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Author's Review

Carbocations from Arene Hydrates and Arene Oxides*

Rory A. More O'Ferrall and S. Nagaraja Rao

Department of Chemistry, University College Belfield, Dublin 4, Ireland

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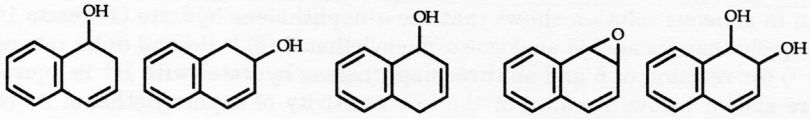
Arene hydrates are water adducts of aromatic molecules that readily dehydrate and aromatise in the presence of acids. The mechanism of this reaction is similar to that for the dehydration of alcohols. Protonation of a hydroxyl group is followed by C–O bond cleavage to form a benzenonium ion-like carbocation intermediate which then loses a proton (in contrast to alcohols, in a fast step) to yield the aromatic product. Rates of reaction are sensitive to the stability of the carbocation. They are also strongly decreased by benzoannelation: thus benzene hydrate is 500 times more reactive than 1-hydroxy-1,2-dihydronaphthalene (naphthalene hydrate) which is 100 times more reactive than 9,10-phenanthrene hydrate. For the analogous dehydration of 3-substituted *cis*-benzenedihydrodiols to phenols ρ has a normal value of –7.2 but, unexpectedly, rate constants for +M resonance substituents MeO, EtO and Me are correlated by σ_p rather than σ^+. Comparison of benzene hydrate with benzene oxide shows, surprisingly, that the latter is the less reactive towards acids despite epoxides normally being 10^6–10^7 times more reactive than structurally related alcohols. For a series of arene oxides and hydrates oxide/hydrate rate ratios are inversely related to the resonance energy of the aromatised ring. This behaviour is tentatively ascribed to homoaromatic stabilisation of the arene oxide ring.

INTRODUCTION

Arene hydrates form an interesting family of compounds in which the elements of water are added to the double bond of an aromatic molecule.[1-5] The first example, 1-hydroxy-1,2-dihydronaphthalene (**1**), was prepared by Bamberger in 1895.[6] This hydrate has since been proposed as an intermediates in the mammalian metabolism of naph-



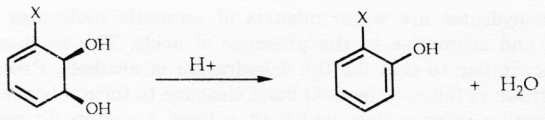
1 **2** **3** **4** **5**

* Dedicated to Profesor Dionis E. Sunko on the occasion of his seventieth birthday.

thalene[7] and dihydronaphthalene[8] following isolation of its glucosiduronic acid derivative and, in the case of dihydronaphthalene, naphthalene itself.

For aromatic molecules, formation of the hydrate is probably a very minor metabolic pathway compared with the better known formation of the arene oxide or dihydrodiol, *e.g.* **4** or **5**.[9,10] However for dihydroaromatic substrates benzylic hydroxylation appears to be of major importance.[11] Bacterial and enzymatic oxidation of the dihydroaromatic molecules also occurs and is particularly efficient with a mutant strain of *Pseudomonas putida* (UV4) which yields hydrates in predominantly chiral form.[11] From 1,2-dihydronaphthalene (**1**) is obtained and from 1,4-dihydronaphthalene (**2**) the further isomers 2-hydroxy-1,2-dihydronaphthalene and 1-hydroxy-1,4-dihydronaphthalene (**3**). These isomers are conveniently referred to as α-, β- and γ-hydrates (for **1**, **2**, and **3** respectively).

Bacterial oxidation of aromatic substrates yields *cis*-dihydrodiols. This process offers a potential commercial source of hydrates and dihydrodiols which may be chemically modified to more useful products. For example acid-catalysed dehydration of substituted *cis*-dihydrodiols offers a route to phenols, as shown in equation (1).[12]



(1)

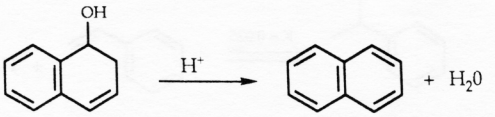
The dehydration reaction also governs the stability of hydrate metabolites under physiological conditions, and partly for this reason we were led to a study of the mechanism of this reaction and of the structure and acidity dependence of its reaction rate.[14] The work was carried out in collaboration with D. R. Boyd and H. Dalton who have extensively investigated the microbiology, isolation, synthesis, structure determination and chemical modification of hydrate and dihydrodiol products.[1,2,11-14]

Our first task was to determine whether dehydration of the arene hydrates occurs by the same mechanism as that of simple alkyl and aralkyl alcohols. This led to a comparison of arene hydrates with the corresponding arene oxides and, especially, the rate dependence of their acid-catalysed aromatisation upon aromatic structure. The work, which is either unpublished or recently published, is summarised in this article.

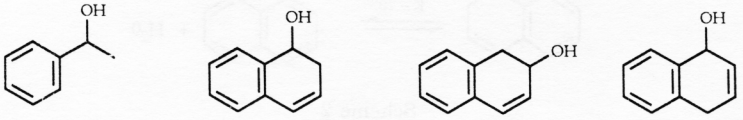
DEHYDRATION OF NAPHTHALENE HYDRATES: COMPARISON WITH ARALKYL ALCOHOLS

Measurements of rates of dehydration of the α- and β-hydrates **1** and **2** to form naphthalene were first reported by Jeffrey and Jerina who showed that the reactions occur readily in dilute acid solutions of mineral acids (equation 2).[3] The rates of reaction are much greater than for structurally related alcohols, and a quantitative comparison in aqueous solution shows that the α-naphthalene hydrate (**1**) reacts 10^8 times more rapidly than its aralkyl analogue α-phenylethanol (**6**).[14] Second order rate constants (M^{-1} s^{-1}) for reaction of **6** and all three naphthalene hydrates with H^+ in aqueous solution are shown below. Because of the low reactivity of α-phenylethanol its rate constant had to be extrapolated from measurements in strongly acidic aqueous sulphuric acid solutions.[15,16]

One reason for the choice of α-phenylethanol as a point of comparison is that its mechanism of reaction has been investigated in detail.[15-18] As shown in Scheme 1, acid-

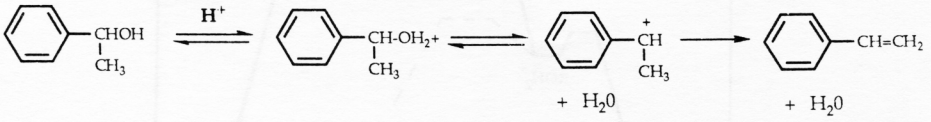


(2)



6.4×10^{-9}	0.35	1.8	240
6	1	2	3

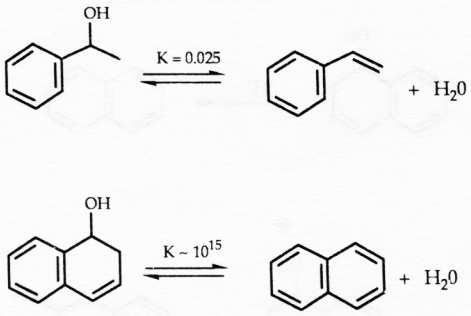
catalysed carbon-oxygen bond breaking in the alcohol reactant yields a carbocation intermediate which is deprotonated to styrene in the rate-determining step. In comparison with arene hydrates obvious factors influencing reactivity are the stabilities of (a) the carbocation and (b) the product.



