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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · DECEMBER 2002

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# Kinetic and Thermodynamic Stability of Naphthalene Oxide and Related Compounds. A Comparative Microcalorimetric and Computational (DFT) Study

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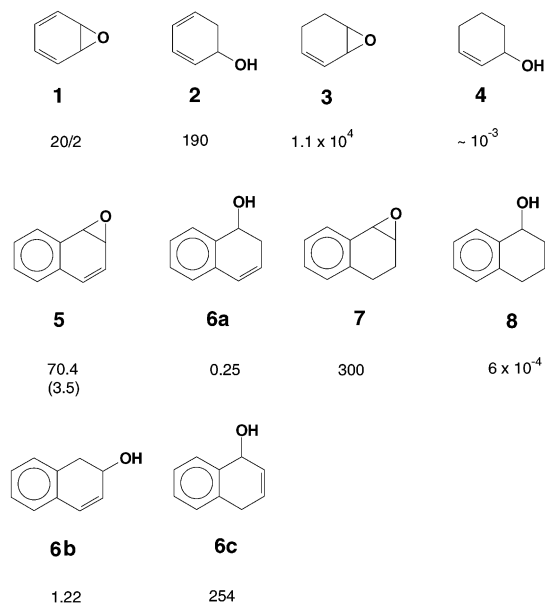
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Received May 22, 2002

The kinetics of the acid-catalyzed ring opening of naphthalene 1,2-oxide (**5**) in highly aqueous media to give naphthols has been measured by heat-flow microcalorimetry. The reaction enthalpy of this aromatization reaction was measured as  $\Delta H = -51.3 \pm 1.7$  kcal mol<sup>-1</sup>. The unexpectedly low reactivity of naphthalene oxide is suggested to be due to an unusually large thermodynamic stability. A crude estimate of the stabilization effect,  $\sim 1$  kcal mol<sup>-1</sup> (not a significant stabilization), is obtained by using the measured reaction enthalpies of structurally related substrates as references. A larger value (2.7 kcal mol<sup>-1</sup>) was obtained by calculation using the B3LYP hybrid functional corrected with solvation energies derived from semiempirical AM1/SM2 calculations. The origin of this effect is discussed in terms of homoconjugative stabilization and homoaromaticity. There is a good linear correlation (with slope = 0.63) between the experimentally measured free energy of activation and the calculated enthalpy of carbocation formation in water.

## Introduction

Aromatic hydrocarbons undergo metabolism through arene oxides. These oxidized products are known intermediates in the metabolic reaction path leading to carcinogenic aromatic diol epoxides that are known to react with nucleic acids.<sup>1</sup> These reactive species are therefore of great biochemical interest.<sup>2–5</sup> Surprisingly, the reactivity of benzene oxide and other arene oxides toward acid-catalyzed ring opening is relatively low compared to the reactivities of structurally related compounds which do not undergo aromatization (Figure 1).<sup>6,7</sup> Thus, the acid-catalyzed ring opening of the cyclohexadiene oxide (**3**) is 7 orders of magnitude faster than the acid-catalyzed dehydration of cyclohexenol (**4**), in sharp contrast to



**FIGURE 1.** Second-order rate constants for acid-catalyzed carbocation formation in water (compounds **1–4** and **8**) and in 25 vol % glycerol in water (compounds **5–7**) at 25 °C. The rate constant for formation of 2-naphthol (via the  $\alpha$ -cation) is given within brackets.

benzene oxide (**1**), which is about 1 order of magnitude less reactive than benzene hydrate (**2**). Similarly, the reaction of naphthalene oxide (**5**) to give 2-naphthol through the  $\alpha$ -carbocation is only about 14 times faster than the naphthalene hydrate **6a**, but carbocation formation from 1,2-dihydronaphthalene oxide (**7**) is  $5 \times 10^5$

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**TABLE 1. Rate Constants and Heats of Reaction for the Reactions of 1–8 at 25 °C (Scheme 1)**

