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Molecular orbital study of the oxidation of steroidal phenols into quinols and epoxyquinols

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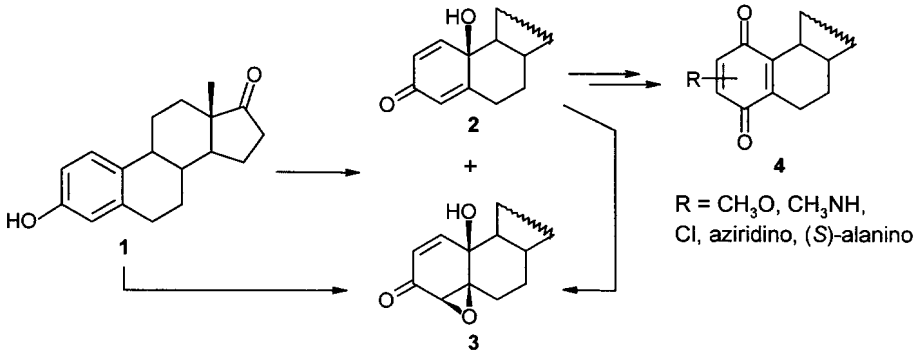
The MO study showed that the radical oxidation of phenols into quinols occurs readily. Further radical oxidation (in the *m*-CPBA / $(BzO)_2$ /*hv* system) of quinols occurs through appropriate biradical species with an activation energy of 79.5 kJ/mol yielding *syn*-epoxyquinols. The stereochemical outcome presented in this study is in full agreement with the experimental results.

Keywords: steroids, phenols, quinols, epoxyquinols, oxidation MNDO-PM3 study.

INTRODUCTION

During the synthesis of the steroidal quinones **4** (Scheme 1), it was found that the phenols **1** can be transformed into the quinols **2** and epoxyquinols **3** using *m*-chloroperoxybenzoic acid (*m*-CPBA) as on oxidant.[1,2] It was shown that the



Scheme 1.

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transformations **1** → **2** + **3** occur by a radical mechanism yielding *m*-chlorobenzoic acid in 96 % yield (on a 15 g scale).[1] The epoxidation reaction **2** → **3** was also found to be a radical one since it does not occur without an initiator and is inhibited in an O_2 atmosphere.

In order to provide further support to our findings, the results of an MO study of the transformations of phenol-to-quinol and quinol-to-epoxyquinol are presented in this paper.

METHOD OF CALCULATION

The structures of the compounds were built by PC MODEL, version 4.0,[3] that involves an MMX force field,[4] and were saved as MOPAC files for PM3 semiempirical calculations.[5]

The MNDO-PM3 method, that has been proved to be highly reliable for investigating the molecular properties of molecules and radicals,[6,7] and MOPAC program package, version 7.01, were used. The geometries of all the molecular species correspond to energy minima in vacuum, and were optimized by the PM3 method. The transition states for all the reactions were located using the corresponding MOPAC facilities (TS, SADDLE). The obtained structures were refined with NLLSQ when needed, and the transition states were proved by vibrational analysis showing only one negative vibration.

