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Is Benzene Oxide Homoaromatic? A Microcalorimetric Study[†]

Zhi Sheng Jia, Peter Brandt,[‡] and Alf Thibblin*

Contribution from the Institute of Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala, Sweden

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Abstract: Rate constants and heats of reaction for the aromatization of benzene oxide (**1**) and the acid-catalyzed aromatization of benzene hydrate (**2**) in highly aqueous solution giving phenol and benzene, respectively, have been measured by heat-flow microcalorimetry. The measured heat of reaction of benzene oxide, $\Delta H = -57.0$ kcal mol^{-1}, is much larger than that of benzene hydrate, $\Delta H = -38.7$ kcal mol^{-1}, despite an unusually low reactivity of benzene oxide, rate ratio 0.08. The measured enthalpies agree with those calculated using the B3LYP hybrid functional corrected with solvation energies derived from semiempirical AM1/SM2 calculations. Comparison with the measured enthalpies of the corresponding reactions of the structurally related 1,3-cyclohexadiene oxide (**3**) and 2-cyclohexenol (**4**) of $\Delta H = -24.9$ kcal mol^{-1} (includes a small calculated correction of -1.2 kcal mol^{-1}) and $\Delta H \sim 0$ kcal mol^{-1}, respectively, gives a smaller aromatization energy for the benzene oxide than for the benzene hydrate reaction ($\Delta\Delta\Delta H = 6.6$ kcal mol^{-1}). This suggests that benzene oxide is unusually stabilized by a significant amount of homoaromatization as has been proposed previously (*J. Am. Chem. Soc.* **1993**, *115*, 5458). This unusual stability accounts for more than half of the $\sim 10^7$ times lower than expected reactivity of benzene oxide toward acid-catalyzed isomerization. The rest is suggested to originate from an unusually high energy of the carbocation-forming transition state.

Introduction

Arene oxides and arene hydrates are reactive compounds of considerable biochemical interest.[1-4] The oxidation of aromatic hydrocarbons to phenols in biological systems has been proposed to occur via arene oxides. This has been strongly supported by the observation of naphthalene oxide.[1] Aromatic compounds also undergo metabolism through arene hydrates, but this route is probably of less importance.[2,4]

It has been proposed by More O'Ferrall and co-workers that arene oxides may be stabilized by homoaromaticity.[5] The low reactivity of benzene oxide suggests a stabilization of at least 10 kcal mol^{-1}. This issue is of great interest in connection with studies of liver enzyme metabolism of aromatic compounds and their ability to provide dihydrodiols and glutathione adducts.[3] The proposed homoaromaticity of arene oxides is of course also of interest from a purely theoretical point of view in connection with the general concept of aromaticity.[6]

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[‡] Present address: Organic Chemistry, Department of Chemistry, Royal Institute of Technology, SE-100 44 Stockholm, Sweden.

(1) Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC Press Inc.: Boca Raton, FL, 1988; p 31.

(2) (a) Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P.; Jenkins, R. O. *J. Chem. Soc., Chem. Commun.* **1989**, 339. (b) Boyd, D. R.; Hand, M. V.; Sharma, N. D.; Chima, J.; Dalton, H.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1991**, 1630. (c) Boyd, D. R.; Dorrity, M. R. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc*. **1991**, *113*, 666.

(3) Jerina, D. M.; Daly, J. W.; Wikop, B.; Zaltzman-Nirenberg, P.; Udenfriend, S. *Biochemistry* **1970**, *9*, 147.

(4) Boyd, D. R.; Jerina, D. M. Oxiranes, Arene Oxides, Oxaziridines, Thietanes, Thietes, Thiazeles. In *Small Ring Heterocycles*−*Part III*; Hassner, A., Ed.; John Wiley & Sons: New York, 1985; p 197.

(5) (a) More O'Ferrall, R. A.; Rao, S. N. *Croat. Chem. Acta* **1992**, *65*, 593. (b) Rao, S. N.; More O'Ferrall, R. A.; Kelly, S. C.; Boyd, D. R.; Agarwal, R. *J. Am. Chem. Soc.* **1993**, *115*, 5458.

(6) Krygowski, T. M.; Cyrański, M. K.; Czarnocki, Z.; Häfelinger, G.; Katritzky, A. R. *Tetrahedron* **2000**, *56*, 1783.

