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Citation for the published paper:

Kudavalli, J., Rao, S., Bean, D., Sharma, N., Boyd, D. et al. (2012)

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Journal of the American Chemical Society, 134(34): 14056-14069

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Base-catalyzed Dehydration of 3-substituted Benzene *cis*-1,2-dihydrodiols: Stabilization of a Cyclohexadienide Anion Intermediate by Negative Aromatic Hyperconjugation.

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ABSTRACT

Evidence that a 1,2-dihydroxycyclohexadienide anion is stabilized by aromatic ‘negative hyperconjugation’ is described. It complements an earlier inference of ‘positive’ hyperconjugative aromaticity for the cyclohexadienyl cation. The anion is a reactive intermediate in the dehydration of benzene-*cis*-1,2-dihydrodiol to phenol. Rate constants for 3-substituted benzene-*cis*-dihydrodiols are correlated by σ^- values, $\rho = 3.2$. Solvent isotope effects for the reactions are $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.2\text{--}1.8$. These measurements are consistent with reaction *via* a carbanion intermediate or a concerted reaction with a ‘carbanion-like’ transition state. These and other experimental results confirm that the reaction is stepwise, with a change in rate-determining step from proton transfer to the loss of hydroxide ion from the intermediate. Hydrogen isotope exchange accompanying dehydration of the parent benzene-*cis*-1,2-dihydrodiol is not found, thus the proton transfer step is subject to internal return. A rate

constant, *ca.* 10^{11} s^{-1} , corresponding to rotational relaxation of the aqueous solvent, is assigned to loss of hydroxide ion from the intermediate. The rate constant for internal return therefore falls in the range $10^{11} - 10^{12} \text{ s}^{-1}$. From these limiting values and the measured rate constant for hydroxide-catalyzed dehydration a $\text{p}K_{\text{a}} = 30.8 \pm 0.5$ is determined for formation of the anion. Although loss of hydroxide ion is hugely exothermic, a concerted reaction is not enforced by the instability of the intermediate. Stabilization by negative hyperconjugation is proposed for 1,2-dihydroxycyclohexadienide and similar anions, and is supported by additional experimental evidence and by computation, including evidence for a diatropic ('aromatic') ring current in 3,3-difluorocyclohexadienyl anion.

INTRODUCTION

The acid-catalyzed dehydration of arene dihydrodiols is now a well-studied reaction.^{1,2,3} As shown in Scheme 1 for the example of benzene-*cis*-1,2-dihydrodiol **1**, it is believed to proceed through a carbocation intermediate **2**. The occurrence and mechanism of the reaction are understandable from analogy with the dehydration of alcohols and vicinal diols of non-aromatic carbon-carbon double bonds.⁴ More surprising is that the dehydration also occurs with base-catalysis under the mild conditions of aqueous sodium hydroxide at room temperature. This reaction is shown in the lower pathway of Scheme 1.

The reaction in basic media is surprising because base-catalyzed dehydration forming a carbon-carbon double bond normally requires activation of the carbon β - to the reacting hydroxyl group by a substituent capable of stabilizing a carbanion intermediate such as a keto, cyano or

Scheme 1

fluorenyl group.⁵ It is quite unexpected that a cyclohexadienide anion such as **3** would be a viable reactive intermediate under such mildly basic conditions. In principle the reaction could proceed in a concerted manner, and this possibility is considered below, but, to our knowledge, there is no example of a dehydration reaction in solution proceeding by such a mechanism.

In this paper we report a study of the base-catalyzed dehydration of a series of 3-substituted benzene-*cis*-1,2-dihydrodiols. Measurements of hydrogen isotope effects and isotope exchange point to a mechanism in which a carbanion intermediate is subject to internal return. Assignment of a rate constant for the rotational relaxation of water (10^{11} sec^{-1}) to the loss of hydroxide ion from the carbanion intermediate allows derivation of a $\text{p}K_{\text{a}}$ for the carbanion and leads to an evaluation of the $\text{p}K_{\text{R}}$ of the phenolic product of the reaction. It is proposed that the carbanion is stabilized by negative hyperconjugation^{6,7,8} from the presence of a β -OH group and this is supported by MP2 calculations for carbanion **3**, the structure of which corresponds to a Meisenheimer intermediate of nucleophilic aromatic substitution. Calculations also confirm that the corresponding β -difluoro-substituted carbanion supports a diatropic ('aromatic') ring current.

RESULTS

Kinetic Measurements. Rate constants for reaction in aqueous sodium hydroxide at 25°C have been measured for benzene-*cis*-1,2-dihydrodiol with 3-substituents (X in **4**) Br, Cl, I, CN, H, Ph, CF_3 , MeSO , EtSO_2 (Scheme 2). The reactants were obtained as products of oxidative biotransformation of the parent aromatic molecules by the UV4 mutant of *Pseudomonas putida*.⁹ As shown in Scheme 2 the reaction leads to *o*- or *m*-phenolic products depending on which of the hydroxyl groups of the reactant is lost. Product ratios were established for selected *cis*-diols by HPLC, GC-MS or NMR

spectra. For benzene-*cis*-1,2-dihydrodiol itself, phenol was the only detectable product. Phenol ratios for other substituted *cis*-dihydrodiols are given in the experimental section. In general for electronegative substituents such as CN and CF₃, the sole product was the *m*-phenol. Only for Br (11%), Me (13%), Ph (25%) and Bu^t (15%) was an appreciable amount of *o*-phenol detected. This behavior is consistent with the expectation that formation of a carbanion intermediate at the 1-position of the ring will be favored by electron-withdrawing substituents at the 3-position. On the basis of the measured product analyses one can, with some confidence, predict product ratios for substituents for which measurements were not made. This can be done with sufficient accuracy to derive rate constants for the reaction of the benzene-*cis*-dihydrodiols to form the major *m*-isomer as product. Thus Cl and I substituents should have product ratios similar to Br while the electron-withdrawing EtSO₂ and MeSO should yield the *m*-product exclusively. The product ratio from the 3-carboxylate derivative was taken to be identical with the 3-phenyl derivative (25% *o*-) on the basis of similar σ values.

Scheme 2

Rate constants for the dehydration reactions were measured spectrophotometrically. Plots of first order rate constants against the concentration of sodium hydroxide showed characteristic saturation with increasing base concentration as illustrated for the 3-cyano substituted reactant in Fig 1. As shown in Scheme 3, the behavior was attributed to the ionization of one of the hydroxyl groups, and the measured rate constants (k_{obs}) were fitted to the kinetic expression of eq 1 in which k_2 is the rate constant for dehydration of the un-ionised diol and $K_b = K_w/K_a$ is the basic dissociation constant of the hydroxyl group.

Figure 1. Plots of rate constants for dehydration of 3-cyanobenzene-*cis*-1,2-dihydrodiol (open circles, H) and its hexadeuterated analogue (closed circles, D) in aqueous sodium hydroxide (M) at 25 °C; the lines represent the best fit of the H and D rate constants to eq 1.