Scheme 1

One's attention is drawn initially to the much greater stability of the aromatic naphthalene product than of styrene. The equilibrium constant for styrene formation was measured by Schubert and Keefe[15] as 0.025 and reminds us that the alcohol is more stable than the alkene. Indeed a rate constant for dehydration was derived by monitoring the thermodynamically favoured hydration reaction and combining this with the equilibrium constant. The corresponding equilibrium constant for dehydration of naphthalene hydrate can be deduced from measured or estimated free energies of formation of reactants and products in aqueous solution as $K \cong 10^{15}$. As expected, formation of naphthalene has a very large thermodynamic advantage. The two equilibria are compared in Scheme 2 below.

In practice the greater stability of the naphthalene product appears to account for only a fraction of the 10^8-fold difference in reactivity between the alcohol and hydrate. One reason for this can be seen from the free energy profile in Figure 1. The full lines in this figure represents the dehydration of α-phenylethanol based on the mechanism of Scheme 1. Protonated alcohol and carbocation intermediates are shown and the highest barrier in the reaction is for loss of a proton from the carbocation to form product. Provided there is no change in mechanism, therefore, the influence of increased product stability is limited to lowering this barrier until it is lower than that



Scheme 2

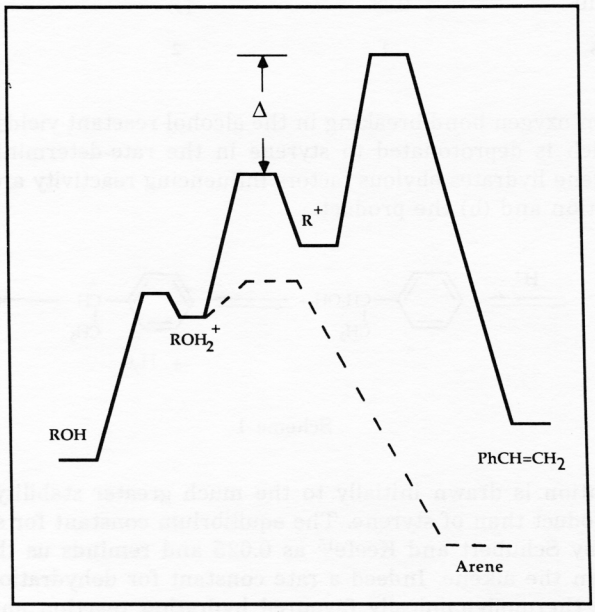


Figure 1. Free eneregy profiles for dehydration reactions: (——) α-phenylethanol; (– – –) hypothetical concerted mechanism for arene hydrate.

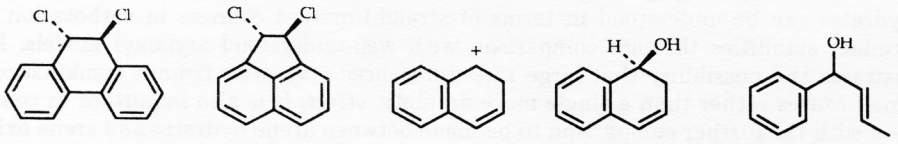
for formation of the carbocation intermediate. The maximum increase in rate thus corresponds to the difference in activation energies (Δ in Figure 1) between these two processes.

The rate of carbocation formation has been ingeniously measured by Richard, Rothenberg and Jencks, by monitoring formation of α-phenylethyl trifluoroethyl ether from reaction of α-phenylethanol in trifluoroethanol-water mixtures by HPLC, and combining this with the partitioning ratio of the carbocation between water and trifluoroethanol measured from reaction of the corresponding chloro substrate in the same solvent mixture.[17] Correction of the measurements for the solvent difference be-

tween water and trifluorethanol[18] (and for use of the more reactive *p*-methyl substituted substrate) shows that carbocation formation is only ~700-fold faster than the dehydration reaction.

In principle a greater influence of product stability upon the reactivity of the naphthalene hydrate would be possible if there was a change from an E1 mechanism of elimination of water to E2, with product formation occurring directly by concerted proton removal and carbon-oxygen bond-breaking from the O-protonated hydrate intermediate ROH_2^+. This possibility is shown by the dashed line in Figure 1. However, measurements with the more reactive 1,4-naphthalene hydrate (**3**) in acetic acid buffers showed no evidence of general acid catalysis, which would be expected of such a mechanism.[14] It is noteworthy also that of the naphthalene hydrates only **3** showed evidence of a (very slow) base-catalysed dehydration in aqueous sodium hydroxide.[19] It seems likely therefore that the aromatic stability of the product is not efficiently expressed in a concerted reaction. Consistent with this, dehydrochlorination of *trans*-9,10-dihydrodichlorophenanthrene (**7**) in $EtO^-/EtOH$ solutions[20] occurs only about twenty times as rapidly as 1,2-dichloroacenaphthene (**8**)[21] despite the large difference in product stabilities.

The simplest conclusion to be drawn from these results is that the principal origin of the reactivity difference between α-phenylethanol and naphthalene hydrate lies not in a difference in product stabilities, but a difference in ease of carbocation formation. In this respect the stabilising influence of the *o*-vinyl group in the carbocation from naphthalene hydrate (**9**) can be recognised. However it is unlikely that this could account for the whole of the remaining 3×10^5-fold difference in reactivities, and indeed in part it reflects the cyclic nature of the carbocation **9**.