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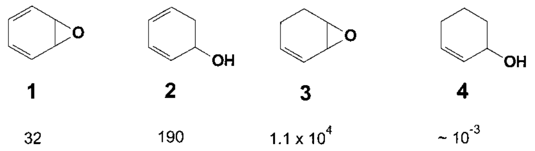
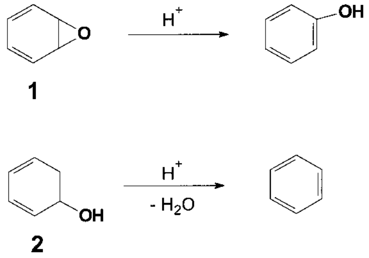
Chart 1



Scheme 1



We now report results on the aromatization reactions of benzene oxide (**1**) and benzene hydrate (**2**) under acidic conditions. These reactions have previously been concluded to be subject to specific acid catalysis with rate-limiting formation of an α-hydroxycyclohexadienyl carbocation intermediate and a cyclohexadienyl carbocation intermediate, respectively.[5,7] Surprisingly, benzene hydrate was found to be 12 times *more* reactive (after statistical correction for the two carbon−oxygen bonds in **1**) than benzene oxide despite acid-catalyzed cleavage of carbon−oxygen bonds in simple epoxides occurring 10^6−10^7 times faster than in the structurally related hydrates.[5] This is illustrated in Chart 1 which gives the previously reported second-order rate constants for the acid-catalyzed reactions measured in aqueous solution.[5]

The aim of our study was to test the hypothesis that the unusually low reactivity of benzene oxide compared to benzene hydrate is due to homoaromatic stabilization of the benzene oxide reactant. The experimental results obtained by heat-flow microcalorimetry and the results of calculation do support this proposal. However, transition-state effects are also of importance.

Results

The substrates benzene oxide (**1**) and benzene hydrate (**2**) were prepared from 1,4-cyclohexadiene following the procedures of Gillard et al.[8] and Stavascik et al.,[9] respectively. 1,3-Cyclohexadiene oxide (**3**) was prepared from 1,3-cyclohexadiene.[10]

The cleavage of **1** in 25 vol % glycerol in water at 25 °C yields phenol as the sole product (Scheme 1). The reaction was followed by a sampling high-performance liquid chromatography procedure and by heat-flow microcalorimetry. The results are presented in Table 1. The kinetics of the reaction has been studied previously in aqueous 1 M KCl at 30 °C by Kasperek and Bruice.[7] They found that an uncatalyzed path ($k_0 = 1.4 \times 10^{-3}$ s^{-1}) accompanies the specific acid-catalyzed path ($k_H = 32$ M^{-1} s^{-1}) according to

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

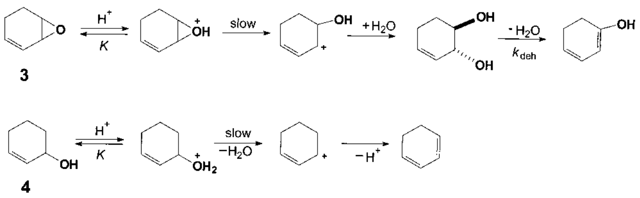
A crude estimate of the second-order rate constant, based upon the observed rate constants given in Table 1, is $k_H \sim 22$ M^{-1} s^{-1} at 25 °C. The uncatalyzed path has a rate constant of $k_0 \sim 0.53 \times 10^{-3}$ s^{-1}. The rate constants reported in Table 1 were measured at relatively high pH values, and the main part of the reaction of benzene oxide is concluded to occur through the uncatalyzed pathway. Microcalorimetric kinetic studies at lower pH were not possible due to the large time constant of the microcalorimeter.