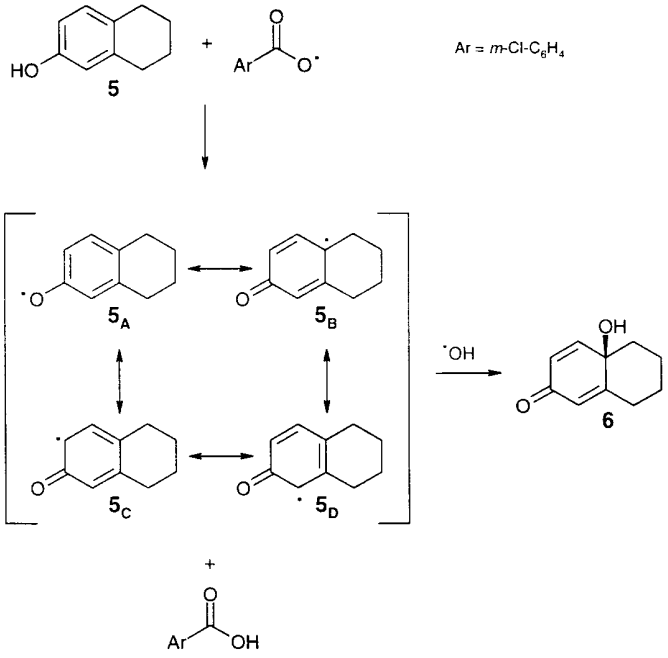
RESULTS AND DISCUSSION

In order to make the most detailed correlation with experimental results, the corresponding 6-hydroxy-1,2,3,4-tetrahydronaphthalene **5** was used instead of steroidal phenol (Scheme 2). Both radicals, •OH and *m*-Cl-C_6H_4COO•, participating in this reaction were generated from *meta*-chloroperoxybenzoic acid (*m*-CPBA) under the influence of a radical initiator, benzoyl peroxide, and light.[1,2*]

The extensive calculations were performed by means of the MNDO-PM3 method, involving the starting compounds, all products and radical intermediates, given in Schemes 2 and 3. The energies of the most stable conformations of the starting compound **5**, intermediates $\mathbf{5_{A–D}}$ and **6A–C**, as well as products **6,7** and **8**, are presented in Table I.

In the first step the reactive species, the *m*-Cl-C_6H_4COO• radical, abstracts the phenol hydrogen atom (ArO-**H**) giving the corresponding radical $\mathbf{5_{A–D}}$. This radical can be described as a superposition (linear combination) of four wave functions. On the basis of the spin densitiy distribution, the wave function $\mathbf{5_B}$ has the greatest weight. Calculation of the reaction trajectory for the attack of the *m*-Cl-C_6H_4COO• radical on the phenol group of compound **5** does not reveal any transition state. The formation of intermediate $\mathbf{5_{A–D}}$ is an exothermic process, and

* It has been confirmed that *m*-CPBA decomposes much faster (*ca.* six times) in the presence of 10 % $(BzO)_2$ under the reaction conditions applied.



Scheme 2.

no activation energy is needed. Based on this finding, it can be concluded that the first step of the reaction is very fast.

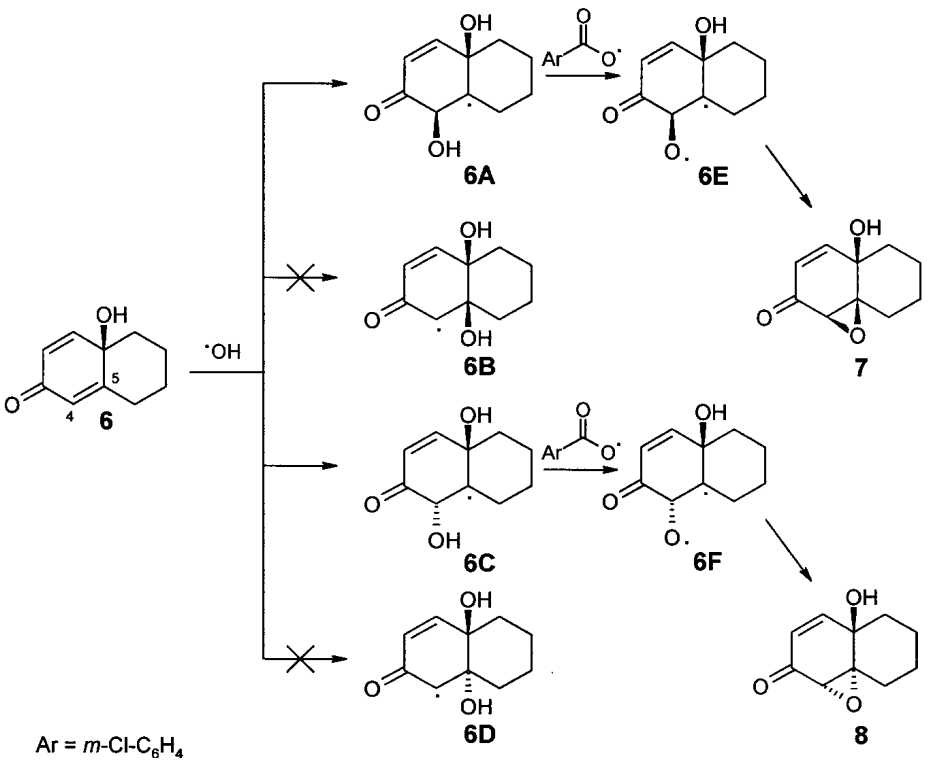
TABLE I. Heats of formation for the products and intermediates [kJ/mol]