Scheme 3

Table 1. Second order rate constants ($\text{M}^{-1}\text{s}^{-1}$) and acid dissociation constants of hydroxyl groups for the dehydration of 3-substituted benzene-*cis*-1,2-dihydrodiols **4** in aqueous sodium hydroxide at 25°.

3-substituent	Base/solvent	k_2^a	% <i>m</i> -phenol in product ^b	$\text{p}K_a$ kinetic ^c	equilib ^d	..
EtSO ₂	HO ⁻ /H ₂ O	1.61×10^{-2}	^e	13.86		
CN	„ „	9.35×10^{-3}	100	13.21		
MeSO	„ „	1.16×10^{-3}	^e	13.51		
CF ₃	„ „	2.64×10^{-4}	100	13.92		
I	„ „	5.48×10^{-5}	^f	13.46		
Br	„ „	4.77×10^{-5}	89	13.25		
Cl	„ „	3.96×10^{-5}	^f	13.48	13.9	
COO ⁻	„ „	2.54×10^{-5}		14.94		
Ph	„ „	9.90×10^{-6}	75	13.76		
H	„ „	5.25×10^{-6}		13.83		
D-d ₅	„ „	4.52×10^{-6}		14.12		
CN-d ₅	„ „	5.61×10^{-4}	100	13.45		
Cl-d ₅ ^g	„ „	1.22×10^{-6}	^f	In 1 M NaOH	14.0	
I-d ₅ ^g	„ „	1.82×10^{-6}	^f	In 1 M NaOH		
Cl	DO ⁻ /D ₂ O	$(2.8 \times 10^{-5})^h$	^f	ⁱ	(14.0) ^{h,j}	
CN	“ “	1.70×10^{-2}	100	13.05	13.5	

^aMeasured values x % *m*-phenol product. ^bProduct analyses were also carried out for Me (89% *m*-) and Bu^t (87% *m*-) for which no kinetic measurements were made. ^cBased on kinetic measurements and eq 1. ^dFrom initial absorbances of kinetic measurements at different [HO⁻], see Table S2 of Supporting Information. ^eFormation of 100% *m*-phenolic product was assumed. ^fFormation of 89% *m*-phenolic product was assumed. ^gThe rate constant is extrapolated from a single measurement as explained in the text. ^hLimited data add to uncertainty of this measurement cf Fig S3. ⁱData unsuitable for obtaining a measurement of $\text{p}K_b$, cf discussion of Fig 3. ^jTaking $\text{p}K_w = 14.85$ for D₂O.

The ionization was assumed to yield an unreactive species owing to the presence of a negative charge close to the site of attack of the hydroxide ion (and formation of a carbanion) on a hydrogen of the carbocyclic ring. Rate constants and apparent $\text{p}K_a$ values of the two

hydroxyl groups are listed in Table 1. These are apparent pK_a values for ionization of one of the OH groups, and are actually a function of the microscopic pK_a values of both OH groups. The experimental rate constants have been multiplied by the fraction of the dominant *m*-phenol product formed to give rate constants k_2 specifically for this reaction path. The pK_as are only ‘apparent’ because normally ionisation of two hydroxyls of different acidities is occurring. There is little correlation between acidity and electron withdrawing character of the 3-substituent. Presumably this is partly because of uncertainty in separating the two parameters (k_2 and K_b) from eq. 1. Measurements in some cases were also based on fairly small but consistent variations in initial absorbances of kinetic measurements with [HO⁻] reported in Table S2 of the Supporting Information. Of the two sets of measurements, these probably yield the more reliable pK_a values.

$$k_{\text{obs}} = \frac{k_2[\text{HO}^-]}{1 + [\text{HO}^-]/K_b} \quad (1)$$

In the case of the carboxylate substituent, the reactant was the corresponding methyl ester, 3-carbomethoxybenzene-*cis*-1,2-dihydrodiol. This substrate showed a rapid hydroxide ion catalyzed decrease in absorbance at 290nm with rate constant $7.0 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. This was attributed to hydrolysis of the ester group and was followed by a much slower hydroxide ion-catalyzed reaction with a rate constant of $2.5 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ consistent with dehydration to form predominantly the *m*-hydroxybenzoate anion and, probably, a lesser concentration of its *o*-isomer. Details of this and other kinetic measurements, including first order rate constants and wavelengths at which the reactions were monitored, are contained in the Supporting Information.

In attempts to extend the study of the dehydration reactions to arene 1,2-dihydrodiols, other than substituted benzene-*cis*-dihydrodiols, it was found that no reaction of the *trans*-dihydrodiol of bromobenzene could be detected in 1 M aqueous sodium hydroxide over a period of three weeks. This implies a strong dependence of the rate of reaction on stereochemistry, with $k_{\text{cis}}/k_{\text{trans}} > 50$. Likewise, no reaction was detected for the *cis*-1,2-dihydrodiol of naphthalene. In an earlier study it was concluded that benzene hydrate (2,4-cyclohexadien-1-ol, *i.e.* benzene-1,2-dihydrodiol lacking one hydroxyl group) did not undergo dehydration in aqueous sodium hydroxide, although reaction occurred readily in acid.

Isotope Effects. A number of measurements of isotope effects were undertaken utilising biotransformation products of deuterated aromatic substrates. Hexadeuterated benzene and pentadeuterated bromobenzene, chlorobenzene and iodobenzene were commercially available. The pentadeutero 3-iodobenzene-*cis*-1,2-dihydrodiol diacetate was converted to pentadeutero 3-cyanobenzene-*cis*-dihydrodiol diacetate by reaction with tributyl tin cyanide. Deprotection then afforded the required deuterated dihydrodiol. Rate constants and pK_a values for the deuterated 1,2-dihydrodiols are also listed in Table 1. Figs. 1 and 2 show plots of first order rate constants against hydroxide ion concentration for deuterated and undeuterated 3-cyanobenzene-*cis*-1,2-dihydrodiol and for the unsubstituted benzene-*cis*-1,2-dihydrodiol respectively.

It is apparent from Figure 1 that deuteration of the 3-cyanobenzene-*cis*-1,2-dihydrodiol leads to a large isotope effect. The deuterated substrate shows the same characteristic saturation of the rate at high base concentrations attributed to ionisation of the hydroxyl groups of the reactant as the protio substrate. However, the rate constants are substantially less than for the undeuterated substrate at all base concentrations while the limiting value of k_H/k_D at low concentrations of hydroxide ion is 16.7. In the case of the benzene-*cis*-1,2-dihydrodiol, by contrast, deuteration causes little change in the measured rate constants and yields a correspondingly small isotope effect $k_H/k_D = 1.16$. The isotope effect is > 1.0 , even though at higher base concentrations the deuterated substrate reacts more rapidly than the undeuterated substrate, with values of k_H/k_D decreasing to 0.8 at high concentrations of sodium hydroxide. This is because k_H/k_D is based on its limiting value at low base concentrations and the hydroxyl groups of the deuterated benzene-*cis*-1,2-dihydrodiol are less acidic than of the undeuterated substrate (with $K_a^H/K_a^D = 1.9$). We infer from Figure 2 that values of k_H will level off at a lower base concentration leading to a lower limiting rate constant at high base concentrations than for k_D .