Table 1. Rate Constants and Heats of Reaction for the Reactions of **1**−**4** at 25 °C

solvent[a]	$10^6 k_{obs}$, s^{-1}	k_H, M^{-1} s^{-1}	P_0, μW	ΔH, kcal mol^{-1}	$\Delta\Delta H$, kcal mol^{-1}
	Benzene Oxide (**1**)				
glyc−water[b]	535 ± 15	~22	169	−57.0 ± 1.9	−18.3
glyc−water[c]	589 ± 15				
	Benzene Hydrate (**2**)				
glyc−water[d]	338	126			
glyc−water[e]	346	129			
glyc−water[f]	155 ± 2	58	43.5	−38.7 ± 0.8	
MeCN−water[g]	246 ± 4	1.7	55.7	−39.9 ± 1.5	
	1,3-Cyclohexadiene Oxide (**3**)				
MeCN−water[h]	173 ± 4		13	−23.7 ± 0.6	−24.9[j]
	2-Cyclohexenol (**4**)				
water[i]		~10^{-3}		~0	

[a] The buffer concentrations and pH values: before mixing with the organic cosolvent. [b] 25 vol % glycerol in water, 0.1 M phosphate buffer pH 7.00. [c] 25 vol % glycerol in water, 0.1 M phosphate buffer pH 5.57. [d] 25 vol % glycerol in water, 0.1 M acetate buffer pH 5.57; kinetics were studied by UV spectrophotometry. [e] 25 vol % glycerol in water, 0.1 M phosphate buffer pH 5.57. [f] 50 vol % glycerol in water, 0.1 M acetate buffer pH 5.57. [g] 50 vol % acetonitrile in water, 0.1 M acetate buffer pH 3.85. [h] 50 vol % acetonitrile in water, 0.1 M phosphate buffer pH 5.99. [i] Reference12. [j] After correction for dehydration (see text and Scheme 2).

Scheme 2



The dehydration reaction of **2** yields benzene as the sole product (Scheme 1). The results, which were obtained by the same methods as described above and by UV spectrophotometry, are reported in Table 1. Due to difficulties in measuring the benzene product concentration accurately in 25 vol % glycerol, a larger fraction of the organic cosolvent was used. A rate constant of 190 M^{-1} s^{-1} has previously been reported for the reaction in water at the same temperature.[5b]

The reactions produce large amounts of heat and are easy to follow by heat-flow microcalorimetry. The reaction heats for the reactions of **1** and **2** were measured as −57.0 and −38.7 kcal mol^{-1}, respectively. The details of the heat-flow microcalorimetric measurements are given in the Experimental Section.

The cleavage reaction of **3** gives a mixture of diols with the trans 1,2-diol as the main product (Scheme 2). The rate constant and the enthalpy were measured in 50 vol % aqueous acetonitrile (Table 1); the reaction was too fast in 25 vol % glycerol in water for measurement by the microcalorimeter. The rate constants and product composition of diols have been studied previously in aqueous solution at 25 °C by Whalen; an uncatalyzed pathway was found to compete with a specific acid-catalyzed reaction.[11] To obtain the reaction heat for the production of the monohydroxy substituted compound (Scheme

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(7) Kasperek, G. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 198.

(8) Gillard, J. R.; Newlands, M. J.; Bridson, J. N.; Burnell, J. *Can. J. Chem.* **1991**, *69*, 1337.

(9) Stavascik, J.; Rickborn, B. *J. Am. Chem. Soc.* **1971**, *93*, 3046.

(10) Ramesh, K.; Wolfe, M. S.; Lee, Y.; Velde, D. V.; Borchard, R. T. *J. Org. Chem.* **1992**, *57*, 5861.

Scheme 3

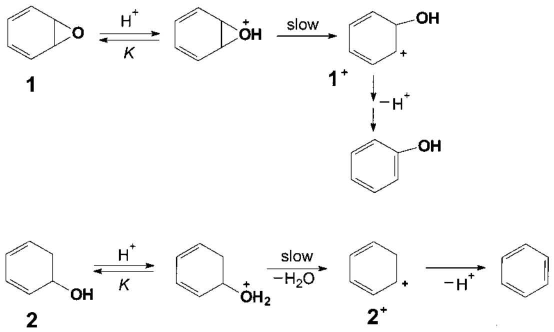

Table 2. Calculated Enthalpies of the Reactions of **1**−**4** Using B3LYP/6-311+G**//B3LYP/6-31G*

substrate	ΔH,[a] kcal mol^{-1}	$\Delta\Delta H$,[a] kcal mol^{-1}	ΔH,[b] kcal mol^{-1}	$\Delta\Delta H$,[b] kcal mol^{-1}
1	−48.0	−18.2	−49.8	−17.7
2	−29.8		−32.1	
3	−17.6	−22.8	−19.7	−23.1
4	+5.2		+3.4	

[a] Without solvation. [b] With solvation (see the Experimental Section).

