

THE QUINONES OF AZULENE.
EXPERIMENTAL TESTS OF THEORETICAL PREDICTIONS

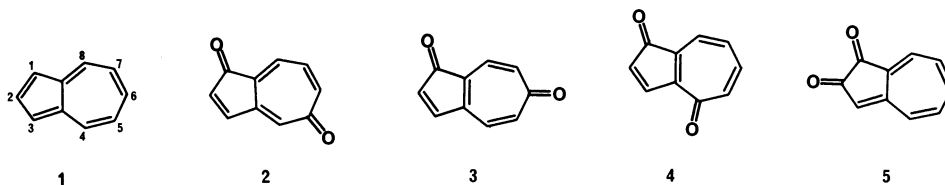
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Abstract - Before any of the eleven possible quinones of azulene were known, predictions were made about their properties on the basis of Hückel, MINDO/3, PPP and *ab initio* SCF (STO-3G) calculations (3). Four unsubstituted quinones of azulene have now been prepared, and the experimental results obtained so far provide information regarding their stability, reduction potentials, cycloadditions with cyclopentadiene, periselectivity of dimerization, and color. The accuracy of the predictions in some instances has been remarkable.

INTRODUCTION

Azulene, **1**, the oldest and most thoroughly studied of all nonbenzenoid aromatic hydrocarbons, has played a central role in the development of π -molecular orbital theory during the last 40 years (2). This classic nonalternant hydrocarbon exhibits many special properties which distinguish it from benzenoid compounds and other alternant hydrocarbons, but most of these peculiarities are presently understood reasonably well. The quinones of azulene, e.g., **2-5** (seven more isomers not shown), constitute an equally fundamental set of nonalternant nonbenzenoid quinones.



Considering the venerability of azulene and the prominence of quinone chemistry throughout history, it is surprising, however, to discover how little is known about the quinones of azulene. As recently as 1976, when these compounds first captured our interest, none of the eleven possible azuloquinones had been reported. That rare opportunity prompted us to carry out extensive calculations (Hückel, MINDO/3, PPP, and *ab initio* STO-3G) so that predictions could be made about the properties of azuloquinones before they were synthesized. This work was published in 1980 (3).

Concurrent with the theoretical studies, potential synthetic routes to several quinones of azulene were explored. It seems appropriate, in the context of the present symposium (4), to report our progress in this direction and to compare our experimental findings with the predictions based on theory. On the whole, we have been greatly impressed with the accuracy of the predictions tested thus far. Where discrepancies between the predictions and the experimental results have been found, they can usually be ascribed to some oversimplification in the theoretical treatment and, therefore, serve to identify those questions which can be answered reliably by simple theories and those which require more sophisticated theories.

Since the details of our calculations have already been published (3), we shall not repeat them here other than to discuss various conclusions drawn therefrom. Our preparative work in this area will soon be submitted for publication elsewhere (5), so we include here only selected experiments of particular relevance to the theoretical predictions. Synthetic chemists, of

course, would most like to know which (if any) of the azuloquinones will be "stable" enough to permit isolation. Although such predictions can rarely be made with great confidence, they do sometimes aid in the selection of reasonable target molecules, as the first section below illustrates.

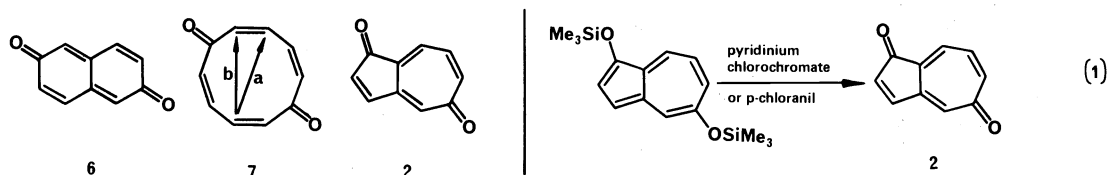
STABILITY

Of all the isomeric quinones of azulene, 1,5-azuloquinone **2** is calculated (3) to have the most negative heat of formation (ΔH_f), the most positive π -delocalization energy (π -DE), the largest energy gap between the π -HOMO and LUMO, and the highest energy LUMO (Table 1). Thus, in the thermodynamic sense, **2** should be the most stable quinone of azulene. The isolability of any compound, however, depends less on its ΔH_f than on its resistance to chemical reactions, i.e., its kinetic stability. In this regard, a large positive π -DE often imparts resistance to attack by external agents on a conjugated π system; a large HOMO/LUMO gap generally ensures a low propensity toward dimerization; and a high-energy LUMO indicates that reduction and nucleophilic attack should not be especially favorable (3). By all measures, then, the 1,5-isomer **2** should be the most stable quinone of azulene in the kinetic sense as well.