solvent <sup>a</sup>	10 <sup>6</sup> <i>k</i> <sub>obs</sub> , s <sup>−1</sup>	<i>k</i> <sub>H</sub> , M <sup>−1</sup> s <sup>−1</sup>	<i>P</i> <sub>0</sub> , μW	Δ <i>H</i> , kcal mol <sup>−1</sup>	ΔΔ <i>H</i> , <sup>g</sup> kcal mol <sup>−1</sup>
Benzene Oxide (1) → Phenol <sup>7</sup>					
glycerol–water <sup>b</sup>		~22		−57.0	−18.3
Benzene Hydrate (2) → Benzene <sup>7</sup>					
glycerol–water <sup>c</sup>		58		−38.7	
1,3-Cyclohexadiene oxide (3) → (1-hydroxy-1,3-cyclohexadiene) <sup>7</sup>					
MeCN–water <sup>d</sup>				−23.7	−24.9 <sup>i</sup>
2-Cyclohexenol (4) → 1,3-Cyclohexadiene <sup>7</sup>					
water <sup>e</sup>		~10 <sup>−3</sup>		~0	
Naphthalene 1,2-Oxide (5) → Naphthols					
glycerol–water <sup>f</sup>	11080	70.4 (3.5) <sup>o</sup>			
MeCN–water <sup>g</sup>	129 ± 4		33	−51.3 ± 1.7 (−52.2) <sup>h</sup>	−29.7 (−30.6) <sup>h</sup>
1-Hydroxy-1,2-dihydronaphthalene (6a) → Naphthalene					
glycerol–water <sup>j</sup>	3043	0.25			
glycerol–water <sup>j</sup>	235	0.25	24	−21.6 ± 0.6	
MeCN–water <sup>k</sup>	134 ± 4	0.030	33	−21.6 ± 0.6	
2-Hydroxy-1,2-dihydronaphthalene (6b) <sup>16</sup> → Naphthalene					
glycerol–water <sup>b</sup>		1.22		−18.4	
1-Hydroxy-1,4-dihydronaphthalene (6c) <sup>16</sup> → Naphthalene					
glycerol–water <sup>b</sup>		254		−23.7	
1,2-Dihydronaphthalene Oxide (7) → 11					
glycerol–water <sup>l</sup>	6414	300			
glycerol–water <sup>m</sup>	283		27	−25.6 ± 1.2	−31.6 <sup>p</sup>
1-Hydroxy-1,2,3,4-tetrahydronaphthalene (8) → 14					
glycerol–water <sup>n</sup>	6.4	6.4 × 10 <sup>−6</sup>	~ 0	0 ± 2.0	

<sup>a</sup> The buffer concentrations and pH values: before mixing with the organic cosolvent. <sup>b</sup> 25 vol % glycerol in water. <sup>c</sup> 50 vol % glycerol in water. <sup>d</sup> 50 vol % acetonitrile in water. <sup>e</sup> In water. <sup>f</sup> 25 vol % glycerol in water, acetate buffer; *k*<sub>0</sub> = 1.3 × 10<sup>−3</sup> s<sup>−1</sup> (eq 1). <sup>g</sup> 50 vol % acetonitrile in water, 0.10 M acetate buffer pH 3.85. <sup>h</sup> Enthalpy for the reaction to give 2-naphthol estimated by using the calculated energy difference (0.9 kcal<sup>−1</sup> mol<sup>−1</sup>) between 1- and 2-naphthol. <sup>i</sup> 25 vol % glycerol in water, perchlorate buffer pH 1.92; kinetics were studied by UV spectrophotometry. <sup>j</sup> 25 vol % glycerol in water, perchloric acid buffer pH 3.03. <sup>k</sup> 50 vol % acetonitrile in water in water, perchloric acid buffer pH 2.35. <sup>l</sup> 25 vol % glycerol in water, 0.10 M acetate buffer, *k*<sub>0</sub> = 154 × 10<sup>−6</sup> s<sup>−1</sup> (eq 1). <sup>m</sup> 25 vol % glycerol in water, 0.10 M phosphate buffer pH 6.23. <sup>n</sup> 50 vol % glycerol in water, 2.00 M perchloric acid. Rate constant measured with UV spectrophotometry. <sup>o</sup> Rate constant for formation of 2-naphthol. <sup>p</sup> Including the enthalpy of dehydration to give 13, calculated as −6.0 kcal mol<sup>−1</sup> (Scheme 1). <sup>q</sup> Relative to the corresponding hydrate.

times faster than from 1,2,3,4-tetrahydro-1-naphthol (8). All these reactions have been concluded to be subject to specific acid catalysis and to proceed through carbocation intermediates.<sup>6–8</sup>

The low reactivity of arene oxides has been proposed to be due to an exceptionally large thermodynamic stability of these compounds.<sup>6</sup> This stability, which has been attributed to homoaromaticity, is of considerable interest in connection with studies of liver enzyme metabolism of aromatic compounds and their possibility to provide dihydrodiols and glutathione adducts.<sup>4</sup> Recent work supports the hypothesis that benzene oxide has an additional ground-state stabilization. Thus, we have estimated the extra stabilization energy for benzene oxide to be ca. 7 kcal mol<sup>−1</sup> in a combined heat-flow microcalorimetric and computational study.<sup>7</sup>

We have now performed a similar study for naphthalene oxide (5) to determine the effect of benzoannulation on the reactivity and reaction heats. The measured low reactivity of this compound suggests an additional ground-state stabilization of about 6 kcal mol<sup>−1</sup>, which in the present work is compared with estimated stabilization energies based upon measured reaction heats and calculations.

## Results

**Synthesis.** Naphthalene 1,2-oxide (5) was prepared from 1,2-dihydronaphthalene in a three-step procedure according to the method by Yagi and Jerina.<sup>9</sup> The same precursor was used for preparation of 1,2-dihydronaphthalene oxide (7).<sup>10</sup> The starting material for the four-step synthesis of 1-hydroxy-1,2-dihydronaphthalene (6a) was α-tetralone.<sup>11</sup>

**Kinetic and Calorimetric Measurements.** All reactions, except the reaction of 1,2,3,4-tetrahydro-1-naphthol (8), produce large amounts of heat (Table 1) and are easily followed by heat-flow microcalorimetry. The details of the calorimetric measurements are given in the experimental part.