Figure 2. Plots of rate constants (k , $\text{s}^{-1}\text{M}^{-1}$) for dehydration in aqueous sodium hydroxide (M) at 25 °C of benzene-*cis*-1,2-dihydrodiol (open circles, H) and hexadeuterated analogue (closed circle, D); the line represents the best fit of the H rate constants to eq.1.

The low isotope effect in the case of the perdeutero benzene-*cis*-dihydrodiol is confirmed by a similar observation in the case of toluene-*cis*-1,2-dihydrodiol and the corresponding perdeuterated substrate 3- $\text{CD}_3\text{C}_6\text{D}_5$ -*cis*-1,2-dihydrodiol. These substrates reacted too slowly for conventional kinetic measurements, but repetitive scans of spectra for reaction in 1M NaOH over 30 hours recorded in Table S1 and Fig. S5 of the supporting information, indicate the similarity of their rates. A crude estimate of the isotope effect gives $k_{\text{H}}/k_{\text{D}} \sim 1.5$.

The isotopic behavior of the *cis*-1,2-dihydrodiols of chlorobenzene and iodobenzene is intermediate between that of the 3-cyano and unsubstituted (or methyl substituted) benzene-*cis*-1,2-dihydrodiols. The reactivities of the 3-chloro- and 3-iodo-pentadeutero benzene-*cis*-1,2-benzene dihydrodiols are very low and only single measurements of rate constants based on UV measurements at 1.0 M NaOH extending over 500 hours were undertaken. Details of this measurement are contained in the Supporting Information, but at the indicated base concentration, the value of $k_{\text{H}}/k_{\text{D}}$ is 8.5 for the chloro-substituted diol and 6.6 for iodo-substituted compound. If the rate constant at 1 M is crudely corrected to its limiting value in dilute base

using eq 1 and $pK_a = 14.0$, we obtain values of $k_D = 6.3 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ and $k_H/k_D = 6.3$ for the chloro compound.

In addition to these substrate isotope effects, a solvent isotope effect $k_{D_2O}/k_{H_2O} = 1.2$ was measured for the 3-chloro substituted benzene-*cis*-1,2-dihydrodiol. In principle this is consistent with a solvent isotope effect on rate-determining proton transfer, for which k_{D_2O}/k_{H_2O} normally falls in the range 1.2-1.5.¹⁰ However, although the measurement was unchanged between 0.3 and 0.9 M hydroxide (or deuterioxide) ion concentrations, it was not possible to separate accurately effects on kinetic and equilibrium steps. Thus the greater rate in D_2O is consistent with the expectation that ionisation of the hydroxyl groups of the *cis*-1,2-dihydrodiol reactant occurs more readily in H_2O than D_2O , and correspondingly, that the reverse of this equilibrium (which is fully expressed at higher base concentrations) is more favorable in D_2O . This makes it likely that the limiting rate constant for the dehydration reaction at low base concentrations is greater in H_2O than D_2O , although the difference cannot be large (say, < 1.5).

On the other hand more extensive measurements for the 3-cyanobenzene-*cis*-1,2-dihydrodiol can be extrapolated to dilute solution and yield $k_{D_2O}/k_{H_2O} = 1.8$. At higher base concentrations the solvent isotope effects for cyano- and chloro-substituted substrates are similar, as may be seen by comparing Figs. S3 and S4 in the Supporting Information. As discussed below there is good evidence that the cyano-substituted substrate reacts by rate-determining proton transfer to form a carbanion intermediate, and the solvent isotope effect is fully consistent with this. The near independence of the isotope effect upon concentration of hydroxide ion suggests that the isotope effect on the equilibrium ionisation of the hydroxyl groups of the benzene-*cis*-1,2-dihydrodiols is small, and this is probably reasonable even though in the equilibrium a hydroxide ion is pitted against an alkoxide ion. For the chloro-substituted substrate there is probably a partial change in rate-determining step (see below), but the similar isotope effect is not unreasonable.

Isotope Exchange The reaction of undeuterated benzene-*cis*-1,2-dihydrodiol in D_2O was also monitored by NMR spectroscopy, and the occurrence of H for D isotope exchange was examined in the reactant and phenolic product. Remarkably, no exchange was detected. Figure 3 shows NMR spectra of the reactant and product after 60% reaction. The two low field-multiplets in the spectrum correspond to the phenoxide ion and the peak at highest field to the

potentially exchangeable methine hydrogen atoms adjacent to the hydroxyl groups of the dihydrodiol. It is apparent that there is no decrease in the 2:1 ratio of vinylic to methine hydrogens (4.3 ppm) of the unexchanged reactant, nor is there any sign of exchange in the product. The hydroxyl peak at 4.8 ppm decreases a little more than expected from the loss of hydrogen from the reactant. This is readily attributable to exchange of D₂O with water from the atmosphere over the 14 h of the reaction. If we suppose that a maximum of 5% of exchange remained undetected, the implication is that exchange is at least ten times slower than the dehydration.

Fig 3. Partially reacted benzene *cis*-1,2-dihydrodiol in NaOD/D₂O at 25°. From the left: peaks at 6.5 and 7.2 ppm correspond to phenol product, peaks near 5.9 and at 4.15 ppm represent unreacted (and unexchanged) benzene-*cis*-dihydrodiol. The peak at 4.8 ppm is assigned to an OH group.

Equilibrium Constant for Dehydration. Of interest in connection with the mechanism of dehydration is the thermodynamic driving force for the reaction. As seen in Scheme 1, this is represented by the energy difference between the phenolic product and *cis*-1,2-dihydrodiol reactant (augmented by ionization of the product in aqueous sodium hydroxide). For phenol, a free energy of formation $\Delta G_f^\circ(\text{aq})$ may be obtained from the convenient compilation of free energies of formation in aqueous solution at 25 °C by Guthrie.¹¹ For the *cis*-1,2-dihydrodiol, $\Delta G_f^\circ(\text{aq})$ may be estimated by analogy with that for the water adduct of benzene: 2,4-cyclohexadien-1-ol (benzene hydrate). As shown in Scheme 4, $\Delta G_f^\circ(\text{aq})$ for this molecule was obtained from that for 1,3-cyclohexadiene by adding an increment representing the energy of replacing a hydrogen atom by a hydroxyl group.¹² In principle, conversion of cyclohexadienol to benzene-1,2-dihydrodiol **1** (Scheme 4) should involve the same increment adjusted for any repulsion between vicinal hydroxyl groups. This repulsion may be estimated from ΔG° for the bond separation equilibrium between ethylene glycol and ethanol shown in eq 2.⁸ The derived value of $\Delta G^\circ(\text{aq}) = -33.2 \text{ kcal mol}^{-1}$ for benzene *cis*-dihydrodiol may be combined with free energies of formation for water and phenol to give $\Delta G^\circ(\text{aq}) = -36.1 \text{ kcal mol}^{-1}$ for the dehydration reaction of Scheme 5. This translates to an equilibrium constant, $\log K = 36.1/1.364 = 26.5$.