TABLE 1. Results of calculations on selected $C_{10}H_6O_2$ quinones (3)

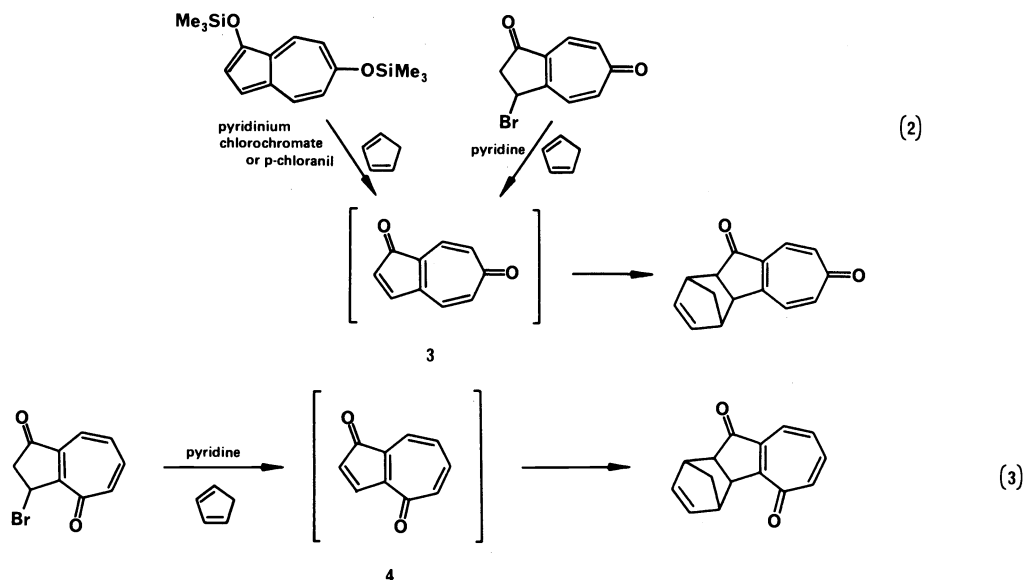
	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
ΔH_f MINDO/3 (kcal/mol)	- 6.4	-0.6	-0.8	- 0.4	-7.1
π -DE MINDO/3 (kcal/mol)	+14.7	+8.9	+9.1	+12.7	-0.7
REPE HÜCKEL (β)	- 0.002	-0.002	-0.003	- 0.001	+0.006
π -HOMO/LUMO gap MINDO/3 (ev)	8.64	7.70	7.77	7.72	8.01
π -HOMO/LUMO gap HÜCKEL (β)	0.53	0.41	0.40	0.46	0.38
π -LUMO energy MINDO/3 (ev)	- 0.63	-1.17	-1.03	- 0.70	-1.41

Will 1,5-azuloquinone **2** be isolable? To predict this we must somehow calibrate the calculations. The isomeric 2,6-naphthoquinone **6** represents an attractive standard. First prepared and isolated in 1907 by Willstätter (6), this "extended" quinone of naphthalene bears a close structural relationship to 1,5-azuloquinone **2** in that both can be viewed as derivatives of the same hypothetical [10]annulene quinone **7** (a and b, respectively). As Table 1 reveals, the azulene isomer **2** is calculated to have a more positive π -DE, a larger π -HOMO/LUMO gap, and a higher energy LUMO than the naphthalene isomer **6**. The slightly higher ΔH_f of **2** relative to **6** can be attributed entirely to angle strain in the former, so the π system of **2** actually appears to be the better one. Thus, except for the Hückel resonance energies per electron (REPES), all the calculations suggest that 1,5-azuloquinone **2** should be even more stable than the known isomer **6**, and we concluded in our 1980 article (3) that "... 1,5-azuloquinone represents a very reasonable goal for synthesis and study."