The reaction of naphthalene 1,2-oxide (5) is fast in 25 vol % glycerol in water at 25 °C, and the kinetics were therefore only studied by UV spectrophotometry (Table 1). The reaction has been studied previously in water and in 10 vol % dioxane in water, respectively.<sup>8,12</sup> Slower reaction conditions were required for studies with our

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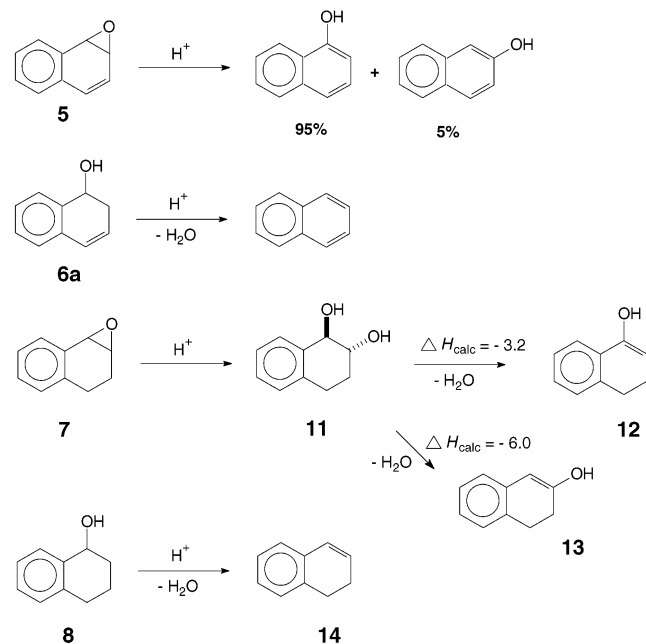
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## SCHEME 1



heat-flow microcalorimeter equipment. Therefore, 50 vol % acetonitrile in water was used as solvent (Table 1). The reaction yields 95% of 1-naphthol and 5% of 2-naphthol (Scheme 1). The kinetics of the reactions involves an uncatalyzed path and a specific acid-catalyzed path according to:

$$k_{\text{obs}} = k_0 + k_H[H^+] \quad (1)$$

The measured second-order rate constant, based upon the observed rate constants in 25 vol % glycerol in water given in Table 1, is  $k_H = 70.4 \text{ M}^{-1}\text{s}^{-1}$  at 25 °C. The uncatalyzed path has a rate constant of  $k_0 = 1.3 \times 10^{-3} \text{ s}^{-1}$ .

The cleavage reaction of 1,2-dihydronaphthalene oxide (7) in 25 vol % glycerol in water gives a mixture of diols with the trans 1,2-diol (11) as the main product (Scheme 1). The rate constants in aqueous solution at 25 °C and 30 °C and product composition of diols (94% trans and 6% cis) have been reported previously.<sup>13,14</sup> The kinetics is in accord with eq 1. To obtain the reaction heat for the production of the mono-hydroxy substituted compounds (Scheme 1), the calculated dehydration enthalpies ( $-21.7 - (-18.5) = -3.2$  and  $-24.5 - (-18.5) = -6.0$  kcal  $\text{mol}^{-1}$ , respectively, Table 1) were used to correct the measured value.

The dehydration of 1-hydroxy-1,2-dihydronaphthalene (6a) has been studied in aqueous acetonitrile and in aqueous glycerol (Table 1). The kinetics of the dehydration has been studied previously in aqueous solution.<sup>4</sup> Table 1 also shows previously reported reaction heats for the two other naphthalene hydrate isomers 6b and 6c.<sup>15</sup>

The second-order rate constants for the acid-catalyzed reactions of compounds 1–4 and 8 in water,<sup>6</sup> and of

compounds 5–7 in aqueous glycerol (this work, Table 1), are shown in Figure 1.

The rate constant for 8 refers to the carbocation formation measured in aqueous trifluoroethanol extrapolated to water.<sup>16</sup> A very similar value is expected for 25% glycerol in water. Carbocation formation is not rate limiting so the rate of product formation is smaller (Table 1). The equilibrium constant has been measured in aqueous solution at 25 °C as  $[14]_{\text{eq}}/[8]_{\text{eq}} = 22$ .<sup>17</sup>

**Calculations.** The thermodynamics of the reactions depicted in Scheme 1, including the intermediate carbocations, was calculated using the Gaussian 98 program<sup>18</sup> and the B3LYP hybrid functional<sup>19</sup> along with the continuum solvation method AM1/SM2<sup>20</sup> in Spartan<sup>21</sup> (see the Experimental Section for more details). The results are given in Tables 2 and 3.

## Discussion

The acid-catalyzed aromatization of naphthalene oxide (5) has been the subject of several mechanistic studies.<sup>8,12,22</sup> There seems to be a consensus that the ring-opening is subject to specific acid catalysis and proceeds through carbocation intermediates (Scheme 2). The reaction, which is analogous to that of benzene oxide, involves a rate-limiting cleavage of one of the carbon–oxygen bonds to give a carbocation that rapidly loses a hydron to give naphthol. This final aromatization step may be preceded by a hydride shift (NIH shift). There is direct evidence of the cation character of the transition state of acid-catalyzed epoxide ring-opening reactions.<sup>8,22–24</sup> There is also a noncatalyzed reaction path (eq 1), but that is not the subject of the present study.