Table 3. Calculated Enthalpies of the Carbocation Intermediates of the Reactions of **1**−**4**, Using B3LYP/6-311+G**//B3LYP/6-31G*

substrate	ΔH,[a] kcal mol^{-1}	$\Delta\Delta H$,[a] kcal mol^{-1}	ΔH,[b] kcal mol^{-1}	$\Delta\Delta H$,[b] kcal mol^{-1}	$\Delta\Delta G^{\ddagger}_{\mathrm{exp}}$
1	−51.8	−3.4	−1.2	−2.0	1.0
2	−48.4		0.8		
3	−45.7	−11.8	4.2	−12.0	−9.6
4	−34.0		16.2		

[a] Without solvation. [b] With solvation (see the Experimental Section).

2), the calculated dehydration enthalpy (−1.2 kcal mol^{-1}) was used to correct the measured value. The error in the calculated dehydration enthalpy is estimated to be less than 1 kcal mol^{-1}.

A rate constant of carbocation formation from 2-cyclohexenol (**4**) estimated by More O'Ferrall is given in Chart 1.[5b] The derived rate constant at 25 °C is smaller ($\sim 0.6 \times 10^4$ M^{-1} s^{-1}, based upon the measured rate constants for reaction in 5.64 M sulfuric acid at 20 and 30 °C),[12] presumably because the carbocation formation is not rate-limiting. A reaction enthalpy of $\Delta H \sim 0$ has been reported.[12]

Calculations. The thermodynamics of the reactions depicted in Schemes 2 and 3 was calculated using the Gaussian 98 program and the B3LYP hybrid functional along with a continuum solvation method (see Computational Details for more information). The results are given in Tables 2 and 3. The pK_a values of the substrates were derived by a calibrated method from local ionization energies (see Supporting Information). The pK_a values were found to be −2.77, −2.13, −2.42, and −1.97, respectively.

Discussion

Carbocation-like Transition States. The mechanisms of acid-catalyzed carbon−oxygen bond breaking of arene hydrates have been the subject of some recent studies.[5,12−15] It was concluded that the high reactivity is mainly related to the stability of their carbocation-forming transition states; reactant stability is of less importance.[13,14] The mechanism of dehydration of **2** is shown in Scheme 3. The proposed mechanism of acid-catalyzed epoxide ring opening is very similar; i.e., the rate-limiting step involves cleavage of a carbon−oxygen bond to provide a carbocation.[5,7] The carbocation intermediate is destabilized to some extent by the β-hydroxy substituent, but this effect is generally small compared to the gain in energy brought about by the release of strain from the cleavage of the epoxide ring. This mechanism for **1** is shown in Scheme 3. The carbocation **1**$^+$ may undergo a hydride shift (NIH shift) before the final aromatization step takes place.[7]

Epoxide ring opening may, in principle, also occur through an S_N2 mechanism. However, it has been pointed out that this is not reasonable for substrates producing stabilized carbocations in the presence of nucleophiles not stronger than water.[5] This is discussed in more detail at the end of the Discussion. There is also direct evidence of the cation character of the transition state of epoxide ring-opening reactions.[7,16−18] Accordingly, the result of our calculations is that the reaction rates are closely related to the stability of the carbocations (vide infra).

Unusually Low Reactivity of Benzene Oxide (1). The kinetic data of the reactions of **1** and **2** in 25 vol % glycerol in water are in accord with the results previously reported for the reactions under slightly different conditions.[5b,7] The acid-catalyzed reaction of **2** is 12-fold *faster* than the corresponding reaction of **1** (after statistical correction, Chart 1). This was unexpected since carbon−oxygen bond breaking in an epoxide generally occurs 10^6−10^7 times faster than in a structurally related alcohol.[5] It seems reasonable to compare these reactions with the reactions of the structurally related compounds **3** and **4**. The reactions of these substrates show an epoxide/hydrate rate ratio as large as $\sim 10^7$ (Chart 1).