Accordingly, it gives us great pleasure to report that we have now synthesized 1,5-azuloquinone (eq 1) and found it to be a perfectly stable yellow crystalline solid. This new quinone can be sublimed at 90° C under vacuum and does not decompose or dimerize on standing for several months, either in solution or in the solid state. It is amazing that this important nonalternant quinone was not synthesized years ago.

We have also synthesized 1,6-azuloquinone 3 and 1,4-azuloquinone 4 by the reactions depicted in equations 2 and 3. As expected (3), these quinones which contain a cyclopentadienone moiety proved to be more reactive than 1,5-azuloquinone 2. They could be trapped in good yield by Diels-Alder reactions (stereochemistry not yet proven) when generated in the presence of cyclopentadiene; however, omission of the trapping agent invariably led to complex product mixtures (presumed to contain dimers, *inter alia*). The only other unsubstituted quinone of azulene presently known, 1,2-azuloquinone 5, was recently synthesized by Morita *et al* and isolated as green needles (7,8).



How good were the calculations at predicting "stability" (isolability)? The fact that quinones 2 and 5 could be isolated whereas 3 and 4 could not correlates well with the MINDO/3 π -DEs and LUMO energies and with the Hückel HOMO/LUMO gaps. By these criteria, however, all four azuloquinones 2-5 are predicted to be more stable than 2,6-naphthoquinone 6. Thus, the calculations proved more reliable for comparisons within the azuloquinone family than for predictions on an absolute scale. The prediction based on MINDO/3 HOMO/LUMO gaps that 1,2-azuloquinone 5 should dimerize as readily as the 1,6- and 1,4-isomers 3 and 4 was found to be inaccurate. A more detailed treatment of dimerization rates would take into account also the magnitudes of the relevant molecular orbital coefficients, and apparently these cannot be ignored in the present case; the observed correlation of stability with Hückel HOMO/LUMO gaps is therefore probably accidental. The Hückel REPEs predict no significant stabilization or destabilization resulting from cyclic conjugation for any of the azuloquinones 2-5, and we have no evidence to the contrary.

In sum, the MINDO/3 π -delocalization energies and the calculated LUMO energies have been found to serve as excellent indicators for the chemical stability of these quinones. Heats of formation, π -HOMO/LUMO gaps, and Hückel REPEs cannot be used with confidence for this purpose.

REDUCTION POTENTIALS

The redox properties of quinones have received considerable attention for nearly a century. On the basis of our calculations (π -LUMO energies) we predicted that azuloquinones 2-5 should all be less easily reduced (i.e., have lower reduction potentials) than the extended naphthoquinone 6 and that the reduction potentials of 2 and 5 should be even lower than that of *p*-benzoquinone (MINDO/3 LUMO $E = -1.0$ eV). Morita (7) has reported a polarographic half-wave potential of $E_{1/2} = -0.56$ V (9) for azuloquinone 5, which does indeed fall slightly below that for *p*-benzoquinone [$E_{1/2} = -0.51$ V (9, 10)]. Such precise values are not yet available for the other azuloquinones; however, the potentials of quinones 2 and 3 cannot exceed that of *p*-chloranil [$E_{1/2} = +0.01$ V (9,10)], the oxidizing agent used for their synthesis (eqs 1 and 2). Since *p*-chloranil has a lower reduction potential than 2,6-naphthoquinone 6 (11), it follows that azuloquinones 2 and 3 must also have reduction potentials below that of 6, as predicted. Thus, all the currently available experimental facts relating to the redox properties of azuloquinones stand in complete harmony with the predictions.

CYCLOADDITIONS WITH CYCLOPENTADIENE

Benzenoid quinones have long been recognized as good dienophiles, and we anticipated similar reactivity for many of the azuloquinones. The reactions illustrated in eqs 2 and 3 nicely fulfilled these expectations. Of course the whole field of cycloaddition chemistry has been revolutionized in recent years by the advent of frontier molecular orbital (FMO) theory (12); how well did this theory predict the cycloadditions of azuloquinones? Let us focus first on the question of periselectivity.

Assuming that cyclopentadiene reacts as a $\pi 4_s$ component and ignoring stereochemistry, each of the azuloquinones 2-5 could combine with cyclopentadiene by as many as four distinct [4 + 2] modes or by a [6 + 4] mode; thus, five different symmetry-allowed products are possible. According to FMO theory, the electronically preferred mode of cycloaddition will correspond to the one for which the sum of the squares of the coefficients of the azuloquinone LUMO at the atoms involved in bonding is largest. Figure 1 tabulates the relevant calculations for each dienophilic site in azuloquinones 3 and 4.

