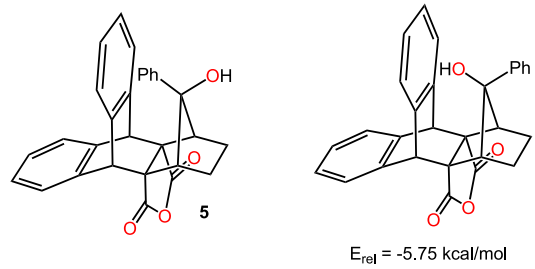
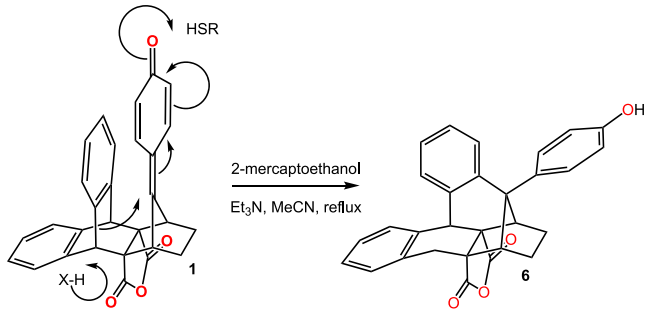


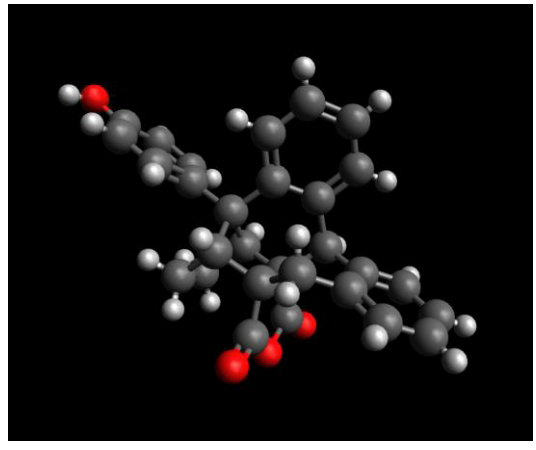
Figure 1. Relative energy of **5** and its diastereomer at ωB97XD/6-311+G**.

atom instead makes a close approach to the plane of the "bottom" aromatic ring (ca. 2.9 Å).

α,β-Unsaturated carbonyl compounds are well-known for undergoing conjugate addition reactions of all kinds;[23,24] thiols are particularly promiscuous nucleophiles for this purpose. A few p-QMs are known to react with nucleophiles through 1,6-addition to yield an aromatic product.[25,26] When **1** was treated with β-mercaptoethanol and triethylamine, it formed the aromatic ring that is expected to result from a 1,6-addition. However, rather than trapping the thiol in what would be a strain-inducing process, a skeletal rearrangement results instead (90% yield by crude NMR, 30% isolated). Presumably, protonation of the carbonyl group is followed by an attack on the adjacent aromatic ring. The resultant putative benzylic carbocation is reduced by a hydride source (either the amine or the thiol itself). The net reaction is addition of a hydrogen molecule to **1** with each H atom attaching to two spatially remote positions and *nine* heavy atoms removed from each other (Scheme 4). That the C_s symmetry of the molecule has been

Scheme 4. Thiol/Amine Reduction/Rearrangement of p-QM 1 to Form 6 and X-ray Structure of 6





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broken is evident in the more complex ^{1}H NMR (in CD_3CN) of the product. Additionally, the coupling constant (15 Hz) between the protons resonating at 2.2 and 3.1 ppm indicates that they are benzylic and geminal to each other. The product was finally confirmed by its X-ray crystal structure, which clearly reveals the rearranged skeleton and the newly installed benzylic methylene.

In conclusion, we have synthesized and characterized an indefinitely solution stable ring-unsubstituted aliphatic *p*-quinone methide **1**. It exhibits counterintuitive reaction chemistry as it resists attempts at aromatization by catalytic reduction but nevertheless aromatizes and rearranges with strong reducing agents in spite of substantial strain induction. Finally, it experiences a skeletal rearrangement upon nucleophilic addition. We hope that these findings provide some new insights into the physical and chemical properties of this important class of organic molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00615.

Synthetic procedures, characterization of new compounds, crystal structure data, mass spectra, and computational information (PDF)

Accession Codes

CCDC 1897938−1897941 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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