The carbon–oxygen bond cleavage of unsymmetrical arene oxides, such as naphthalene oxide, yields generally two isomeric cations. The product composition is expected to reflect the relative stabilities of the  $\alpha$ - and  $\beta$ -carbocations. The ratio decreases by benzoannellation adjacent ( $\alpha$ ) to the cation center from a  $k_\alpha/k_\beta$  ratio of 1.0 for the symmetrical benzene oxide to  $k_\alpha/k_\beta = 0.05$  for naphthalene oxide (Table 1), and 1,2-anthracene oxide shows an even lower ratio.<sup>6a</sup> This effect has been rationalized by less resonance stabilization owing to the benzoannellation

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**TABLE 2.** Calculated Enthalpies of the Reactions of 1–8 Using B3LYP/6-311+G\*\*//B3LYP/6-31G\*

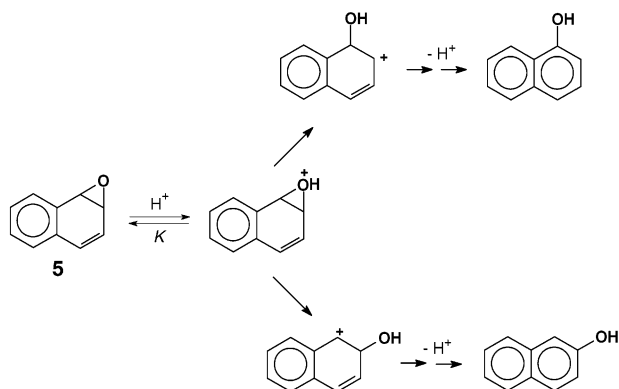
substrate	product	$\Delta H_i^a$ kcal mol <sup>-1</sup>	$\Delta\Delta H_i$ kcal mol <sup>-1</sup>	$\Delta H_i^b$ kcal mol <sup>-1</sup>	$\Delta\Delta H_i^b$ kcal mol <sup>-1</sup>
1 <sup>7</sup>	phenol	-48.0	-18.2	-49.8	-17.7
2 <sup>7</sup>	benzene	-29.8		-32.1	
3 <sup>7</sup>	1-hydroxy-1,3-cyclohexadiene	-17.6	-22.8	-19.7	-23.1
4 <sup>7</sup>	cyclohexadiene	+5.2		+3.4	
5	1-naphthol	-37.9		-38.9	
	2-naphthol	-38.2	-19.6 <sup>c</sup>	-39.7	-18.1 <sup>c</sup>
6a	naphthalene	-18.6		-21.6	
6b	naphthalene	-17.6		-20.3	
6c	naphthalene	-21.4		-24.5	
7	11	-17.6		-15.5	
7	12	-17.4		-18.7	
7	13	-19.4	-21.4 <sup>d</sup>	-21.5	-20.9 <sup>d</sup>
8	14	+2.0		-0.7	

<sup>a</sup> Without solvation. <sup>b</sup> With solvation (see the Experimental Section). <sup>c</sup> Reference: reaction of 6a. <sup>d</sup> Reference: reaction of 8.

**TABLE 3.** Calculated Enthalpies of the Carbocation Intermediates ( $\alpha$  to the Benzene Ring) of the Reactions of 5–8, Using B3LYP/6-311+G\*\*//B3LYP/6-31G\*

substrate	$\Delta H_i^a$ kcal mol <sup>-1</sup>	$\Delta\Delta H_i^a$ kcal mol <sup>-1</sup>	$\Delta H_i^b$ kcal mol <sup>-1</sup>	$\Delta\Delta H_i^b$ kcal mol <sup>-1</sup>	$\Delta\Delta G_{\text{exp}}^c$
5	-54.6		4.1		
	-58.3 ( $\beta$ )		0.8 ( $\beta$ )		
6a	-48.3	-6.3 <sup>d</sup>	7.7	-3.5 <sup>d</sup>	-1.6 <sup>d</sup>
6b	-50.3 ( $\beta$ )	-8.0 <sup>e</sup>	6.5 ( $\beta$ )	-5.7 <sup>e</sup>	-2.4 <sup>e</sup>
6c	-52.8 ( $\beta$ )	-5.5 <sup>e</sup>	3.2 ( $\beta$ )	-2.4 <sup>e</sup>	0.8 <sup>e</sup>
7	-54.4		3.9		
8	-42.4	-15.1	14.4	-13.4	-7.8