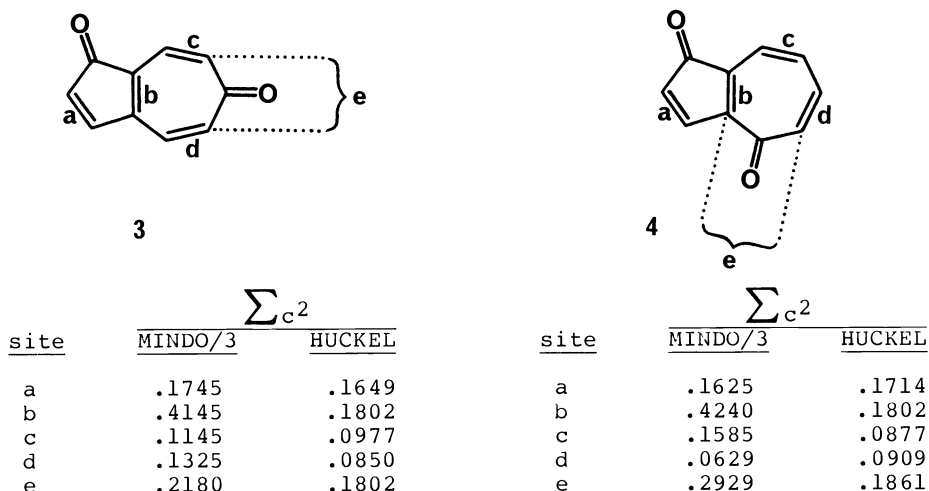
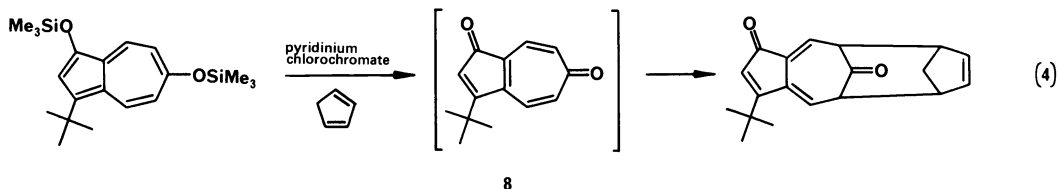


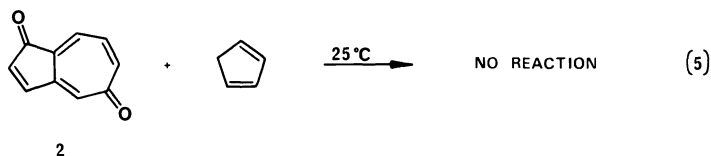
FIGURE 1. Sums of the squares of the LUMO coefficients at each $\pi 2_s$ and $\pi 6_s$ site of azuloquinones 3 and 4.

Based on these considerations, the fastest [4 + 2] cycloaddition in each case should occur at the double bond common to both rings (b). Experimentally, however, we observe only cycloaddition at site a, the second most dienophilic double bond in each quinone (eqs 2 and 3). Of course the FMO treatment does not take into account steric effects, and these may well explain the lower reactivity of bond b. The observed preference for cycloaddition at bond a over cycloaddition by the [6 + 4] mode (e) for both azuloquinones 3 and 4 likewise contradicts the theoretical predictions, but this discrepancy cannot be rationalized so easily. Such [6 + 4] cycloadditions are perfectly reasonable, as the reaction in eq 4 demonstrates. In this case, a bulky t-Bu group retards the [4 + 2] cycloaddition at bond a and forces the reaction to follow an alternative course.



How can we explain this apparent violation of theory? At least two possibilities deserve consideration: 1) Perhaps the MINDO/3 and Hückel calculations give LUMO coefficients which do not reflect the true electronic nature of azuloquinones 3 and 4; with a "better" set of coefficients, FMO theory might predict the correct products. 2) Perhaps the energetics of these cycloaddition reactions depend on more factors than just FMO interactions and steric effects. In either case, the failure could be attributed to an over-simplified theoretical treatment.