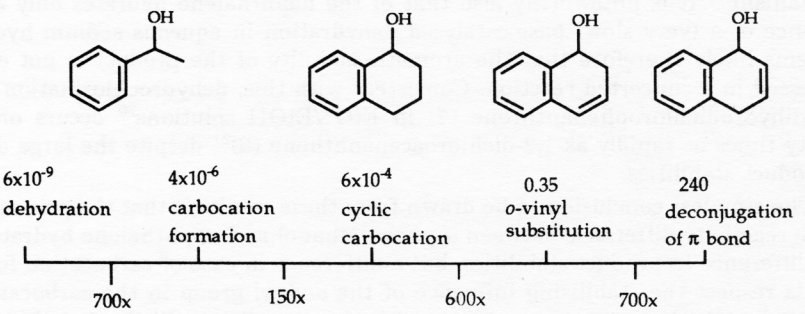
7 **8** **9** **10** **11**

The influence of the cyclic carbocation is apparent from measurements of the rate of acid-catalysed racemisation of the optically active tetralol **10**. Assuming that this represents the rate of carbocation formation, the carbocation is formed over one hundred times faster than from α-phenylethanol.[14] The difference may be ascribed to a loss of entropy accompanying freezing out of free rotation of the phenyl ring in resonance stabilisation of the non-cyclic carbocation, as well as steric hindrance from the α-methyl group to achievement of a planar structure favourable to resonance.

We are left with a factor of 10^3 for the influence of the *o*-vinyl group. Attempts to model this effect for the α-hydrate **1** directly have so far been unsuccessful. However a comparison can be made between the γ-hydrate **3** and the alcohol **11**. Assuming that rearrangement of the double bond in **11** into conjugation with the benzene ring is a measure of carbocation formation, the difference in reactivities between **11** and **3** should again reflect the cyclic character of the cation from **3**. The measured difference is 400-fold which is not far from the difference of 150-fold for formation of non-cyclic carbocations from α-phenylethanol and tetralol.[14] This implies that the activating effects of the vinil groups in **3** and **11** are comparable.

The origin of the substantially greater reactivity of the γ-hydrate **3** than the isomeric α- and β-hydrates **1** and **2** almost certainly stems from a difference in reactant stabilities, arising from conjugation of the double bond with the ring in **1** and **2** but not **3**.* Thus **3** is 130-fold more reactive than **2** despite yielding the same allylic carbocation intermediate. This difference corresponds fairly closely with the difference in energies of 1,2- and 2,3-dihydronaphthalenes.[22]

If, for the present, we neglect the small (5-fold) difference in reactivity between **1** and **2** we may summarise contributions to the differences in reactivities of α-phenylethanol and the α- and γ-hydrates **1** and **3**, as in Scheme 3.



Scheme 3

This rather lengthy analysis establishes that the reactivity of the naphthalene hydrates can be understood in terms of straightforward changes in carbocation and product stabilities through comparison with well-understood arylalkyl models. It illustrates the possibility that large rate differences may arise from a combination of small causes rather than a single more dramatic effect. It is also important in connection with the further comparison to be made between arene hydrates and arene oxides. As will become clear, an understanding of this depends on a correct assessment of the influence of carbocation stability upon reactivity.

STRUCTURE AND REACTIVITY OF ARENE HYDRATES

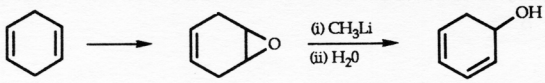
Benzoannelation

Before introducing the comparison with arene oxides it is appropriate to consider the influence of structure upon reactivity of arene hydrates for a wider range of aromatic structures. The parent benzene hydrate **12** was prepared twenty years ago by Stavascik and Rickborn[4] using the reactions shown below, and readily undergoes dehydration in acetic acid buffers to form benzene.[23] A number of isomeric phenanthrene and anthracene hydrates have also been prepared, making use of synthetic methods developed by Boyd for the naphathalene hydrates.[24]

The relationship between reactivities towards acid of benzene hydrate and naphthalene or other polycyclic aromatic hydrates can be considered in terms of replacing

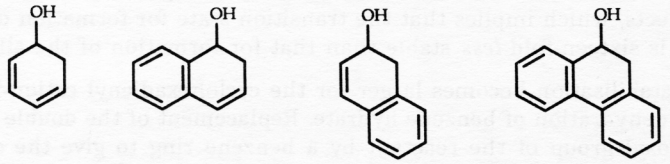
* There is probably also a ground state effect arising from a change in geminal interactions of the hydroxyl group: this is discussed below.

a double bond conjugated with the carbocation centre with a benzene ring, *i.e.* benzoannelation. Rate constants (M^{-1} s^{-1}) for dehydration of a series of arene hydrates are shown in Scheme 4 where it can be seen that benzoannelation of benzene hydrate to α- and β-naphthalene hydrates reduces reactivity, and dibenzoannelation to phenanthrene hydrate reduces it further. Substitution of benzene for the double bond adjacent to the hydroxyl group reduces the rate by 500-fold and for the remote double bond by 100-fold. The effect of two benzene rings, in phenanthrene hydrate, is equal to the product of these effects and the reduction in rate is 50,000 fold.



12

These apparently straightforward results need to be interpreted with a little care. A comparison of rates of solvolysis of allyl chloride and benzyl chloride shows that replacement of an allylic double bond by a benzene ring increases the rate of carbocation formation by a factor of 2-fold,[25] and a comparison of rates of carbocation formation from tetralol **11** and 2-cyclohexenol (**13**) shows a similar difference in the opposite direction.[23] These rather small effects contrast with the large rate-retarding effects of benzoannelation in Scheme 4.

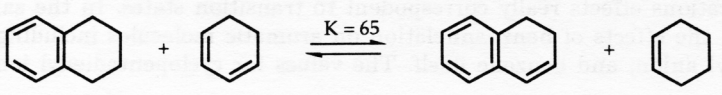


180 0.35 1.8 3.9×10^{-3}

Scheme 4

The large reductions in rate and, presumably, in the stability of the carbocation intermediates, appear to be characteristic of strongly conjugated systems. However, to interpret the behaviour satisfactorily it is necessary to separate effects of benzoannelation in the reactants and in the transition state, and this can be done by writing appropriate isodesmic reactions. Such a reaction is illustrated in equation (3), which shows the stabilising effect on one of the double bonds of cyclohexadiene of replacing the other by a benzene ring. From free energies of formation of reactants and products[26] the equilibrium constant for this reaction (in aqueous solution) is calculated as 65.