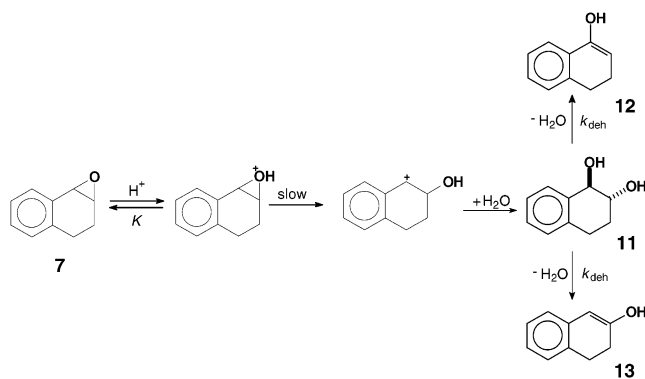
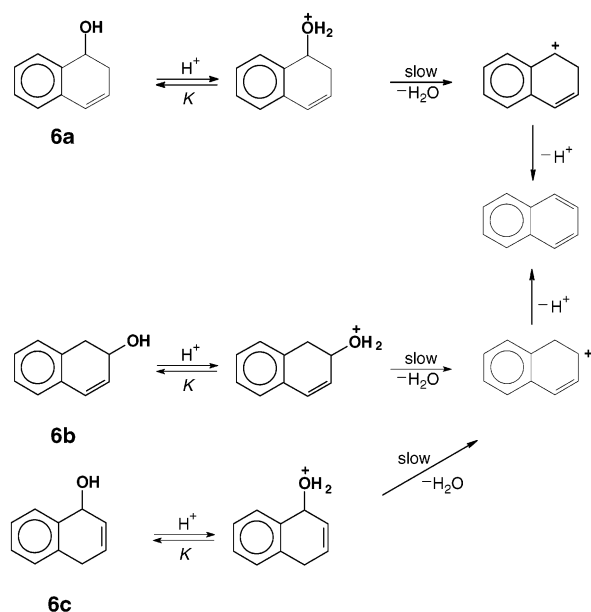
<sup>a</sup> Without solvation. <sup>b</sup> With solvation (see the Experimental Section). <sup>c</sup>  $\Delta\Delta G_{\text{exp}}^c = -RT \ln(k_{\text{oxide}}/k_{\text{hydrate}})$ . <sup>d</sup> Carbocation compared to the carbocation intermediate of 5 en route to 2-naphthol. <sup>e</sup> Carbocation compared to the carbocation intermediate of 5 en route to 1-naphthol.

**SCHEME 2**

and has been discussed thoroughly by More O'Ferrall and co-workers.<sup>6a</sup>

The acid-catalyzed cleavage of the structurally related epoxide 7, but which does not involve aromatization, is expected to give only the benzylic  $\alpha$ -carbocation. The  $\beta$ -carbocation should be much less stable (Scheme 3).

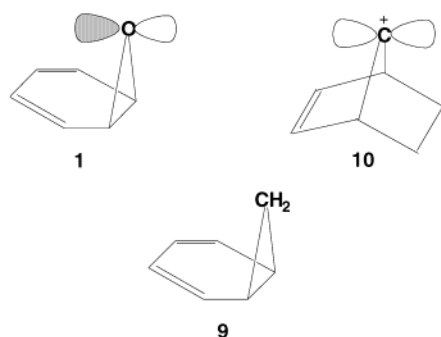
There are close similarities between the transition state of the acid-catalyzed reaction of naphthalene oxide and the transition state of the acid-catalyzed aromatization of the naphthalene hydrates 6a and 6b (Schemes 3 and 4). It has been concluded that the high reactivity of these hydrates is mainly related to the stability of their cation-forming transition states, and that the stability of the reactant is of less importance.<sup>15,16</sup> The carbocation stability in the reaction of naphthalene oxide is disfavored by the presence of the hydroxy substituent. How-

**SCHEME 3****SCHEME 4**

ever, this effect is generally small when comparing the reactivity of arene oxides and hydrates since the major factor should be the gain in energy brought about by the release in strain from the cleavage of the epoxide ring. Thus, the acid-catalyzed reaction of naphthalene oxide



## SCHEME 5



is expected to be much faster than the corresponding reactions of the naphthalene hydrates **6a** and **6b**. However, the reaction to give 2-naphthol, which occurs through the  $\alpha$ -cation, is only about 14 times faster than the reaction of **6a**. The reactions through the  $\beta$ -carbocation show a similar behavior; the reaction of **5** producing 1-naphthol is only 55 times faster than the reaction of **6b**. This is in sharp contrast with the corresponding reactions of **7** and **8**, which exhibit a rate-ratio for acid-catalyzed carbocation formation of  $\sim 5 \times 10^5$  (Table 1, Figure 1). The rate-ratio of the latter reactions, which are assumed to occur exclusively through the  $\alpha$ -carbocations (vide supra, Scheme 3), should be a reasonable reference for prediction of the relative reactivity of **5** (to give 2-naphthol) and **6a** through the  $\alpha$ -carbocations. This estimated rate ratio of  $\sim 5 \times 10^5$  is about  $3.6 \times 10^4$  times larger than the measured ratio. This corresponds to a difference in free activation energy of about 6 kcal mol<sup>-1</sup>. Since there is no reason to expect anomalous reactivity of the naphthalene hydrates, we attribute the difference in predicted and measured free activation energy to an unusually low reactivity of naphthalene oxide. The reason for the unusually slow reaction is discussed below.