Scheme 4

Scheme 5

Computed Energies and Geometries of Cyclohexadienide and Cycloheptadienide anions.

Energies of substituted cyclohexadienide and cycloheptadienide anions in the gas phase have been computed using G3MP2 and MP2 calculations. In Table 2, these are expressed as proton affinities (PA) in kcal mol^{-1} of mono- and di-substituted anions $\text{C}_6\text{H}_6\text{X}^-$ **5** and $\text{C}_6\text{H}_5\text{X}_2^-$ **6** (or $\text{C}_7\text{H}_8\text{X}^-$ and $\text{C}_7\text{H}_7\text{X}_2^-$) where the X substituents are at the 6-position of the cyclohexadienide anion or 7-position of the cycloheptadienide anion and protonation yields the corresponding neutral X-substituted cyclohexadiene or cycloheptadiene.

Also shown are ΔPA values, which are differences in proton affinities from the unsubstituted cyclohexadienide ion. The effectiveness of the G3 method was demonstrated by showing that it gives proton affinities which correlate well with experimental values for eighteen anionic bases: $\text{PA}_{\text{G3}} = 1.10\text{PA}_{\text{EXP}} + 5.2$, $r^2 = 0.999$.¹³ This correlation is shown in Fig S8 based on data summarised in Table S3. More details of calculated energies, zero point energies and geometries of cyclohexadienide and cycloheptadienide ions and their isomeric complexes and transition states are shown in Table S4 (G3MP2) and Table S5. Included in Table S4 (no. **8a**) is a 1,6-dihydroxycyclohexadienide anion hydrogen bonded to a water molecule. This is the immediate (stable) product of proton transfer from the corresponding 1,6-dihydroxycyclohexadiene to hydroxide ion in the gas phase. Enthalpies and free energies (G3MP2) of conjugate acids of the calculated anions are given in Table S8 of the Supporting Information.

The X substituents correspond to leaving groups in an elimination reaction in which the cyclohexadienide anion is a reactive intermediate. The products of this elimination are shown in Table 2. The anions also correspond to Meisenheimer intermediates in nucleophilic substitution reactions, for which the reverse of the loss of leaving group represents the initial attack of a nucleophile on the aromatic ring. Table 2 lists energies and activation energies for these reactions. For the reaction of C_6H_5X with X^- the intermediate $C_6H_5X_2^-$ is the product of reaction at the *ipso* carbon of the aromatic ring. Enthalpies and free energies (G3MP2) of nucleophiles and substrates in the nucleophilic substitutions are given in Table S3.

When X is bound to the aromatic ring by a second row element, as with F, OH, NH_2 and CH_3 (and CN or $C\equiv CH$), the cyclohexadienide anion exists as an energy minimum. Indeed this Meisenheimer π -complex is more stable than the separated nucleophile (X^-) and aromatic molecule. However for third row elements, only SiR_3 gives a stable *mono*-substituted anion with benzene. The *di*-phosphino anion is also stable, but for the other third row elements SR or Cl there is no energy minimum for mono- or di-substituted ions and it appears that these are too reactive as leaving groups to maintain attachment to the benzene ring (see footnote in Table 2). The same was shown to be true of $X = Br$ or NO_2 . Previous work indicates that for these groups the corresponding nucleophilic substitution reaction proceeds by a concerted mechanism without formation of a Meisenheimer intermediate.^{14,15,16} As also shown previously, the stability of the intermediate is increased by inclusion of one or more nitro or other electron withdrawing groups in the aromatic ring.¹⁶

It should be mentioned that for the fluoride anion, the most reactive of the second period leaving groups, although a stable Meisenheimer complex with a highly extended fluoride bond is found at the G3 level, it is not found at MP2/6-311+G**. Rather, a hydrogen-bonded benzene-fluoride complex is formed. For the difluoro anion, on the other hand, the complex is stable, probably as a result of the stabilizing influence of geminal fluorine atoms. In this case also the enthalpy of activation for the identity aromatic substitution of fluoride by fluoride ($-4.9 \text{ kcal mol}^{-1}$) is in satisfactory agreement with that found by Glukhotsev *et al* (-2.2 and $-3.7 \text{ kcal mol}^{-1}$ by MP2 and B3LYP respectively, both at MP2/6-31 + G(d)).¹⁵

A previously calculated geometry of the cyclohexadienide anion gave a planar structure.¹⁷ Our calculations for the monosubstituted ions correspond to shallow boat conformations in which the 1,2,4 and 5 carbons define a plane and the X substituent is at C6, leading to overall C_s symmetry.

The carbon at position 6 has an out-of-plane tilt that varies from 45° for groups of low electronegativity such as H or CH₃ to smaller values for electronegative groups, *e.g.* 6° for OH. The 3-carbon is 15-18° out of plane. All the X substituents occupy pseudoaxial positions with C-X bonds which are longer than the axial C-X bonds in their neutral protonation products. A pseudoaxial-pseudoequatorial disposition of the X substituents is maintained for the disubstituted ions, except for the difluoro and diamino ions both of which have C_{2v} heavy atom frameworks. Further geometric details are contained in Tables S4 and S5 of the Supporting Information.

Table 2. Calculated G3MP2 proton affinities, kcal/mol, of 6-substituted cyclohexadienide anions, $C_6H_5XY^-$ and enthalpies ΔH_{add} and activation energies $\Delta H_{add}^\ddagger$ for addition reactions of elimination products $C_6H_5X + Y^- \rightarrow C_6H_5XY^-$. Proton affinities of selected cyclohexadienide anions.

X, Y (point group) ^b	PA ^c , kcal/mol	ΔPA^d , kcal/mol	Elim ⁿ products	ΔH_{add}	$\Delta H_{add}^\ddagger$
1. H, H (C_s)	374.3 ^e	-0-	benzene + H^-	-17.0	+6.6
2. CH_3 , H (C_s)	371.5	2.8	benzene + CH_3^-	-28.3	-1.7
3. CH_3 , CH_3 (C_s)	370.2	4.1	toluene + CH_3^-	-30.5	-3.7
4. $-CH_2-CH_2-$ (C_s) ^f	369.7	4.6	$C_6H_5-CH_2-CH_2^-$	4.3	-
5. NH_2 , H (C_s)	364.2	10.1	benzene + NH_2^-	-15.2	-3.7
6. NH_2 , NH_2 (C_1)	361.0	13.3	aniline + NH_2^-	-16.6	-6.8
7. ax OH , H (C_s) ^g	357.7 ₅	16.5	benzene + OH^-	-6.9	-6.6
8. eq OH , H (C_s) ^g	364.0	10.3	benzene + OH^-	-0.6	
8. OH , OH (C_1)	356.9	17.4	phenol + OH^-	-15.1	-12.9
9. F , H (C_s) ^h	350.9	23.4	benzene + F^-	+3.7	-3.7
10. F , F (C_{2v})	345.8	28.5	fluorobenzene + F^-	-10.7	-4.9
11. SiH_3 , H (C_s)	369.2	5.1	benzene + SiH_3^-	+5.8	+12.1
12. SiH_3 , SiH_3 (C_s)	363.8	9.5	silylbenzene + SiH_3^-	-0.9	+4.2
13. $(CH_3)_3Si$, H (C_s)	371.8	2.5	benzene + $(CH_3)_3Si^-$	-7.2	-
14. PH_2 , H^i (C_s)	-	-	benzene + PH_2^-	-5.1	-
15. PH_2 , PH_2 (C_s) ^j	359.5	14.9	phosphinobenzene + PH_2^-	-6.2	+5.6