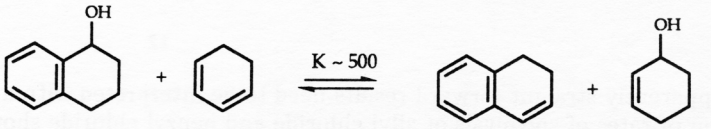
On the face of it the factor of 65 represents the reactant contribution to the difference in rates of hydrolysis of benzene and naphthalene hydrates (**12** and **1**). How-



(3)

ever, the reactants in the dehydration reactions contain a hydroxyl group, and the equilibrium constant of equation (3) appears to be modified by a further difference arising from geminal interactions of this hydroxyl group with the double bond of the benzene hydrate and the benzene ring of the naphthalene hydrate.[23]

The influence of the hydroxyl group[27] may be assessed from the further isodesmic reaction shown in equation (4). Based on measurements for the hydration of cyclohexadiene and benzocyclohexadiene an equilibrium constant $K \sim 500$ may be derived for this reaction.[23] From the ratio of equilibrium constants for reactions (3) and (4) we then deduce that the geminal interaction of a hydroxyl group with the double bond of 2-cyclohexenol (**13**) is more favourable than with the benzene ring of tetralol by a factor of $500/65 \sim 8$



(4)

13

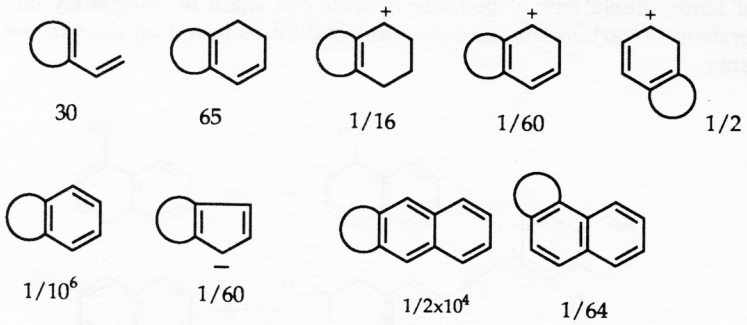
We are now in a position to correct our rate measurements for reactant contributions from both benzoannelation and geminal interactions of the hydroxyl group. Thus for the ionisation of 2-cyclohexenol (**13**) and tetralol **10** the ~2-fold rate-retarding effect of benzene substitution should be modified by an eight-fold difference in geminal hydroxyl effects, which implies that the transition state for formation of a cyclic benzylic cation is sixteen-fold *less* stable than that for formation of the allyl cation.

This destabilisation becomes larger for the cyclohexadienyl cation-like transition state in the dehydration of benzene hydrate. Replacement of the double bond adjacent to the hydroxyl group of the reactant by a benzene ring to give the α-naphthalene hydrate **1**, as we saw, decreased the rate by 500-fold. However correction of this for the influence of a reactant double bond and hydroxyl group reduces it by a factor of 65/8 (8-fold) to 60-fold (equation 5). Interestingly, when benzene replaces the remote double bond in benzene hydrate, so that the conjugation in the carbocation is not interrupted, the destabilising effect disappears. The observed rate difference between benzene hydrate and the β-naphthalene hydrate of 100-fold is reduced by the full factor of 65-fold for stabilisation of the double bond in the reactant (equation 3), and the transition state effect is then only 1.5-fold, less than that for the allyl cation.

(5)

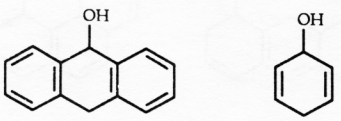
The magnitudes of these benzoannelation effects are shown under the appropriate structures in Scheme 5. The position of benzoannelation is indicated by a circle and the carbocations effects really correspodent to transition states. In the same scheme are shown the effects of benzoannelation on aromatic molecules including the cyclopentadienyl anion, and benzene itself. The values for cyclopentadienyl ion are based

on pK_a measurements in DMSO[28] corrected for the appropriate reactant contributions. It can be seen that the destabilising effect of benzoannelation is again greater for aromatic rings than non-aromatic conjugated double bonds, and the larger effect for benzene than the cyclopentadienyl ion presumably reflects the greater aromaticity of the latter. As expected, the effect of benzoannelation of benzene is also larger than that of naphtalene (to form anthracene or phenanthrene). It may also be noted that although effects of benzoannelation have been analysed in terms of valence bond resonance they are also generally consistent with relative π-delocalisation energies[29,30] or coefficients of the HMO non-bonded molecular orbitals of the carbocations.[31]



Scheme 5

Turning to the γ-hydrate of naphthalene (**3**) we suppose that, because the double bond is unconjugated, the only effect of benzoannelation in the reactant is a difference in geminal interactions of the double bond and benzene with the hydroxy group. Taking this again as 8-fold we deduce that the 25-fold rate reduction for the 9,10-anthracene hydrate (**14**) represents an effect of 200-fold in the transition state. Unfortunately, there is no information on the parent 1,4-benzene hydrate (**15**), but it is likely that the first benzoannelation will have a greater rate retarding effect than the second, so we may expect a rate constant for acid-catalysed dehydration of this compound to be substantially greater than the value of 10^4 M^{-1} s^{-1} estimated by supposing the effects are the same. This compares with 180 M^{-1} s^{-1} for the 1,2-hydrate **12** and implies a fairly rapid reaction of **15** in water at pH 7.



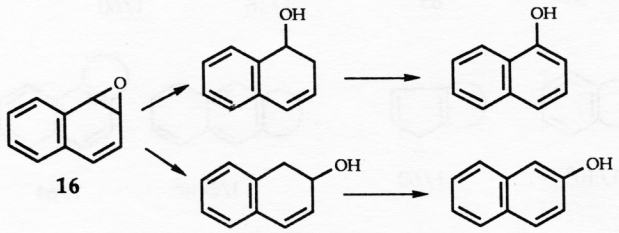
14 **15**

22 $M^{-1}s^{-1}$ $>10^4 M^{-1}s^{-1}$

Also of interest are the relative stabilities of the carbocations formed from the α- and β-naphthalene hydrates (**1** and **2**). Correction for the 8-fold difference in geminal hydroxyl effects in the reactants suggests that differences in carbocation stability con-

tribute a factor of 40-fold to the greater reactivity of β- than α-hydrates. The observed rate-difference of five-fold reflects compensation between these effects. In this connection it is noteworthy that the ratio of ring-opening of the 1,2-naphthalene oxide (**16**) under acidic conditions to give α- and β-naphthols, presumably *via* the isomeric carbocations shown in Scheme 6, is 20 : 1.[32] This is, as expected, greater than the observed difference in rates for dehydration of the α- and β-naphthalene hydrates (because there is no hydroxyl geminal effect) but less than the contribution of carbocation stability to this difference (because ring strain in the epoxide should render the reaction less sensitive to carbocation stability).

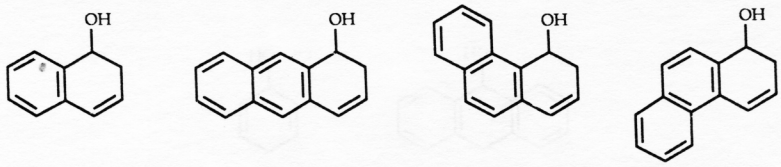
The general conclusion to be drawn from this discussion is that the rate-retarding effect of benzoannelations of benzene hydrate can again be adequately understood from consideration of carbocation and reactant stabilities based on conventional resonance arguments.