Molecular species	ΔH_f	Molecular species	ΔH_f	Molecular species	ΔH_f	Molecular species	ΔH_f
5	–171.1	**6A**	–410.5	**6D**	–383.3	**7**	–331.0
$5_{A–D}$	–72.4	**6B**	–397.5	**6E**	–255.5	**8**	–321.3
6	–257.7	**6C**	–405.4	**6F**	–63.6		

Next step of this reaction, the approach of the two radical moieties (**$5_{A–D}$** and •OH), proceeds smoothly giving the product **6**. Calculation of a reaction trajectory for this attack does not reveal any transition state. The formation of compound **6** from radical **$5_{A–D}$**, by the approach to the β-side, is thermodynamically strongly favoured because of the larger steric congestion at the α-side.

For the next step it was assumed that an •OH radical is the reactive species which attacks the C_4–C_5 double bond* in compound **6**. Carbons C_4 and C_5 can be attacked from either the α- of β-side. The approach of two reacting species would proceed giving intermediates **6A-6D** (Scheme 3).

* Steroid numbering.



Scheme 3.

As expected, the calculations showed that attack at C_5 is unfavourable for two reasons. Access to C_5 from α-side is impossible because of steric bulk near the reactive site. For this reason intermediate **6D** is not further considered. The approach to the β-side (intermediate **6B**) is energetically less favoured as compared to **6A** and **6C** as it is higher in energy by 13 and 8 kJ/mol, respectively. For this reason, the intermediate **6B** is also excluded from the discussion below.

The arguments presented above indicate that the approach of an OH radical to C_4 is preferred to the C_5 attack. The calculations also show that the β-attack of C_4 is favoured over the α-attack by 5.0 kJ/mol, corresponding to a 6.4 times faster formation of the 4α-intermediate **6A**. This calculation indicates the formation of the β-epoxy compound **7** as the major product, which is in good agreement with the experimental data.[1,2]

The final step is the ring closure reaction of **6A**(→**7**) or **6C**(→**8**). Two possibilities were anticipated (Scheme 3): a) *H*-OC(4) abstraction by a *m*-Cl-C_6H_4COO· radical followed by the collapse of the formed biradical **6E**. b) Formation of protonated epoxide (**7**H•) followed by hydrogen abstraction. It was found that the corresponding transition states differ by 150.5 kJ/mol: a) $E_{a\mathbf{6A}\rightarrow\mathbf{6E}}$ = 79.5 kJ/mol, b) $E_{a\mathbf{6A}\rightarrow\mathbf{7H}\bullet}$ = 230 kJ/mol (structure **7**H• is actually the transition state for the conversion **6A** to **6B**) and, consequently, it is proposed that the epoxyquinol

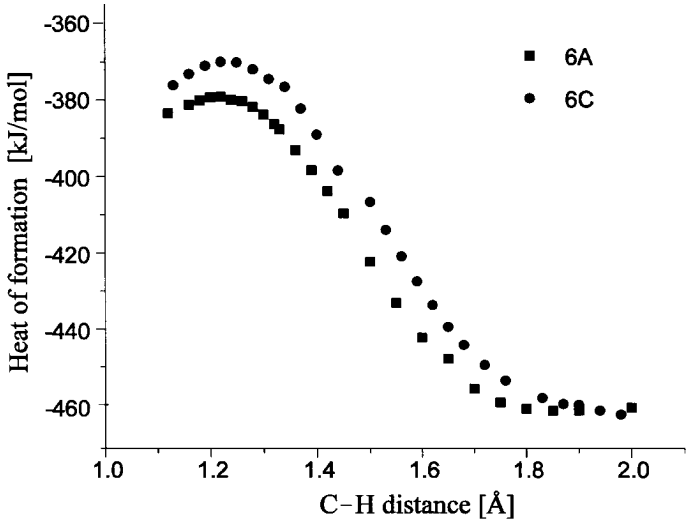


Fig. 1. Energy profile for hydrogen abstraction from **6A**(→**6E**) and **6C**(→**6F**) by *m*-Cl-$C_6H_4COO^{\cdot}$ radicals.