16. HC≡C, H (C_s)	368.8	5.5	benzene + HC≡C ⁻	+3.1	+13.1
17. CN, H (C_s)	359.5	14.8	benzene + CN ⁻	+18.4	+23.5
cycloheptadienide anions					
18. cycloheptadienide⁻ (C₂)	371.6	2.7			
19. 7-fluoro cycloheptadienide (C₁)	362.4	11.9			
20. 7,7-difluoro cycloheptadienide (C₁)	355.8	18.5			
21. 7-hydroxy cycloheptadienide (C₁)	360.5	13.7			
22. 7,7-dihydroxy cycloheptadienide (C₁)	360.3	14.0			

^aInitial step of nucleophilic aromatic substitution. ^bPseudoaxial group is indicated in bold type. Geometries are outlined in main text. ^cPA = $-\Delta H_{RXN}$ for the protonation of the anion giving the corresponding 1,3-cyclohexadiene. ^d $\Delta PA = PA_{HH} - PA_{XY}$. Thus, a positive ΔPA value indicates the anion is less basic (more stable) than the parent cyclohexadienide ion, X = Y = H, relative to their respective protonation products. ^eThe experimental PA for cyclohexadienide⁻ is 373.3 ± 4.1 kcal/mol. ^fspiro[2.5]octa-4,6-dienide⁻. ^gThe OH bond is *endo* to the ring. The *exo* form is a transition state, $\nu = 306$ cm⁻¹ (C-O torsion) lying 4.4 kcal/mol above the *endo* form. ^{7eq} was obtained by constraining dihedral angles to ensure C_s symmetry. ^hA covalent addition complex is found at the G3MP2 level with a bond-length extension of 0.193 Å relative to its conjugate acid. However at MP2/6-311+G** this structure optimizes to a H-bonded benzene-fluoride⁻ complex. ⁱOptimization at the G3MP2 or MP2/6-311+G** level gives a H-bonded benzene-PH₂⁻ complex. ^jAt the G3MP2 level, MP2/6-31G* frequencies, a stable covalent adduct is formed. At MP2/6-311+G** the structure becomes a transition state, $\nu = 117$ cm⁻¹.

DISCUSSION

The dehydration of benzene-*cis*-1,2-dihydrodiol shows a first order dependence on hydroxide ion concentration, albeit modified by partial ionization of a hydroxyl group as in Scheme 3. This observation, coupled with a positive value of $\rho = 3.2$, and the correlation of the effect of 3-substituents by σ^- values shown in Figure 4 is clearly consistent with reaction occurring *via* a carbanion intermediate. However, these criteria do not rule out a concerted mechanism involving a carbanion-like transition state.^{6,18} Indeed, the following facts and observations appear to favour a concerted mechanism.

Figure 4. Plot of $\log k$ versus σ^- for the dehydration of 3-substituted benzene-*cis*-1,2-dihydrodiols in aqueous NaOH at 25 °C: $\log k = -5.16 + 3.21\sigma^-$.

The very high exothermicity of the reaction suggests that the stability of the double bond of the product, which reflects its aromatic character, should strongly stabilize the partially formed double bond in the transition state of a concerted reaction. The much greater reactivity of a *cis*-1,2-dihydrodiol of benzene than of a dihydrodiol of naphthalene is consistent with this possibility. Also consistent with a concerted mechanism is the much greater reactivity of a *cis*-dihydrodiol compared to a *trans*-dihydrodiol. In the case of the *cis*-dihydrodiol the OH leaving

However, the measurements of hydrogen isotope effects for deuterated reactants appear to be decisive in indicating reaction *via* a carbanion intermediate. For the 3-cyanohexa-deuterobenzene-*cis*-dihydrodiol **7**, the measured value of $k_{\text{H}}/k_{\text{D}}$ is 16, which must represent a large primary isotope effect. This isotope effect is still consistent with operation of either a concerted mechanism or a stepwise (E1cB) mechanism in which the step forming the carbanion intermediate is rate-determining, as shown in Scheme 6. However, when the 3-substituent is changed from cyano to chloro, the primary isotope effect is reduced to ~ 6.3 and when it is changed to deuterium, *i.e.* for the *cis*-1,2-dihydrodiol of hexadeuterobenzene, it disappears altogether; for the benzene *cis*-1,2-dihydrodiol, $k_{\text{H}}/k_{\text{D}} = 1.2$, which is a normal magnitude for a secondary isotope effect.

An obvious test for a mechanistic change is to look for rapid exchange of hydrogen for deuterium isotopes in the pre-equilibrium proton transfer step in the case of benzene-*cis*-1,2-dihydrodiol. As shown in Scheme 7, reaction of the protio benzene *cis*-1,2-dihydrodiol with

NaOD in D₂O should lead to exchange of a hydrogen for deuterium in two C-H bonds in the dihydrodiol reactant and one in the phenolic product.

Scheme 7

Remarkably, when the reaction was monitored by NMR spectroscopy, no exchange was observed in the reactant or product over a period which implied that the rate of exchange was at least ten times slower than the overall dehydration reaction. At first sight, this appears to exclude the possibility of a pre-equilibrium proton transfer. However, a number of examples of related behavior are known for carbanion reactions^{19,20}. They have been interpreted as implying the occurrence of ‘internal return’ of the initial proton transfer reaction, *i.e.*, formation of a carbanion hydrogen-bonded to the hydrogen atom to which it was originally attached. In the present instance, the carbanion would be bound to a water molecule formed by proton transfer between the dihydrodiol and hydroxide ion reactants. Provided that further reaction of the carbanion (to form phenol) occurs within this reversibly formed ion-molecule hydrogen-bonded pair, and that dissociation of the pair leading to isotope exchange is slower than product formation, the observed behavior becomes explicable.

A schematic representation of the dehydration reaction embodying these mechanistic features is shown in Scheme 8, in which the benzene-*cis*-1,2-dihydrodiol is denoted H-Ar-OH or H-Ar-OD (in D₂O) and phenol as Ar. The H-Ar bond of the reactant is the carbon-hydrogen bond which undergoes ionisation to form the carbanion intermediate.