Scheme 6

Polycyclic Arene Hydrates

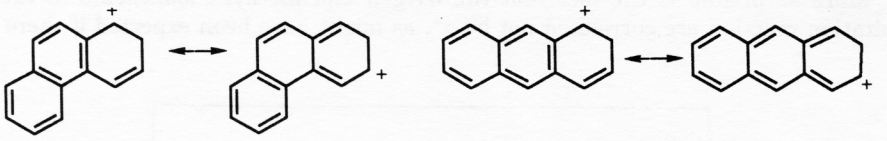
A second rank of benzoannelation may be considered in relation to the naphthalene hydrates, through replacement of double bonds in the aromatic rings by benzene. We will consider the effect only for the α-hydrate **1**, partly because more data are available than for the β-hydrate and partly because reactant effects are less easily estimated than for benzene hydrate. Thus in the α- but not the β-hydrate, there is substantial cancellation between the hydroxyl geminal effect and double bond stabilisation associated with benzoannelation of the reactant.



1	**17**	**18**	**19**
0.35 $M^{-1}s^{-1}$	0.05	7.5	2.5

There are three possible positions of benzoannelation of the α-hydrate yielding the hydrates of anthracene and phenanthrene as shown in structures **17-19.** Rate con-

stants (M^{-1} s^{-1}) for their acid-catalysed dehydrations are appended below these structures. As already noted benzoannelation has a substantial destabilising effect on the benzene ring of the reactant. However, this will be largely cancelled between reactants and transition state and we may be justified in viewing the influence of benzoannelation in conventional terms as either enhancing or suppressing conjugation between the double bond and carbocation centre in the transition state. This conjugation indeed should be enhanced in the phenanthrene hydrates, where resonance stabilisation of the carbocation can be achieved without disruption of the valence bond structure of both rings (**20**), and suppressed in the case of the anthracene hydrate where resonance stabilisation of the carbocation does not have this effect (**21**).

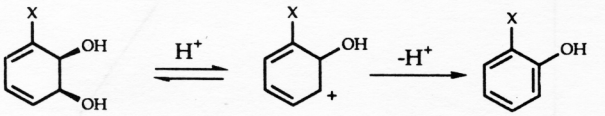


20 **21**

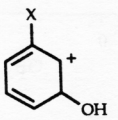
Examination of the relative reactivites of **10** and **17-19** shows indeed that the phenanthrene hydrates are more, and anthracene hydrates is less, reactive than the naphthalene hydrate, as expected. The rate enhancements for the phenanthrene hydrates (7-fold and 22-fold) are, again as expected, less than for restoring the intact double bond of benzene hydrate (over 500-fold).

Substituent Effects on Dehydration

Following this assessment of the effects of benzoannelation it is worth considering conventional substituent effects on the dehydration reaction. Although data are not available for hydrates themselves a series of 3-substituted *cis*-1,2-benzenedihydrodiols **22** have been prepared from microbial oxidation of the corresponding substituted benzenes or by chemical modification of the microbial product.[12,33,34] Although a complete set of product analyses is not yet available the predominant product is normally the *o*-substituted phenol, as shown in equation (6).



22 **23** (6)



24

If we suppose that the mechanism of this reaction is the same as that for the benzene hydrates, then the preferred formation of the carbocation **23** leading to *o*-substituted product is consistent with the expected stabilisation of this cation relative to that leading to the *m*-isomer **24** both by +M resonance effects of the substituent and a lower sensitivity to adverse electronegativity effects.

This is consistent with the negative value of $\rho = -7.2$ obtained from a Hammett plot of log k *versus* σ_p for sixteen substituted diols shown in Figure 2. It can be seen that the carbocation intermediate **23** has the same structure as a benzenonium ion formed in the hypothetical electrophilic aromatic substitution of a *m*-substituted phenol by the electrophile OH^+. Appropriately the magnitude of ρ is in the mid-range of values observed for electrophilic aromatic substitution.[35]

More surprising is the fact that the oxygen and methyl substituents in the dehydration reaction are correlated not by σ^+, as might have been expected if there was

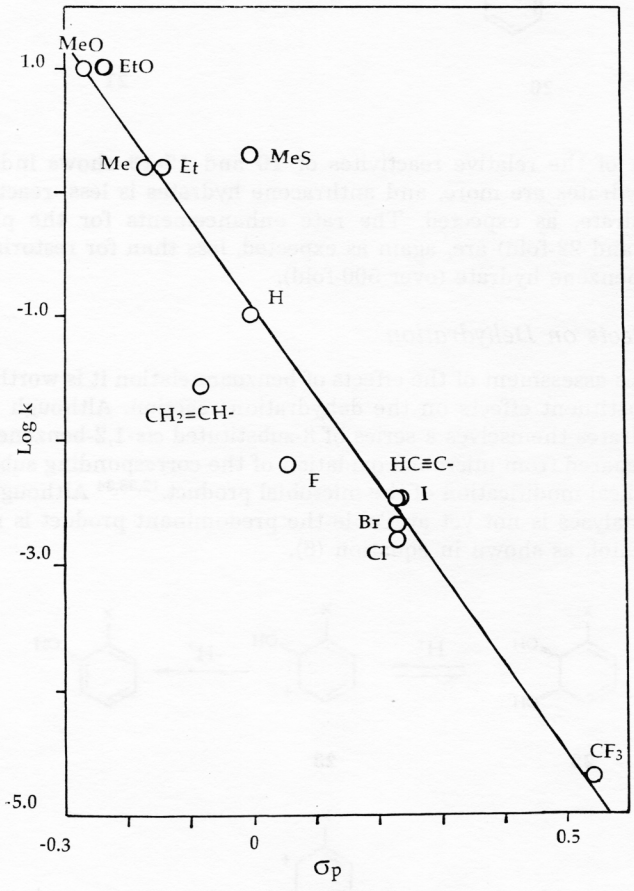


Figure 2. Hammett plot of log k (M^{-1} s^{-1}) *versus* σ_p for H^+ catalysed dehydration of substituted *cis*-benzenedihydrodiols (**22**).

a +M resonance interaction between the substituent and the carbocation centre, but by σ_p. For the ρ value observed the difference between substituent parameters is large and the methoxy and ethoxy substrates are nearly 1000-fold less reactive than expected on the basis of σ^+. It is noticeable, however, that the more polarisable substituent CH_3S *is* correlated by σ^+, while the poorly polarisable fluorine substituent appears to show even less resonance stabilisation than implied by the σ_p substituent constant (based on the ionisation of substituted benzoic acids).