More O'Ferrall and co-workers have thoroughly examined the rate ratios of other relevant epoxide/hydrate derivatives.[5] They found that other arenes show behavior similar to that of benzene. Benzoannelation greatly slows down dehydration, but the effect on epoxide reactivity is smaller. The result is that the oxide/hydrate rate ratio increases with more unfavorable benzoannelation and decreasing stability of the carbocationic transition state. Thus, while $k_{\mathrm{oxide}}/k_{\mathrm{hydrate}}$ of the benzene derivatives is 0.08, naphthalene exhibits a ratio of 31 and 56 (depending on structure), and anthracene a ratio of 1430. The nonaromatic isobutene derivatives show a ratio of 4.3×10^6. Thus, the large epoxide/hydrate rate ratio of nonaromatic compounds is not related to the cyclic nature of the reactants. As discussed in detail previously,[5] there is no reason that the unusually small rate ratios of the arene derivatives are caused by an unusually high reactivity of arene hydrates. Therefore, the question arises: why do arene oxides show such a low reactivity?

Homoaromatic Stabilization of Arene Oxides? A hypothesis presented by More O'Ferrall and co-workers is that **1** and other arene oxides show unusual stability attributable to homoaromaticity.[5] The homoaromatic stabilization effect is expected to be largest for the smallest molecule **1**. Epoxides of alkenes do not have this possibility of stabilization.

Homoaromaticity is generally considered to be unimportant for neutral molecules, but there is a consensus about its impor-

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(11) Ross, A. M.; Pohl, T. M.; Piazza, K.; Thomas, M., Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658.

(12) Jensen, J. L.; Uaprasert, V. *J. Org. Chem.* **1976**, *41*, 649.

(13) Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; More O'Ferrall, R. A.; Kelly, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 7822.

(14) Pirinccioglu, N.; Thibblin, A. *J. Am. Chem. Soc.* **1998**, *120*, 6512.

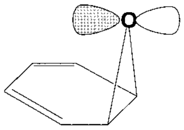
(15) Jia, Z. S.; Thibblin, A. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 247.

(16) Kasperek, G. J.; Bruice, T. C.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Chem. Commun.* **1972**, 784.

(17) Pritchard, J. G.; Siddiqui, I. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 452.

(18) Lamaty, G.; Maleq, R.; Selve, C.; Sivade, A.; Wylde, J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1119.

Chart 2



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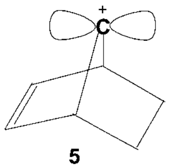

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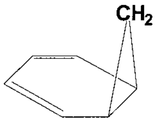

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tance in stabilizing carbocations. However, Kollman and coworkers have suggested that **1** is stabilized by interaction of a lone pair on the oxygen atom with the π-orbitals of the benzene oxide ring.[19] Thus, **1** might be considered a 6π-analogue of the 2π-homoaromatic 7-norbornenyl carbocation (**5**) (Chart 2). Also the neutral norcaradiene (**6**) has been suggested to be homoaromatic with a stabilizing resonance energy of 5−8 kcal mol^{-1}.[20] This molecule does not have any lone pair electrons, and the proposed stabilization should come from σ-π interactions.

A homoaromatic stabilization effect of at least 10 kcal mol^{-1} for benzene oxide is suggested by the about 10^7-fold lower than expected reactivity. However, the microcalorimetric measurements gave reaction heats of the reactions for **1** and **2** (Table 1) of $\Delta H = -57.0$ and -38.7 kcal mol^{-1}, respectively. Thus, there is a large driving force in both reactions but a very much greater one for the epoxide ring opening reaction ($\Delta\Delta H = -18.3$ kcal mol^{-1}).

The enthalpy of formation, ΔH_f^0(aq), for **1** and **2** can be derived from the reaction heats and the enthalpies of formation of the products (Scheme 1). The results are ΔH_f^0(**1**,aq) = 20.7 kcal mol^{-1} and ΔH_f^0(**2**,aq) = −17.4 kcal mol^{-1}, respectively.[21] Thus, the enthalpy difference $\Delta\Delta H_f^0$(aq) of the two reactants **1** and **2** is 38.1 kcal mol^{-1}. This is a large difference, but, without having appropriate reference compounds, it is not possible to conclude whether benzene oxide is substantially stabilized or not.