Perhaps the simplest interpretation of the slow isotope exchange reaction is that it involves dissociation of the hydrogen-bonded carbanion to give an unsolvated species of significantly higher energy.²⁰ This feature is incorporated in Scheme 8, in which the relative rates of the processes controlling dehydration, exchange and internal return are indicated. The reaction is shown as occurring in D₂O in order to include the exchange feature. Richard has

suggested rearrangement of the hydrogen bonded water molecule as an alternative to dissociation,²¹ but, as noted below, this fails to account for the slowness of the reaction.

Scheme 8

Scheme 8 is complicated in that it includes the initial low-energy step representing diffusion together and resolution of the reactants to form the ion molecule pair within which proton transfer occurs. The reaction is more clearly represented by the free energy diagram of Figure 5, in which the initial diffusion step is omitted, and further simplified in Scheme 9, in which the preequilibrium and rate-determining steps for the dehydration reaction only are shown. As usual, k_1 in Scheme 9 represents the composite of an equilibrium constant for formation of the encounter complex between the substrate and hydroxide ion (*i.e.*, in the initial diffusion step) and a rate constant for the reaction of this complex.

Scheme 9

A clue to the interpretation of the observed behavior is provided by the large exothermicity of the dehydration reaction. This must apply *a fortiori* to the reaction step leading to formation of the phenolic product from a high-energy carbanion intermediate such as **8**. As discussed in more detail below, this must in turn imply that loss of hydroxide ion from the carbanion occurs at a rate limited only by relaxation of water to and from the solvation shell of the ion, with $k_2 \approx 10^{11} \text{ s}^{-1}$.^{22,23,24}

Figure 5. Schematic plot of free energy against reaction coordinate for base-catalyzed dehydration and isotope exchange of benzene-*cis*-1,2-dihydrodiol. The deuteron transfer step completing the exchange reaction is omitted.

If the internal return of the proton to reform the benzene-*cis*-1,2-dihydrodiol is faster than this step, i.e., loss of the hydroxide ion to form the product (phenol), then the dehydration reaction would indeed occur without a significant primary isotope effect.

An upper limit to proton transfer within a hydrogen bond is probably given by the rate constant 10^{12} s^{-1} for proton transfer between H_3O^+ and H_2O in ice.²⁵ It is reasonable that k_{-1} should be as large as $10^{11} - 10^{12} \text{ s}^{-1}$ if the thermodynamic driving force for the protonation of the carbanion is sufficiently great. What this driving force amounts to can be determined by deriving the equilibrium constant K_b for protonation of the carbanion intermediate. This is given by the ratio of rate constants for formation of the carbanion from the benzene-*cis*-1,2-dihydrodiol and hydroxide ion reactants and for reversion to these reactants, k_1/k_{-1} . A value of k_1 may be obtained from the experimentally measured rate constant for the hydroxide-catalyzed dehydration reaction $k_{\text{OH}} = 1.0 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ and its relationship to k_1 and k_{-1} implied by Scheme 9 and shown in eq 2.

$$k_{\text{OH}} = k_1 k_2 / (k_{-1} + k_2) \quad (2)$$

It follows that $k_1 = k_{\text{OH}}(1 + k_{-1}/k_2)$, which, if $k_2 = 10^{11}$, becomes $1.1 \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ if $k_{-1} = 10^{12} \text{ s}^{-1}$, and $2.0 \times 10^{-6} \text{ M}^{-1}\text{s}^{-1}$ if $k_{-1} = 10^{11} \text{ s}^{-1}$. Corresponding values of K_b are 1.1×10^{-17} and 2.0×10^{-17} . From the average of these values $\text{p}K_b$ for the 1,2-dihydroxycyclohexadienide anion becomes 16.8 and $\text{p}K_a = 14.0 + \text{p}K_b \approx 31$ with an estimated uncertainty of ± 0.5 log units. We consider it possible that k_2 is somewhat less than 10^{11} as HOD, hydrogen bonded to the carbanion, imposes a barrier to reorganization. If so, k_{ex} must be smaller yet.

A more detailed argument regarding the limiting rate constant values focuses on the possible relative magnitudes of k_{-1} , k_2 (Scheme 9) and k_r , which we will call the rate constant for solvent reorganization within the hydrogen bonded $\text{DOH} \cdots \text{Ar-OD}$ complex (Scheme 8 and Fig. 5). These are the three rate constants leading from the complex. The absence of exchange implies that k_r is less than k_2 , and therefore that $k_{-1} > k_2 > k_r$. All three rate constants must be very fast. We can also state that the observed rate constant k_{OH} is given by: $k_{\text{OH}} = k_1 k_2 / (k_{-1} + k_2 + k_r) \approx k_1 k_2 / (k_{-1} + k_2)$ and the rate constant for the unobserved exchange process, k_{ex} , is given by: $k_{\text{ex}} = k_1 k_r / (k_{-1} + k_2 + k_r) \approx k_1 k_r / (k_{-1} + k_2)$. We can conclude from experiment that $k_{\text{ex}}/k_{\text{OH}} < 0.1$ and that $k_{\text{ex}}/k_{\text{OH}} = \{k_1 k_r / (k_{-1} + k_2)\} / \{k_1 k_2 / (k_{-1} + k_2)\} = k_r / k_2$. The hydrogen bond (even though it is between C and O) in $\text{DOH} \cdots \text{Ar-OD}$ will make solvent reorganization slower than in the solvent itself by perhaps as much as 2 orders of magnitude; thus $10^9 < k_r < 10^{11} \text{ s}^{-1}$. This implies that $10^{10} < k_2 < 10^{12} \text{ s}^{-1}$. We argue above that k_{-1} lies between 10^{11} and 10^{12} s^{-1} . Thus the constraint that $k_{-1} > k_2 > k_r$ leaves very little freedom. Assuming that “greater than” means a factor of 10 or more, the set of rate constants is then: $10^{11} < k_{-1} < 10^{12}$; $10^{10} < k_2 < 10^{11}$, and $10^9 < k_r < 10^{10}$ (all s^{-1}). This is sufficient to put narrow limits on k_1 and thus on the proposed $\text{p}K_a$ for benzenediol. We thank a reviewer for this analysis.

Thermodynamic Driving Force. The thermodynamic driving force (exothermicity) required to ensure that the chemical barrier to reaction is less than that of the limiting value for solvent relaxation depends on the intrinsic barrier to the reaction. Without entering into a full discussion of the point here, we note that Richard has shown that for proton transfer to a hydroxide ion from carbon activated by a series of carbonyl, carbethoxy, amido and carboxylate groups that the intrinsic barrier is 10 kcal mol^{-1} and that the reaction becomes diffusion

controlled as the pK_a of the carbon acid approaches a value of 30.²⁶ Our assignment of a limiting rate constant to the reaction with water of a 1,2-dihydroxycyclohexadienyl anion for which the pK_a of its conjugate acid is 30.8 is therefore reasonable.