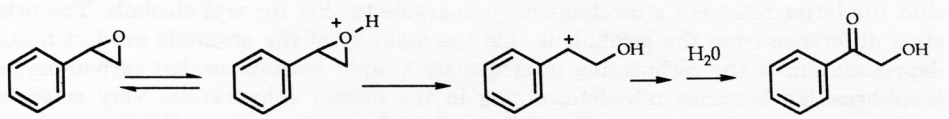
While it is not possible to interpret this pattern of resonance effects in detail some differences from an electrophilic substitution can be recognised. In the first place the reactant is a diene rather than an aromatic molecule and the reaction may be more sensitive than normal to compensating resonance effects in the reactants. However, it seems unlikely that this could account fully for the impairment of normal resonance effects observed, and a further difference from a conventional aromatic substitution is that the substituent is formally separated by two double bonds from the charge centre rather than one, as it would be for a *p*-substituent, or none, as for an *o*-substituent. Thus a more limited set of measurements for acid catalysed aromatisation of benzene oxides where the substituent has a *p*-relationship to the carbocation centre appear to show a normal sensitivity to resonance.[36] While no firm conclusion can be drawn it seems possible that the curious pattern of resonance effects observed represents an imbalance in resonance stabilisation arising from the unusually large separation of positive charge and substituent.[37]

Despite this apparent anomaly, the magnitude of ρ and the evidence of a substantial resonance effect, at least in the case of the methylthio substituent, are consistent with the proposed mechanism of dehydration involving reaction *via* a carbocation intermediate, which in the case of benzene dihydrodiols, has the structure **23**.

COMPARISON OF ARENE HYDRATES AND ARENE OXIDES

A principal purpose of this detailed examination of the aromatisation of arene hydrates has been to provide a basis for the comparison with the corresponding reaction of arene oxides. Before making this comparison, however, it is necessary to examine the reactions of the arene oxides themselves and to compare them with aliphatic and aralkyl epoxides in the same way that arene hydrates were compared with aliphatic alcohols.

It is appropriate first to review evidence that acid-catalysed ring-opening of simple epoxides can occur *via* a carbocation mechanism. This mechanism has been extensively considered in the literature[38-44] and is illustrated for styrene oxide (**25**) in Scheme 7. It has strong similarities with the corresponding mechanism for α-phenylethanol and reference to Scheme 1 shows that the intermediate carbocation (**26**) differs from the α-phenylethyl cation only in the presence of β-hydroxy substituent.

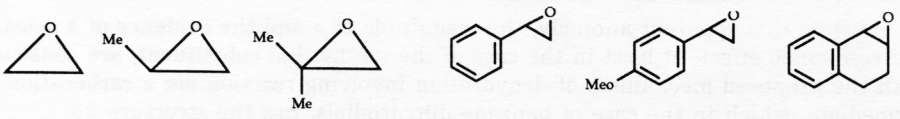


25 **26**

Scheme 7

Where this mechanism prevails, therefore, we expect relative rates for different epoxides to reflect the stability of the carbocation intermediates formed in the reaction. That this is so is evident from the second order rate constants summarised in Scheme 8. The rather small rate differences between acid-catalysed opening of ethylene oxide and its mono-methyl derivative are, as expected, consistent with an S_N2 reaction opening the O-protonated ring of these primary and secondary substrates. However, the strong acceleration from further methyl substitution, or from a phenyl substituent, indicates that in most cases a carbocation mechanism operates, at least in the absence of stronger nucleophiles than water. Based on relative rates of styrene oxide and *p*-methoxystyrene oxide ρ^+ for the hydrolysis reaction is –3.4 compared with –4.5 for carbocation formation from ring substituted α-phenylethanols.[17]

Two principal mechanistic differences exist between the behaviour of structurally related alcohols and epoxides: (a) in aqueous solution epoxides commonly show an uncatalysed pathway in addition to the acid-catalysed reaction,[42] and (b) carbon-oxygen bond-breaking to form the carbocation is rate-determining in the reaction of epoxides, whereas for alcohols the carbocation is normally formed reversibly and deprotonation to form the alkene product is rate determining. Although a degree of reversibility of ring-opening has been detected for the uncatalysed reaction of *p*-methoxystyrene oxide,[44] there seems no likelihood that this could occur for the acid-catalysed pathway.

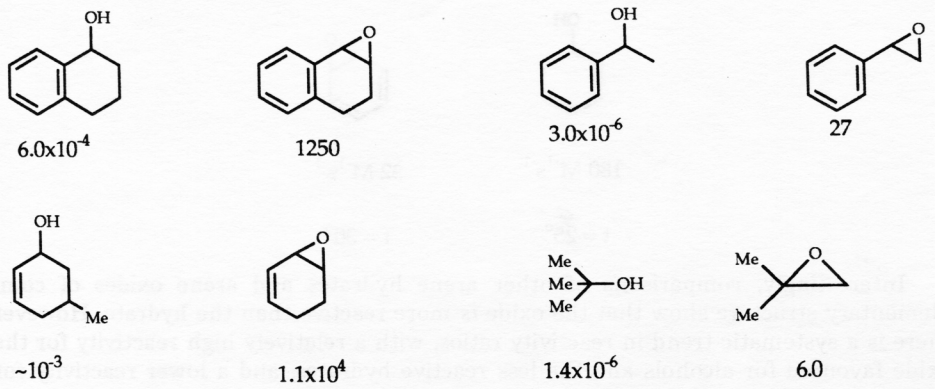


.009 .06 6.8 27 1.1×10^4 1250

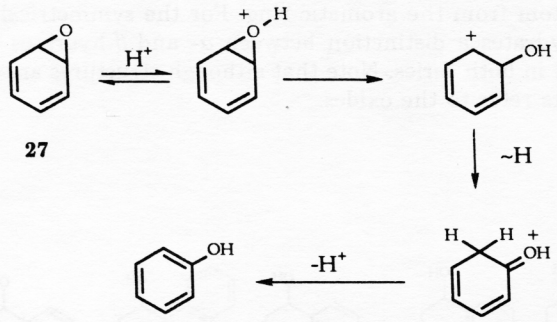
Scheme 8

A further important difference between alcohols and epoxides is the higher rate of acid-catalysed carbon-oxygen bond breaking in the latter. This is sensibly ascribed to strain in the epoxide ring. Second order rate constants for H^+-catalysed reactions of structurally related substrates are shown in Scheme 9. It can be seen that the reactivity of the epoxides is consistently 10^6–10^7 times greater than that of the alcohols notwithstanding a rate-retarding effect from the α-hydroxy group in the carbocation from the epoxide. It should be noted that in this scheme rate constants for the alcohols refer specifically to carbocation formation, although, as we have seen, this step is usually not rate determining in the dehydration reaction.