**Homoaromatic Stabilization of Naphthalene Oxide?** In analogy with what has been proposed for benzene oxide, the slow reaction of naphthalene oxide may reflect an increased stability of this compound caused by homoaromaticity.<sup>6,7</sup> Thus, we have recently reported that the low reactivity of benzene oxide in acid-catalyzed aromatization, corresponding to an increase in reaction barrier of about 10 kcal mol<sup>-1</sup>, is accompanied by an experimentally determined stabilization energy of 6.6 kcal mol<sup>-1</sup>.<sup>7</sup> This value was derived from the calorimetrically measured reaction enthalpies. A similar value (5.4 kcal mol<sup>-1</sup>) was obtained by calculations.<sup>7</sup>

Two decades ago Kollman and co-workers proposed that an interaction in the benzene oxide (**1**) between the  $\pi$ -orbital system of the diene with a lone pair of the oxygen results in stabilization of the ground state (Scheme 5).<sup>25</sup> Thus, as was pointed out by More O'Ferrall and co-workers,<sup>6</sup> benzene oxide is a 6- $\pi$  analogue of the 2- $\pi$  homoaromatic 7-norbornenyl cation **10**. However, they concluded that the stabilization should be dominated by  $\sigma$ - $\pi$  interactions. These orbital interactions could be

accounted for by considering a homoconjugative effect between the pair of epoxide C–O molecular orbitals and the  $\pi$ - and  $\pi^*$  orbitals of the butadiene moiety. In the case of norcaradiene **9**, this effect has been thoroughly discussed by Jorgensen.<sup>26</sup>

Our computational results support this latter explanation. A second-order perturbation theory analysis of the Fock matrix in a natural bond order basis for benzene oxide indeed shows that the most important stabilizing interaction is electron donation from the C–C  $\pi$  bonds to the nearest C–O antibonding orbital and from the C–O bonding orbitals to the  $\pi^*$ -orbital system of the diene. The symmetry requirement of the participating molecular orbitals determining whether the system becomes homoaromatic or homoantiaromatic has previously been discussed for cyclopropane derivatives.<sup>26</sup>

Do the calorimetric data of Table 1 support the assumption of an increased stability of naphthalene oxide? It is more complicated to compare the reactions of naphthalene oxide with suitable references owing to the lack of symmetry of the reactant. The reaction heat ( $\Delta H$ ) of  $-51.3$  kcal mol<sup>-1</sup> refers to the formation of a mixture of 95% of 1-naphthol and 5% of 2-naphthol. The experimental results do not give information about the individual reaction enthalpies. However, the calculations indicate that the two enthalpies are similar, 2-naphthol is only 0.9 kcal mol<sup>-1</sup> more stable than 1-naphthol in water (Table 2).

Let us assume that the reaction enthalpy for formation of 2-naphthol is  $-51.3 - 0.9 = -52.2$  kcal mol<sup>-1</sup>. This could be compared with the reaction enthalpy of  $-21.6$  kcal mol<sup>-1</sup> for the aromatization of **6a** by acid-catalyzed dehydration. Thus, as expected, the ring-opening aromatization of naphthalene oxide has a driving force that is much larger than that of aromatization of the naphthalene hydrate **6a**,  $\Delta\Delta H = -52.2 - (-21.6) = -30.6$  kcal mol<sup>-1</sup>.

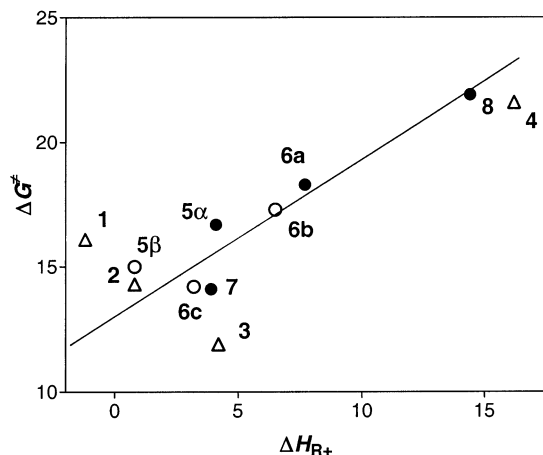
The analogous reactions of **7** and **8**, but which do not involve aromatization, may be used for estimation of the aromatization energies involved in the reactions of **5** and **6a**. However, first we have to correct the measured enthalpy of the reaction of **7**, which experimentally yields the diol, for the elimination of one water molecule to give the enol **13** (Scheme 3 and Table 1). Calculations estimate this enthalpy to be  $-6.0$  kcal mol<sup>-1</sup>.<sup>27</sup> Accordingly, the corrected enthalpy is  $\Delta H = -25.6 + (-6.0) = -31.6$  kcal mol<sup>-1</sup>. The aromatization energies for the naphthalene oxide and naphthalene hydrate reactions are then estimated as  $\Delta\Delta H = -52.2 - (-31.6) = -20.6$  kcal mol<sup>-1</sup> and  $\Delta\Delta H = -21.6 - (0) = -21.6$  kcal mol<sup>-1</sup>, respectively. According to this estimation, there is experimental support for some homoaromatic stabilization of naphthalene oxide,  $\Delta\Delta\Delta H = -20.6 - (-21.6) = 1.0$  kcal mol<sup>-1</sup>. However, because this estimate is based upon several reaction heats, the maximum error in this value is larger than 2 kcal mol<sup>-1</sup> so there is no conclusive evidence for a stabilization. The calculated gas phase enthalpies of the same four reactions (Table 2) suggest a slightly stronger stabilization:  $\Delta\Delta\Delta H = (-38.2 - (-19.4)) - (-18.6 - (2.0)) = 1.8$  kcal mol<sup>-1</sup>. Correcting for solvation in water gives  $\Delta\Delta\Delta H = (-39.7 - (-21.5)) - (-21.6 - (-0.7)) = 2.7$  kcal mol<sup>-1</sup>. These values should be com-