A difference between Richard and Williams's study²¹ and our own is that they use hydrogen isotope exchange of nitriles to measure their rates of ionisation to form anions. Where reprotonation of the anion is sufficiently exothermic, the isotope exchange ceases to be catalyzed by buffer base, and Richard supposes that the rate-determining step for the exchange is rearrangement of a HDO solvent molecule, with a rate constant k_{reorg} . This is shown in Scheme 10, in which AH denotes a reactant and A its conjugate base anion.

Scheme 10

Richard assumes that $k_{\text{reorg}} \sim 10^{11} \text{ sec}^{-1}$, which corresponds to rotational relaxation of the solvent.¹⁶⁻¹⁹ In our case, however, a rate constant corresponding to rotational relaxation is assigned to loss of hydroxide ion from a dihydroxycyclohexadienide anion intermediate. Loss of hydroxide occurs at least two orders of magnitude more rapidly than the isotope exchange reaction. This implies that the isotope exchange cannot be controlled by solvent relaxation.

Similarly, Koch has shown that loss of a leaving group, typically F^- or Cl^- , from a carbon β - to a carbanion centre can occur more rapidly than hydrogen isotope exchange in deuterated methanol as solvent.²⁷ Formation of a desolvated higher energy carbanion intermediate with a rate constant $< 10^{11} \text{ s}^{-1}$ seems to offer the simplest explanation of the behavior he observed and which we observe here.

Is the thermodynamic driving force for the expulsion of hydroxide ion from the dihydroxy cyclohexadienide anion sufficient to ensure that this occurs at the limiting rate of solvent relaxation? Bernasconi has shown that the intrinsic barrier to loss of a β -hydroxide ion to form a double bond is significantly greater than for protonation of the same carbanion.²⁸ The magnitude of the exothermicity (strictly, free energy of reaction) can again be assessed from the equilibrium constant for the reaction. It was shown above that $\log K$ for the overall reaction of

benzene *cis*-1,2-dihydrodiol to form phenol corresponds to 26.5 log units. To arrive at log*K* for the conversion of the carbanion intermediate to product, we add to this the value of p*K*_b = 16.8 to obtain an overall value of log*K* = 43.8 or Δ*G* = -1,364 log*K* = -59 kcal mol⁻¹ at 25 °C. This is an overwhelmingly large thermodynamic driving force and leaves little doubt that the rate of expulsion of hydroxide ion must indeed occur at the limit of solvent relaxation.

Cycle of equilibrium constants. Log *K* corresponds to log*K*_c, the log of the equilibrium constant for addition of hydroxide ion to an *o*-position of phenol. Values of log*K*_c for addition of hydroxide ion to various electrophiles have been discussed by Hine.²⁹ They may be converted to values of p*K*_R by recognising that *K*_R and *K*_c are related in a manner comparable to that of *K*_a and *K*_b, *i.e.*, *K*_R/*K*_c = *K*_w where *K*_w = 10⁻¹⁴ is the autoprotolysis constant of water.³⁰ For phenol, p*K*_R = 43.3 + 14 = 57.3 and refers to the equilibrium of eq 3.

Normally p*K*_R refers to carbocations and has a negative value implying that hydrolysis of the carbocation (*R*⁺ + H₂O → ROH + H⁺) is a favorable reaction; *e.g.* for the *t*-butyl cation p*K*_R = -16.³¹ Hydrolysis becomes unfavorable and p*K*_R positive for weaker electrophiles such as aldehydes or ketones. For benzaldehyde, *e.g.* for which the resonance form PhCH⁺-O⁻ may be considered to represent a highly stabilized carbocation, p*K*_R = 14.7. The much larger positive value for phenol reflects both the stability of the double bond of the weakly electrophilic reactant and the instability of the carbanionic adduct. These are reflected also in the large exothermicity associated with expulsion of hydroxide ion from the adduct.

The two equilibrium constants *K*_R and *K*_a may be related to each other through the equilibrium constant *K*_{H₂O} for addition of water to phenol, which corresponds to the inverse of the equilibrium constant for the overall dehydration reaction calculated above. When expressed in their logarithmic forms, the three equilibrium constants can be related through a Hess-like thermodynamic cycle, as shown in Scheme 11. Single rather than double arrows are used to represent the equilibria in order to indicate the direction of reaction to which the equilibrium constants refer.

Scheme 11

Isotope effects. The appearance of isotope effects on the dehydration reaction when the 3-chloro or 3-cyano substituents are present in the benzene-*cis*-1,2-dihydrodiol reactant is readily understandable. The electronegative substituents stabilise the carbanion and increase the barrier to reprotonation. This will render the proton transfer rate-determining, insofar as the much greater exothermicity of the loss of hydroxide ion will ensure that this reaction step will remain close to its limiting value of 10^{11} s^{-1} . This is illustrated schematically in Fig. 6, in which the upper free energy profile corresponds to the unsubstituted benzene-*cis*-1,2-dihydrodiol and the lower (dashed) profile to its 3-cyano substituted derivative. The sharp change in isotope effect between chloro ($k_{\text{H}}/k_{\text{D}} = \sim 6.3$) and cyano compounds ($k_{\text{H}}/k_{\text{D}} = 16.0$) suggests that in the case of the chloro substituent, the isotope effect may be reduced because the proton transfer step is only partially rate-determining.

A similar dependence of isotope effects on substituent was observed by Eaborn in the cleavage of benzylic trimethylsilanes **9** in methanolic sodium methoxide shown in Scheme 12³². The isotope effect was measured from the ratio of H to D in the toluene product ($[\text{R-H}]/[\text{R-D}]$) following reaction of the benzylic anion intermediate in a mixed MeOH/MeOD solvent. Values of $k_{\text{H}}/k_{\text{D}}$ are shown in Table 2 as a function of substituent and logs of relative rate constants for generating the anions from the benzyl trimethylsilane precursors (k_{rel}).

Figure 6. Schematic free energy profiles for hydroxide ion-catalyzed dehydration of unsubstituted (upper profile – from Figure 4) and 3-cyano substituted (lower profile) benzene-*cis*-1,2-dihydrodiols.

Scheme 12

Table 3. Isotope effects for protonation of substituted benzylic anions by methanol.

Substituent	H	<i>m</i> -CN	<i>m</i> -NO ₂	<i>p</i> -CN	<i>p</i> -SO ₂ Ph	<i>p</i> -COPh	<i>o</i> -NO ₂	<i>p</i> -NO ₂
[R-H]/[R-D]	1.2	1.2	1.3	2.0	2.9	7.0	10.0	10.0

$\log k_{\text{rel}}$	0	3.45	3.72	5.80	5.97	6.11	6.67	7.36
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One question that remains is why, for so apparently unstable an intermediate as a cyclohexadienide anion, does the reaction proceed so readily? The following may provide at least a partial answer.