Calculation of thermodynamic reaction energies using the B3LYP hybrid functional and the continuum solvation method AM1/SM2 yielded energies somewhat smaller than those measured,[22] $\Delta H = -49.8$ and -32.1 kcal mol^{-1} for **1** and **2**, respectively (Table 2), i.e., a difference of $\Delta\Delta H = -17.7$ kcal mol^{-1}, which is very close to the measured value of −18.3 kcal mol^{-1} (Table 1). The calculated reaction energy for the related compound **3** is much smaller −19.7 kcal mol^{-1}, and the reaction of **4** is endothermic by 3.4 kcal mol^{-1} (Scheme 2). An experimental value of $\Delta H \sim 0$ for the reaction in 5.64 M sulfuric acid has been reported.[12] The enthalpy of the reaction of **3** to the alcohol product shown in Scheme 2 could be derived as −24.9 kcal mol^{-1} from the measured enthalpy of −23.7 kcal mol^{-1} to give diol products (Table 1) combined with the calculated enthalpy for dehydration (k_{deh} in Scheme 2) of the trans 1,2-diol of −1.2 kcal mol^{-1} (see Results).

Approximative energies of aromatization may be estimated as the difference in reaction energies of the two reaction pairs, i.e., using the reactions of **3** and **4** as references (Scheme 2).[23] The measured/derived aromatization energies calculated in this way are for benzene oxide, $\Delta\Delta H = -57.0 - (-24.9) = -32.1$ kcal mol^{-1}, and for benzene hydrate, $\Delta\Delta H = -38.7 - 0 = -38.7$ kcal mol^{-1}. Thus, benzene oxide seems to be particularly stable, and the homoaromaticity could be estimated as $\Delta\Delta\Delta H = -32.1 - (-38.7) = 6.6$ kcal mol^{-1}. In the same way, using the calculated energies (Table 2) yields in the gas phase for benzene oxide, $\Delta\Delta H = -48.0 - (-17.6) = -30.4$ kcal mol^{-1}, and for benzene hydrate, $\Delta\Delta H = -29.8 - (+5.2) = -35.0$ kcal mol^{-1}, which corresponds to a homoaromatization energy of $\Delta\Delta\Delta H = -30.4 - (-35.0) = 4.6$ kcal mol^{-1} (5.4 in water). However, this stabilization energy does not fully account for the low reactivity of benzene oxide.

The differences in free enthalpy of formation in aqueous solution have been calculated as $\Delta\Delta H_f^0 = -33.9$ kcal mol^{-1} for **1** and **2** and −37.7 kcal mol^{-1} for **3** and **4**. This also suggests that **1** is unusually stable (by 3.8 kcal mol^{-1}).

Carbocation Intermediates. When discussing factors affecting the rate of a reaction, it is relevant to consider the relative stability of the intermediates. Thus, we have calculated, in a way similar to that for the total reactions, the energies of carbocation formation employing B3LYP in combination with AM1/SM2 to account for solvation effects. As shown in Table 3, there is a good correlation between the experimentally derived $\Delta\Delta G\ddagger$ and the calculated $\Delta\Delta H$ for the formation of cations from **1** and **2** and for the formation of cations from **3** and **4**, respectively. If we use the reactions of **3** and **4** as references as we did for the calculation of homoaromatization (vide supra), we obtain for **1** and **3**: $\Delta\Delta H = -1.2 - 4.2 = -5.4$ kcal mol^{-1} and for **2** and **4** $\Delta\Delta H = 0.8 - 16.2 = -15.4$ kcal mol^{-1}, i.e., a difference between the two pairs of 10.0 kcal mol^{-1}. This is in good agreement with the experimentally derived difference in activation energy of ∼10.6 kcal mol^{-1} (Table 3).

In addition to the activation barrier of the C−O bond breaking step, the energy of the rate-limiting step is directly dependent on the pK_a of the hydronated substrate (Schemes 2 and 3). Thus, the rate difference could in principle be due to a difference in basicity. A careful analysis using a calibrated model based on average local ionization energies suggests a difference of less than 0.4 pK_a-units for substrates **1** and **3**, corresponding to 0.5 kcal mol^{-1}, with benzene oxide being the more acidic species, pK_a = −2.77 (the acidities of all four substrates are within 1 pK_a unit; see Computational Details). Thus, an unfavorable preequilibrium (K, Schemes 2 and 3) could only explain a minor part of the low reactivity of benzene oxide. The fact that benzene oxide is more difficult to hydronate than the other substrates is in accord with its unusual stability (homoaromaticity), which is partially lost in the hydronated species.