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**FIGURE 2.** The experimentally measured free energy of activation versus the calculated enthalpy of carbocation formation in water (in kcal mol<sup>-1</sup>, Table 3) for the reactions of the naphthalene derivatives **5–8** through the  $\alpha$ -cations (filled circles, slope 0.63) and  $\beta$ -cations (open circles). The corresponding data for the “benzene derivatives” **1–4** are included in the plot (triangles; the rate constant for **1** is statistically corrected).<sup>7</sup>

pared to the homoaromatic stabilization energy calculated for benzene oxide; 4.6 and 5.4 kcal mol<sup>-1</sup> in the gas phase and in water, respectively.

To conclude, the combined heat-flow microcalorimetry and computational study suggests that the homoaromatic stabilization is lower for naphthalene oxide than for benzene oxide. This is in contrast to the purely theoretical study, which suggests that the hyperconjugative effects should be very similar.

**Carbocation Stabilities and Kinetics.** The rate-limiting C–O bond breaking step is preceded by an acid–base preequilibrium (Schemes 2–4). The basicities of the benzene derivatives **1–4** have been found to be very similar.<sup>7</sup> There is only a small difference in  $pK_a$  of the protonated substrates (<0.4 kcal mol<sup>-1</sup> according to calculations). Very similar  $pK_a$  values are also expected for the compounds **5–8**. Thus, we conclude that an unfavorable preequilibrium could only explain a minor part of the low reactivity of naphthalene oxide.

The rates of the cation-forming step of the studied reactions are expected to be closely related to the stability of the carbocation (vide supra). Indeed, the enthalpies for the formation of the cations (Table 3), which are calculated in a way similar to that for the total reactions, show a good correlation with reactivity (Figure 2, the data for the corresponding benzene derivatives are plotted in the same diagram). The regression line for the reactions of the compounds **5–8** through the  $\alpha$ -cations has a slope of 0.63. Thus, the carbocation stability is substantially, but not fully, reflected in the reactivity.

The large  $\Delta G^\ddagger$  for benzene oxide (Figure 2) is in accord with the previous proposal that its unusually low reactivity is due to a combination of an unusually stable compound (homoaromaticity) and an unusually high energy of the carbocationic transition state.<sup>7</sup>

**Conclusions.** The heat-flow microcalorimetry measurements and computational analysis presented in this work have been aimed at increasing the understanding of the homoaromaticity concept in connection with arene

oxides. For benzene oxide, the calculations support a homoconjugative effect between the pair of epoxide C–O bonds and the  $\pi$ -system of the butadiene part of the molecule. As previously suggested electron donation between the epoxide oxygen lone-pair and the  $\pi$ -system could be rejected.

The experiments indicate that benzoannulation decreases the effect of homoaromaticity. Thus, the stabilization energy decreases from 7 kcal mol<sup>-1</sup> for benzene oxide to 1 kcal mol<sup>-1</sup> for naphthalene oxide. In conflict with experiments, calculations suggest that benzene oxide and naphthalene oxide should be stabilized to the same extent. The reason to this inconsistency is not understood.

The rates of the reactions of the arene oxides and the arene hydrates are well described by the calculated carbocation stabilities. The results indicate that the carbon–oxygen bond is substantially broken and that there is a large carbocation character in the transition state.

## Experimental Section

**General Procedures.** NMR spectra were recorded for CDCl<sub>3</sub> solutions with a 300 MHz spectrometer. Chemical shifts are indirectly referenced to TMS via the solvent signal (chloroform-*d*<sub>1</sub> 7.26 and 77.0 ppm). The high-performance liquid chromatography analyses were carried out with a liquid chromatograph equipped with a diode-array detector on an Inertsil 5 OSD-2 (3 × 100 mm) reversed-phase column. The chromatography was performed isocratically using acetonitrile in water as the mobile phase. The UV spectrophotometry was performed on a spectrophotometer equipped with an automatic cell changer kept at constant temperature using a thermostated water bath. The reaction solutions for the kinetic experiments were prepared by mixing acetonitrile or glycerol with water at room temperature, ca. 22 °C. The pH was measured before and after reaction using a micro glass electrode. The pH values given are those measured before mixing with the organic solvent. The microcalorimetric experiments were carried out with a dual channel calorimeter (Thermometric Thermal Activity Monitor 2277). The signals were recorded on both a two-channel potentiometric recorder and on a computer.

**Materials.** Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium and benzophenone. Methanol and acetonitrile were of HPLC quality and HPLC UV gradient quality, respectively. All other chemicals used for the kinetic experiments were of reagent grade and used without further purification.

**Naphthalene 1,2-oxide (5)** was prepared from 1,2-dihydronaphthalene by reaction with *N*-bromosuccinimide (NBS) in acetic acid followed by reaction with NBS in carbon tetrachloride with UV radiation using  $\alpha, \alpha'$ -azoisobutyronitrile as an initiator. The final step with sodium methoxide in dry tetrahydrofuran afforded **5** as product.<sup>9</sup> The NMR spectrum of the recrystallized product showed 3.0 mol % of 1-naphthol but no other impurities.