oxirane ring formation (from quinol, by *m*-CPBA) proceeds through biradicals **6E** or **6F***. In addition, the formation of only the *cis*-isomer of epoxyquinol is also the consequence of the surplus activation energy difference of 10.9 kJ/mol in favour of

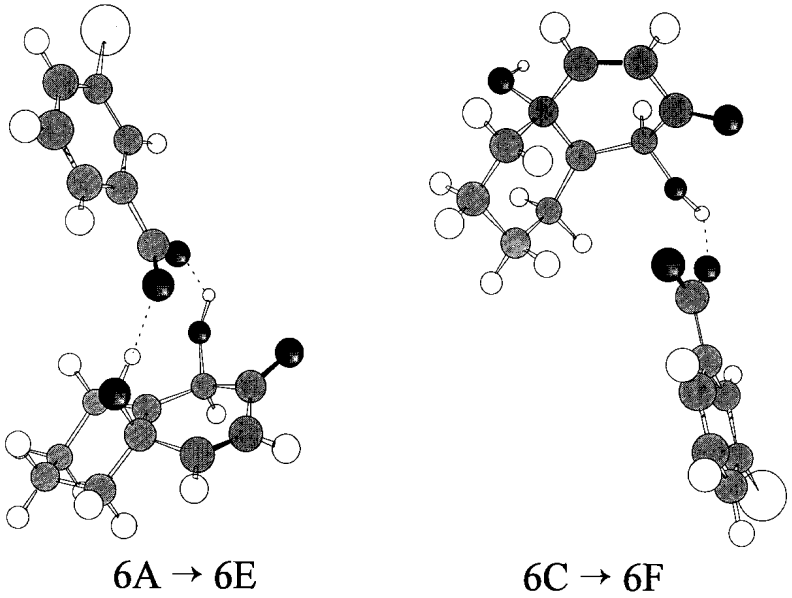


Fig. 2. The transition state geometry for **6A**→**6E** and **6C** →**6F** abstractions.

* No activation energy for the collapse of the biradical.

the **6A** → **6E** → **7** process ($E_{a\mathbf{6A}\rightarrow\mathbf{6E}}$ = 79.5 kJ/mol; $E_{a\mathbf{6C}\rightarrow\mathbf{6F}}$ = 90.4 kJ/mol). The ΔE_a of 10.9 kJ/mol (Fig. 1), taken together with the preferred formation of **6A** as compared to **6C** is in good agreement with the experimental results. The transition states of the two reaction pathways are shown in Fig. 2. It is obvious that the α-approach is facilitated by hydrogen bonding with the C(10)-β-OH group.

CONCLUSION

In the presented MO study it was shown that the radical oxidation of phenols to quinols (**5** → **6**) is the favoured reaction pathway. The radical epoxidation reaction of quinol **6** occurs through appropriate biradical species with an activation energy of 79.5 kJ/mol, yielding *syn*-epoxyquinol **7**.

The stereochemical implications resulting from this study are in full agreement with the experimental results. Corollary, the MO calculations confirm that free-radical mechanism is a reasonable explanation of experimental findings.

И З В О Д

МОЛЕКУЛСКО-ОРБИТАЛНО ПРОУЧАВАЊЕ ОКСИДАЦИЈЕ ФЕНОЛА У ХИНОЛЕ И ЕПОКСИХИНОЛЕ

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Молекулско-орбиталним проучавањем потврђено је да лако долази до радикалске оксидације фенола у одговарајуће хиноле. Даљом оксидацијом системом *m*-CPBA/$(BzO)_2$/hν хиноли се преко бирадикалских реакционих врста оксидују у одговарајуће епоксихиноле. Израчунато је да активациона енергија ове реакције износи 79.5 kJ/mol. Стереохемијске последице наших израчунавања су у потпуном складу са експерименталним резултатима.

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