In conclusion, the results suggests that roughly half of the unusually low reactivity of **1** is due to a transition-state effect (∼4 kcal mol^{-1}) which also seems to be reflected in a high energy of the hydroxy-substituted carbocation. As discussed above, an unusual stability (homoaromatization) of benzene oxide accounts for the other half.

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(19) Hayes, D. M.; Nelson, S. D.; Garland, W. A.; Kollman, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 1255.

(20) Roth, W. R.; Klärner, F.-G.; Siepert, G.; Lennartz, H.-W. *Chem. Ber.* **1992**, *125*, 217.

(21) Based upon ΔH_f^0(phenol,aq) = −36.34 kcal mol−1, ΔH_f^0(benzene,aq) = 12.24 kcal mol−1, and ΔH_f^0(water,aq) = −68.32 kcal mol−1. These values include the solvation energies for phenol and benzene given in the following references: Nichols, N. F.; Wadsö, I. J. Chem. Thermodyn. **1975**, 7, 329. Gill, S. J.; Nichols, N. F.; Wadsö, I. J. Chem. Thermodyn. **1975**, 7, 175.

(22) Also other aromatization reactions show smaller than calculated measured heats of reaction, presumably owing to an underestimation of the solvation energies in the calculation methods.

(23) The reaction of **3** produces diols, mainly the trans 1,2- and trans 1,4-isomers.[14]

An attempt to find direct evidence for an electronic/structural difference in the transition states was carried out using gas-phase calculations on transition states solvated by one or two water molecules. The transition-state structure for benzene oxide was easily found (Figure S5, Supporting Information). Unfortunately, no complete set of structures could be achieved due to barrierless C−O bond cleavage in several cases. Clearly, there is need for more sophisticated solvation methods to tackle this problem.

Unusually High Reactivity of Nonaromatic Epoxides? Concerted Ring-Opening? In principle, an alternative explanation to the unusually low rate ratio of the benzene oxide reaction compared with that of 1,3-cyclohexadiene might have been that simple epoxides do not react through the carbocation but via another faster reaction route. On the other hand, there is good evidence that the acid-catalyzed ring opening of benzene oxide goes through the carbocation; e.g., there is no build up of diol, and there is no chloride ion effect reported for the reaction under nonacidic conditions.

The reaction of **3** has been found to be catalyzed by added chloride ion.[11] Only nucleophilic attack of the chloride ion on the neutral substrate was discussed. However, the hydronated epoxide, having an even better leaving group, should be even more prone to react by an S_N2 mechanism. Therefore, the large reactivity of **3** and other simple epoxides in acidic solution may arise from S_N2 and S_N2' reactions of the hydronated substrate with water and added nucleophiles. The S_N2 transition state of such a reaction is positively charged and consequently should show characteristics similar to the transition state of the proposed stepwise mechanism.

The reaction of **3** did not show any bimolecular reaction in acidic solution. The small increase in observed rate at pH 5.28 with added chloride ion was attributed to a salt effect.[11] This is consistent with a very reactive protonated epoxide substrate showing a very small discrimination between different nucleophiles. Reactions of S_N2' type are expected to show syn stereochemistry. Thus, the large amount (ca. 35%) of trans 1,4-diol product, which accompanies the main product trans 1,2-diol, indicates that the reaction is stepwise. Therefore, we conclude that the reaction of **3** also occurs through the carbocation.

Experimental Section

General Procedures. NMR spectra were recorded for $CDCl_3$ solutions with a Varian XL 300 spectrometer. Chemical shifts are indirectly referenced to tetramethylsilane (TMS) via the solvent signal (chloroform-d_1 7.26 and 77.0 ppm). The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 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 Kontron Uvicon 930 spectrophotometer equipped with an automatic cell changer kept at constant temperature using a thermostated water bath (HETO 01 PT 623). 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 Radiometer PHM82 pH meter equipped with an Ingold 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 (LKB 2210) 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.