**1-Hydroxy-1,2-dihydronaphthalene (6a)** was prepared by a four-step procedure:<sup>11</sup> reduction of  $\alpha$ -tetralone with sodium borohydride, acetylation with acetic acid anhydride, bromination with NBS, and elimination with sodium methoxide. Analysis by NMR and HPLC showed pure material besides a small amount of naphthalene (3.0 mol %).

**1,2-Dihydronaphthalene oxide (7)**<sup>10,13</sup> was prepared by the following procedure, which is a slight modification of the previously published methods.<sup>10</sup> 1,2-Dihydronaphthalene was reacted with NBS in acetone followed by reaction of the isolated and purified bromohydrin (flash chromatography) with

sodium methoxide in tetrahydrofuran. Flash chromatography gave pure material (HPLC and NMR).

**trans-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (11)**<sup>10,13,14,28</sup> was prepared in accord with a previously published method.<sup>10</sup> The crude product was purified by recrystallization from chloroform, mp 110–111 °C.

**Kinetics. UV Spectrophotometric Procedure.** The reactions were run in 3-mL standard quartz cells using the above-mentioned equipment. Addition of a few microliters of a concentrated solution of the substrate in acetonitrile to 2.5 mL of reaction solution gave an initial concentration of the substrate in the reaction flask of about 0.1 mM. The change in absorbance was followed as a function of time and the pseudo first-order rate constant calculated by a nonlinear regression computer program.

**Kinetics. Microcalorimetric Procedure.** This technique has the advantage that both kinetic data and reaction heats are obtained from the same kinetic experiment.<sup>29</sup> The reactions were run in parallel in the two channels, both composed of a sample compartment and a reference compartment. Glass vials (3 mL) were used as reaction and reference vessels. All four vessels were filled at the same time with 2.5 mL of premixed buffer solution (glycerol–water or acetonitrile–water). After this step, 20  $\mu$ L of substrate in acetonitrile was added to the two reaction vessels (final concentration  $\sim$ 0.5 mM) while 20  $\mu$ L of pure acetonitrile was added to the reference vessels. The vials were sealed with gastight PTFE septa and slowly introduced into the compartments of the instrument for about 15 min of prethermostating. They were then lowered further down into the detection chambers. After a total time of about 45 min it was possible to start recording the first-order heat-flow decay. The reactions were followed for at least 10 half-lives. The substrate concentrations in the reaction vials were obtained indirectly by measuring the concentration of the product by HPLC, i.e., 1- and 2-naphthol, naphthalene, 1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene, and 1,2-dihydronaphthalene, respectively, after more than 10 half-lives.

The microcalorimeter was statically calibrated after a kinetic experiment using the reaction solutions. No correction

for the cooling constant parameter ( $\kappa$ ) of the instrument was necessary for calculation of the rate constants of the reaction heat decay.<sup>29</sup> Very good first-order rate constants ( $k_{\text{obs}}$ ) were measured. These agree well with those measured in the kinetic studies using the UV spectrophotometric technique (Table 1).

The extrapolated heat flow at time zero ( $P_0$ ) was used for calculation of the reaction heat ( $\Delta H$ ) according to eq 2:<sup>29</sup>

$$P_0 = \Delta H k_{\text{obs}} n_0 \kappa / (\kappa - k_{\text{obs}}) \quad (2)$$

where  $n_0$  is the amount of substrate (mol) in the reaction vial.

The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors.

**Computational Methods.** All geometry optimizations reported in this work were conducted using the Gaussian 98 program<sup>18</sup> and the B3LYP hybrid functional<sup>19</sup> together with the 6-31G\* basis set. Thermal corrections to enthalpies were also determined at this level of theory. The final energies were subsequently determined using B3LYP in combination with the larger basis set 6-311+G\*\*. The B3LYP results have recently been compared with calculations at the MP2/6-311+G\*\*/MP2/6-31G\* level of theory without any significant change in either geometry or thermodynamics for a similar set of molecules.<sup>7</sup>

Free energies of solvation were estimated at the gas-phase geometries using the continuum solvation method AM1/SM2<sup>20</sup> in Spartan.<sup>21</sup> The free energy of solvation has been used directly as an approximation of the enthalpy of solvation in the estimation of solvation effects.

This combination of calculations was also used in the conformational searches of the hydroxy-containing compounds to ensure that the global minimum was used in the calculation of homoaromaticity.

**Acknowledgment.** We thank the Swedish Natural Science Research Council for supporting this work.

**Supporting Information Available:** Geometries at B3LYP/6-31G\* and Cartesian coordinates/energies in Hartrees of optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO025953P

(27) The error in the enthalpy of dehydration ( $\Delta H_{\text{calc}}$ , Scheme 1) should be less than  $\pm 2$  kcal mol<sup>-1</sup>. This estimation is based upon our calculation of the enthalpy of dehydration of ethanol in the gas phase ( $-9.9$  kcal mol<sup>-1</sup>, which is 1.0 kcal mol<sup>-1</sup> lower than the literature value) and the error given for solvation by Cramer and Truhlar (0.7 kcal mol<sup>-1</sup>, mean absolute error).

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