Finally, we should mention that 1,5-azuloquinone 2 does not react with cyclopentadiene to a perceptible extent under conditions employed for trapping the isomeric quinones 3 and 4 (eq 5). Such a lack of dienophilic reactivity correlates well with the relative LUMO energies of 2, 3 and 4. A comparatively low dienophilicity is also predicted for 1,2-azuloquinone 5; however, no experiments have yet been reported which bear on this point.



PERISELECTIVITY OF DIMERIZATION

Many unstable molecules, e.g., cyclobutadiene, pentalene, cyclopentadienone, etc, dimerized too rapidly to permit their isolation under normal laboratory conditions, and we have long suspected that the instability of azuloquinones 3 and 4 may likewise result from rapid dimerization. Although we have not yet succeeded in isolating and characterizing any azuloquinone dimers, it was our hope that the t-Bu group in quinone 8 might suppress dimerization and thereby permit isolation of a simple 1,6-azuloquinone derivative. Stabilization of the highly reactive compounds mentioned above by such "steric protection" has proven exceedingly effective (13). Unfortunately, the t-Bu derivative 8 does not enjoy appreciably greater stability than the parent quinone 3 and could only be trapped as a transient species (eq 4).

Simple theoretical considerations provide a plausible explanation for failure of the t-Bu group in 8 to confer additional stability. FMO theory predicts that the 1,6-azuloquinones 3 and 8 should dimerize preferentially via the [6 + 4] mode depicted in Fig. 2. Clearly the t-Bu group in 8 could not exert much influence on the rate of such a reaction. It remains to be seen whether or not t-Bu groups in other positions can better stabilize 1,6-azuloquinone.

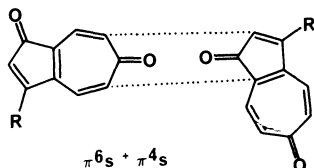


FIGURE 2.

Predicted mode of dimerization for azuloquinones 3 (R = H) and 8 (R = t-Bu).

COLOR

From the $\pi\pi^*$ transition energies calculated by the PPP π -electron method, we predicted (3) that 1,5-azuloquinone 2 should be yellow with a long wavelength $\pi\pi^*$ λ_{\max} at 371 nm. Experimentally we have found that this quinone is indeed yellow with a long wavelength λ_{\max} at 373 nm. Such spectacular agreement between theory and experiment obviously cannot be ascribed entirely to the strength of the PPP method, especially since the calculations ignored $n\pi^*$ transitions. Nonetheless, we were reasonably confident that 1,5-azuloquinone 2 would appear yellow, and that advanced knowledge proved valuable in the synthesis and isolation of this previously unknown compound. The isomeric 1,2-azuloquinone 5 was predicted (3) to be blue-green in color with λ_{\max} at 572 and 397 nm. In fact, this compound crystallizes as "green needles" and exhibits long wavelength absorption maxima at ca. 594 and 386 nm (7). The 594 nm band extends over a very broad region and tails out beyond 800 nm. Again the calculations gave a reasonably accurate prediction of the color. The success of the PPP π -electron method in predicting the long wavelength absorption maxima of quinones 2 and 5, which differ by more than 200 nm, engenders confidence in the predictions of colors for the other azuloquinones.

CONCLUSIONS

Since our original theoretical prognosis (3), four of the eleven quinones of azulene have been synthesized (2 - 5). The calculations correctly predicted that 1,5-azuloquinone 2 would be isolable and that the 1,6- and 1,4-isomers 3 and 4 would be less stable, i.e., more reactive. The fact that 1,2-azuloquinone 5 could be isolated, whereas 3 and 4 could not, revealed the relative reliability of various molecular orbital criteria for predicting the "chemical

stability" of such systems. All the observed redox properties of these azuloquinones were correctly predicted, as were the colors of the two isolable quinones 2 and 5. In fact, we found no serious discrepancy between the original calculations and subsequent experiments except for the periselectivity exhibited by 3 and 4 in their cycloaddition reactions with cyclopentadiene.

From the pragmatic perspective, the calculations showed us which azuloquinones represented the most reasonable targets for synthesis and told us what colors they would be. They also helped in the choice of oxidizing agents and will guide our attempts to stabilize the more reactive azuloquinones by the judicious incorporation of t-Bu groups. Clearly molecular orbital theory and organic synthesis can no longer be regarded as independent branches of chemistry.

ACKNOWLEDGMENTS

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