Benzene oxide (1) was prepared by a three-step synthesis.[8] First, 4,5-dibromocyclohexene was prepared from 1,4-cyclohexadiene. This material was oxidized by *m*-chloroperoxybenzoic acid in chloroform, followed by base-promoted elimination of the 4,5-dibromo-1,2-epoxicyclohexane using potassium *tert*-butoxide in dry diethyl ether. The NMR spectra of the product **2** were in accord with those previously published.

Benzene hydrate (2) was also prepared from 1,4-cyclohexadiene, in a two-step process.[9] Oxidation with *m*-chloroperoxybenzoic acid in chloroform afforded 1,2-epoxi-4-cyclohexene. Subsequent cleavage of the epoxide with methyllithium in dry diethyl ether gave a colorless liquid. The purity was checked by NMR.

1,3-Cyclohexadiene oxide (3) was prepared from 1,3-cyclohexadiene and *m*-chloroperoxybenzoic acid in a one-step process.[10] Distillation afforded pure product (NMR[10] and HPLC).

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 in that both the kinetic data and reaction heats are obtained from the same kinetic experiment. The reactions were run in parallel in 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 μL of substrate in acetonitrile was added to the two reaction vessels (final concentration ∼ 0.5 mM), while 20 μL 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 30−45 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., phenol and benzene, respectively, after more than 10 half-lives. However, the acetonitrile solution of **3** was prepared by weighing the pure substrate.

The microcalorimeter was statically calibrated after a kinetic experiment using the reaction solutions. The cooling constant of the instrument was found to be 140 s; i.e., no correction for this parameter was necessary for calculation of the rate constants of the reaction heat decay.[24] Very good first-order rate constants (k_{obs}) were measured. These agree well with those obtained by the UV-spectrophotometric technique (Table 1).

The extrapolated heat flow at time zero (P_0) was used for calculation of the reaction heat (ΔH) according to

$$P_0 = \Delta H k_{obs} n \qquad (4)$$

where n 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 Details. All geometry optimizations reported in this work were conducted using the Gaussian 98 program[25] and the B3LYP hybrid functional[26] together with the 6-31G* basis set. Energies were subsequently determined using B3LYP in combination with the larger basis set 6-311+G**. Zero point energies and thermal corrections to enthalpy were determined at the B3LYP/6-31G* level of theory. To ensure that the B3LYP results were of sufficient quality, geometry optimizations of benzene oxide and phenol were performed at MP2/

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[24] Thibblin, A. *Chem. Scr.* **1983**, *22*, 70.

6-31G* with energies at MP2/6-311+G**. This showed no significant changes in structure or thermodynamics.

Free energies of solvation were estimated at the gas-phase geometries using the continuum solvation method AM1/SM2[27] in Spartan.[28] The free energy has been used directly as a substitute for the enthalpy of solvation in the estimation of solvation effects. Most of the AM1/SM2 calculations were repeated using the CPCM[29] solvation model with parameters for water in combination with the HF/6-31+G* wave function. However, these derived energies did not show as good a correlation to the experimental data as the AM1/SM2 results.

The pK_a values of the substrates **1**−**4** were derived from average local ionization energies calculated using the program Hardsurf 95[30] with the HF/6-31G* wave function and the B3LYP/6-31G* geometries. The method was calibrated using the experimentally measured pK_a values of methanol, ethanol, dimethyl ether, and diethyl ether (see Supporting Information for details).[31]

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Supporting Information Available: Tables showing calculations of pK_a values using the Hardsurf 95 method and graphical presentation of some calculated structures (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.3; Gaussian, Inc.: Pittsburgh, PA, 1998.

(26) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(27) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.

(28) Cramer, C. J.; Truhlar, D. G. *Science* **1992**, *256*, 213.

(29) *Spartan*, version 5.0.3; Wavefunction, Inc.: Irvine, CA, 1997.

(30) Brinck, T.; Murray, J. S.; Politzer, P. *J. Org. Chem.* **1991**, *56*, 5012. Brinck, T.; Murray, J. S.; Politzer, P.; Carter, R. E. *J. Org. Chem.* **1991**, *56*, 2934.

(31) Scorrano, G.; More O'Ferrall, R. *Rev. Chem. Intermed.* **1987**, *7*, 313.