Turning to the comparison between arene oxides and arene hydrates, we recall that the latter react *via* a mechanism comparable to that for aryl alcohols. The principal difference from the alcohols is that the stability of the aromatic product makes deprotonation of the carbocation intermediate a rapid reaction so that carbon-oxygen bond-breaking becomes rate-determining in the overall dehydration. Very extensive studies of arene oxides by Jerina,[32,45-49] Sayer,[48,49] Whalen,[49] and Bruice[32,46,50] have shown that a similar analogy exists between aromatisation of arene oxides and the hydrolysis of simple epoxides, with both reactions occurring *via* β-hydroxy carbocation intermediates. As shown by Jerina, and illustrated for benzene oxide (**27**) in Scheme 10,



Scheme 9

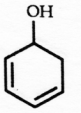


Scheme 10

there is a tendency for the carbocation formed from the arene oxide to undergo a hydride rearrangement to the keto form of phenol (NIH Shift). However this occurs after the rate-determining step and does not influence the rate of the reaction.

In comparing reactivities of arene oxides and arene hydrates therefore we expect both reactions to show a structure dependence dominated by carbocation stability, as discussed in detail for the arene hydrates. Moreover, as with the epoxides and alcohols in Scheme 9, we expect ring strain in the arene oxides to lead to a higher reactivity of oxides than hydrates. It is remarkable therefore that, although the smallest difference in Scheme 9 is a factor of 10^6-fold in favour of the epoxide, benzene oxide is found to be *less* reactive towards acid than benzene hydrate! As shown below, if account is taken of a statistical factor to allow for breaking of either one of the carbon-oxygen bonds in the oxide, the difference is 11-fold. Indeed the difference should be increased by a further small factor because measurements for the benzene hydrate were made at 25° and those for the benzene oxide at 30° (both in aqueous solution).

The discussion presented above sought to establish that the reactivity of benzene hydrate is normal for an alcohol yielding a cvyclohexadienyl carbocation. If this is correct the implication is that benzene oxide is unusually unreactive. Why should this be so?

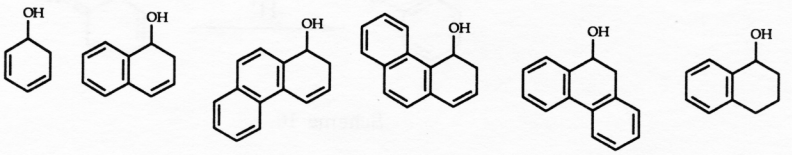



$180\ M^{-1}s^{-1}$ $32\ M^{-1}s^{-1}$

$t = 25°$ $t = 30°$

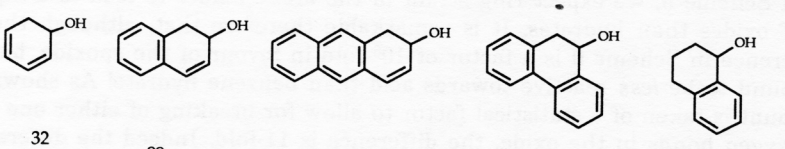
Interestingly, comparisons of other arene hydrates and arene oxides of complementary structure show that the oxide *is* more reactive than the hydrate. However there is a systematic trend in reactivity ratios, with a relatively high reactivity for the oxide favoured for alcohols and the less reactive hydrates, and a lower reactivity for the more reactive hydrates. This is shown in Scheme 11 for two series of structures, one for α-hydrates, in which the hydroxyl group is adjacent to an aromatic ring, as in the α-naphthalene hydrate (**1**), and the other for β-hydrates in which it is separated by one carbon atom from the aromatic ring. For the symmetrical benzene and 9,10-phenanthrene hydrates a distinction between α- and β-hydrates does not arise and they are included in both series. Note that although structures are shown for hydrates the rate constants refer to the oxides.

α-Series



$k_{ox}/M^{-1}s^{-1}$	32	11	220	810	130	1250
k_{ox}/k_{hyd}	0.9	31	88	108	3.3×10^4	2.1×10^6

β-Series



$k_{ox}/M^{-1}s^{-1}$	32	99	300	130	1250
k_{ox}/k_{hyd}	.09	55	1500	3.3×10^4	2.1×10^6

Scheme 11

TABLE I

Second order rate constants (M^{-1} s^{-1}) for H^+ catalysed dehydration and epoxide ring-opening reactions in aqueous solution

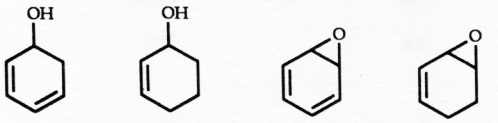
Aromatic or arene/alkene product	Hydrate or alcohol[a]	Oxide	$k_{hydrate}$[b] 25 °C	k_{oxide} 30 °C	$k_{oxide}/k_{hydrate}$
Benzene	**12**		180	32	0.09
Naphthalene	**1** (α)	1,2	1.8	11	31
Naphthalene	**2** (β)	1,2	0.35	99	56
Phenanthrene	**19** (α)	1,2	2.50	220	88
Phenanthrene	**18** (α)	3,4	7.50	810	108
Anthracene	(β)	1,2	0.10	300[c]	1500
Phenanthrene		9,10	3.9×10^{-3}	130	3.3×10^4
1,2-dihydronaphthalene		3,4	6.0×10^{-4}	1250[c]	2.1×10^6
Styrene			3.0×10^{-6}	27[c]	9×10^6
Cyclohexadiene			(10^{-3})[d]	1.1×10^4[c]	(10^7)
Isobutene			1.4×10^{-6}	6.0[c]	4.3×10^6

[a] Greek letter indicates position of hydroxyl substitution: see p. 594 of text. [b] Rate constants for carbocation formation from hydrate or alcohol. [c] 25 °C. [d] Estimated from the rate constant (3.0×10^{-4}) for *cis-trans* isomerisation of *cis*-3-methylcyclohexenol at 30 °C in 35% *v/v* aqueous acetone.

One reason for separating results into two series is that for unsymmetrical arene oxides ring-opening can occur in two directions leading to isomeric phenolic products. For example, as shown in Scheme 6, 1,2-naphthalene oxide can yield α- or β-naphthol. From the product ratio we can partition the measured rate constant for aromatisation into contributions from carbon-oxygen bond-breaking at α- and β-carbon atoms respectively. It is these partitioned rate constants which are appropriately compared with rate constants for dehydration of the corresponding α- and β-hydrates and which are included in Scheme 11.

Fuller details of these results are shown in Table I. There it can be seen that there is a close correlation between the oxide-to-hydrate rate ratio (k_{ox}/k_{hyd}) and the reactivity of the arene hydrate, stemming from the fact that as the reactivity of the hydrate decreases that of the oxides remains approximately constant or even increases. This is apparent from the second order rate constants for the H^+ catalysed reactions in Scheme 12 which show that benzene hydrate is approximately 10^5 times as reactive as 1,2-cyclohexenol whereas benzene oxide is 3×10^3 times less reactive than cyclohexadiene oxide.

The increase in reactivity of the oxides is particularly noticeable if one considers epoxides of cycloalkenes. However, inclusion of styrene oxide in the table shows that



180 ~10^3 32 1.1x10^4

Scheme 12

the difference from the hydrates is not linked to the cyclic nature of the reactants. For the reasons discussed above for tetralol, carbocation formation in a ring is more favourable than in an analogous open chain molecule, but as this affects both epoxide and alcohol reactivities it leaves their relative rates unaffected.

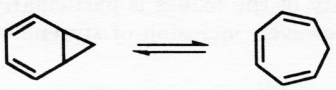
Schemes 11 and 12 show perhaps more clearly than the table the structural implications of these trends in reactivities and rate ratios. As we have seen, benzene oxide and benzene hydrate on the one hand and non-aromatic epoxides and alcohols on the other represent opposite extremes of behaviour. What the schemes suggest is that the trend in hydrate/oxide rate ratios correlates with *the resonance energy of the aromatic ring being formed in the reaction.*

This conclusion is surprising because we have seen that reactivities of arene hydrates are sensitive to carbocation stabilities and not to the stability of the aromatic product. What it suggests is that the arene oxides *themselves* are subject to an aromatic-like stabilisation. The most obvious explanation of this is that it results from a homoaromatic interaction of the π-bonds of the arene oxides with the epoxide ring. This interaction is likely to be decreased by benzoannelation in corresponding all π-electron rings, as is observed.

Observations of substantial homoaromatic stabilisation have hitherto been confined mainly to carbocations.[51] Although stabilisation has been suggested for neutral molecules the effects proposed have been relatively small and not easily detectable experimentally or by calculations.[52] However, Jorgensen[53] has calculated a stabilisation energy for norcaradiene (**28**) of ~ 5 kcal/mole and this has been confirmed experimentally in a study of heats of formation of an extensive series of related molecules by Roth and Klarner.[54] The possibility of homoaromatic stabilisation has also been considered for benzene oxide[55] but to our knowledge no stabilisation energy has been calculated.[56]

The advantage of kinetic measurements in investigating homoaromaticity is that they provide a sensitive experimental probe of stabilisation energies. Thus the 10^7-fold difference in rate ratios of oxide to hydrate for benzene oxide and a non-aromatic epoxide implies that benzene oxide is stabilised by 10 kcal/mole.

The likelihood that the stabilisation of benzene oxide is larger than that for norcaradiene seems to be confirmed by the fact that norcaradiene exists as its more stable isomer cycloheptatriene (**29**), while the solvent and temperature sensitive equilibrium between benzene oxide and the monocyclic oxepin (**30**), at least in aqueous solution at room temperature, lies in favour of benzene oxide.[57] A simple view would be that

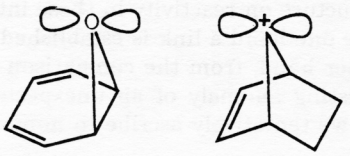


28 **29**

27 **30**

replacement of CH_2 in cycloheptatriene by oxygen should stabilise the double bonds of the ring-opened oxepin. The fact that on the contrary benzene oxide is favoured suggests a significant compensating stabilisation of this species.

Two possible interactions of the oxide ring with the π-electrons of the benzene oxide can be envisaged. Thus Kollman *et al.* have suggested involvement of the lone pair of electrons on oxygen.[55] In this case an analogy may be made between the 6-electron stabilisation of benzene oxide and the strongly homoaromatic 2-electron 7-norbornenyl cation (**31**) originally investigated by Winstein and Stafford.[58]



27 **31**

In practice, however, norcaradiene (**28**) has no lone pair of electrons and is known to be stabilised relative to cycloheptatriene (**29**) by electron withdrawing substituents in the methylene group of the cyclopropane ring.[59] It is possible therefore that stabilisation of benzene oxide involves the sigma orbitals of the epoxide ring and that the greater electronegativity of oxygen than carbon (or some other feature of the oxide ring) favours the homoaromatic interaction.

Indeed at this stage it must be said that the interpretation in terms of homoaromaticity is speculative. Nevertheless the difficulty of finding an alternative explanation is summed up by the four way comparison of reactivities of benzene and cyclohexadiene oxides and hydrates in Scheme 12. Thus if we ascribe the 10^5-fold greater reactivity of benzene hydrate than cyclohexenol to the greater stability of a cyclohexadienyl than cyclohexenyl carbocation intermediate we might expect a smaller difference for the corresponding oxides on a reactivity–selectivity basis. However we cannot explain the 1000-fold *lower* reactivity of benzene oxide. Similarly, it seems unlikely that a stereoelectronic effect could inhibit ring opening of benzene oxide because this should be controlled by the double bond adjacent to the epoxide ring (which is also present in the normally reacting cyclohexadiene epoxide) not the remote double bond.

The evidence for some form of stabilisation of the benzene oxide ring therefore seems clear, and so far we have not found an alternative to homoaromaticity. However evidence based on kinetic measurements should be supplemented by calorimetric measurements and further calculations.

Irrespective of the nature of the stabilisation, it has significant implications. Thus arene oxides are intermediates in the oxidative metabolism of polycyclic aromatic hydrocarbons leading to well known carcinogenic species.[10,60] Clearly the stabilisation of these reactive molecules may influence their ability to survive in a cellular environment. Certainly some of the arene oxides, had they lacked such stabilisation, would be degraded quite rapidly in aqueous media at physiological pHs.

CONCLUSION

It can be seen that a study of arene hydrates in a small but significant way extends the scope of carbocation chemistry. For this reason our article is dedicated to Professor D. E. Sunko who has been a major contributor to developing our understanding of this field. In particular, arene hydrates provide a bridge between polycyclic aromatic structures and the more familiar chemistry of aliphatic and aralkyl carbocations. They show that stabilisation of carbocation transition states involving polycyclic conjugation can be understood in terms of conventional concepts of valence bond resonance. They also provide a bridge to carbocation reactions of arene oxides, and thence offer a basis for interpreting the effect of structure on reactivity in these interesting and metabolically important molecules. On the one hand a link is established between arene oxides and simple epoxides. On the other hand, from the comparison of arene oxides and arene hydrates appears the interesting anomaly of an unexpectedly low reactivity for the arene oxides. It is this that we tentatively ascribe to homoaromatic stabilisation.

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SAŽETAK

Karbokationi iz aren-hidrata i aren-oksida

Rory A. More O'Ferrrall i S. Nagaraja Rao

Razmotren je mehanizam dehidratacije aren-hidrata i aren-oksida u prisutnosti kiselina. Posebna je pozornost posvećena utjecaju supstituenata i anelacije benzenske jezgre na brzinu reakcije. Nađeno je da aren-oksidi daleko teže podliježu dehidrataciji, što se pripisuje homoaromatskoj stabilizaciji aren-oksidnog prstena.