Negative Hyperaromatic Stabilization of the Hydroxycyclohexadienide Anion. A number of clues suggest that the *cis*-1,2-dihydroxycyclohexadienide anion may be unusually stable. We have seen that no reaction is observed if the benzene-*cis*-1,2-dihydrodiol as reactant is replaced by benzene hydrate (2,4-cyclohexadien-1-ol **10**, i.e., the dihydrodiol lacking a 2-hydroxyl group), by naphthalene-*cis*-1,2-dihydrodiol **11** or by benzene-*trans*-1,2-dihydrodiol **12**. The structures of these potential reactants are compared below.

The more than 50-fold greater reactivity of the *cis*- than *trans*-benzene dihydrodiol in particular recalls the behavior observed for the *acid*-catalyzed dehydration reaction for which the reactivity difference amounted to $k_{\text{cis}}/k_{\text{trans}} = 4,500$.² This difference was attributed to hyperconjugative stabilization of a carbocation intermediate in the case that the carbocation was formed with a pseudoaxial C-H bond β - to the centre of charge and the β -C-OH bond in a pseudoequatorial position. It was argued that this occurred for reaction of the *cis*-dihydrodiol but that for the *trans* isomer the carbocation was formed with a β -C-OH bond in a pseudoaxial position and β -C-H pseudoequatorial and that this geometry is much less favorable to hyperconjugation. The large magnitude of the effect was attributed to the aromatic character of the no-bond resonance structure associated with the hyperconjugation illustrated in **13**; it is further magnified by good electron-donating groups at the β -carbon, *e.g.*, silyl.

It is natural to hypothesize that the difference in reactivities in the base-catalyzed reaction is also due to hyperconjugation. In this case, however, stabilization of a cyclohexadienide anion would be by negative hyperconjugation, with a pseudoaxial β -C-OH bond being *more* favourable than a C-H bond. The preferential formation of carbanions with respectively C-OH and C-H bonds in β -pseudoaxial positions from reaction of *cis* and *trans* reactants is illustrated in Scheme 13. (Hydrogen bonding between newly formed water and the carbanion is omitted). An important assumption is that the proton transferred from the reactant benzene dihydrodiol departs from a pseudoaxial position. This should optimise overlap between the developing negative charge and π -orbitals of the cyclohexadienyl ring.

Scheme 13

Calculated Stabilities of Cyclohexadienide Anions. Support for the concept of negative hyperaromaticity comes from MP2 calculations for substituted cyclohexadienide anions in the gas phase. As noted above, these ions have the structure of Meisenheimer intermediates in nucleophilic aromatic substitution reactions. Thus the 2-hydroxycyclohexadienide anion **3** corresponds to a Meisenheimer complex formed by nucleophilic attack of a hydroxide ion on benzene. Previous computational studies of Meisenheimer complexes have focused on their formation from different combinations of aromatic substrate and nucleophile in the gas phase.^{14,15} They have emphasised *ipso* reactions, especially of halide ions with the corresponding halobenzenes. Depending on the aromatic molecule and nucleophile, the Meisenheimer structure may correspond to a stable intermediate or a transition state.

A difficulty with these calculations is that the energy of the intermediate is computed relative to the strongly variable energies of the nucleophile and aromatic molecule. In this study we assess stabilization of cyclohexadienide ions (**14**) through comparisons of gas phase proton affinities for X- and X₂-substituted ions, where the X substituents are located at the 6-position with respect to the carbanionic charge. The approach is similar to that used to investigate stabilization of cyclohexadienyl cations through comparisons of hydride ion affinities.^{2,3} As shown for these ions it is particularly effective for investigating stabilization by hyperconjugation. Thus it seems reasonable to suppose that geminal (anomeric) interactions between electronegative atoms, which can be expected to stabilize X₂-substituted cyclohexadienide anions, will be largely cancelled with the cyclohexadiene reactant.

Calculated proton affinities (PA) of monosubstituted cyclohexadienide ions and proton affinities relative to the unsubstituted cyclohexadienide ion (Δ PA) are summarised in Table 4. Additional substituents and energies of nucleophilic substitution reactions are given in Table 2 in the Results. A further difficulty with the computations is that the barriers to reaction of the anion to form the product aromatic molecule and nucleophile, *i.e.*, the second step of an elimination reaction of a substituted cyclohexadiene such as benzene-*cis*-1,2-dihydrodiol (or of a two-step nucleophilic substitution), has a very low energy barrier and the structures of anions for which X is a good leaving group correspond to transition states for this reaction rather than true energy minima. Nevertheless, electronegative atoms F, HO and NH₂ all give minima as do less electronegative groups, such as SiH₃ and CH₃. All substituents are stabilizing, but the effect is much larger for electronegative groups than *e.g.* for CH₃ or SiH₃.

Table 4. Proton Affinities (PA) and Relative Proton Affinities (Δ PA) of 6-Monosubstituted Cyclohexadienide Ions **11**^a

Substituent	H	CH ₃	NH ₂	OH	F	SiH ₃	C≡CH	CN
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PA	374.3	371.5	364.2	357.8	350.9	369.2	368.8	359.5
Δ PA	0	2.8	10.1	16.5	23.4	5.1	5.5	14.8

^aAbstracted from Table 2 in the Results

For the stable cyclohexadienide anions the X substituents consistently occupy pseudoaxial positions (**14**), and there appear to be no minima for the corresponding isomers with X in a pseudoequatorial position. If a conformation with X equatorial is constrained, the difference in energy between this and the equilibrium geometry is greatest for electronegative substituents, with an energy difference of 6.3 kcal/mol for an OH group if the dihedral angle between the axial hydrogen, C6, C1 and the H atom at C1 is 80°. This difference compares with 8.8 kcal mol⁻¹ for the corresponding 6-hydroxycyclohexadienyl cation, in which C-OH rather than C-H is constrained to be pseudoaxial.² This result provides the first computational argument for the importance of hyperconjugation. The stabilizing effect of electronegative substituents is apparent in the relative proton affinities, Δ PA, of the cyclohexadienide anions in Tables 2 and 4. The geometrical dependence of this stabilization confirms that it is not solely an inductive effect.

Another approach to assessing the stabilization derived from hyperconjugation is to compare proton affinities of 6-substituted cyclohexadienide ions with those of carbanions which cannot profit from hyperconjugation. For this comparison we have chosen *p*-substituted phenyl anions **15p**. A plot of the computed proton affinities of the *para*-phenyl anions³³ against the proton affinities of correspondingly substituted stable cyclohexadienide anions is given in Figure 7. Groups that are not expected to have a strong contribution from hyperconjugation give a reasonable correlation line with slope 0.8. These include H, CH₃, SiH₃, CCH and CN. The groups where hyperconjugation is expected (F, OH, NH₂) fall below this line and may be considered to provide extra stabilization to the cyclohexadienide relative to the phenyl anions. The magnitude of the implied stabilization is large and amounts to 19 kcal/mol for F, 15 kcal/mol for OH and 11 kcal/mol for NH₂. The relative magnitudes of the stabilizations fall in the order expected of negative hyperconjugation.

These comparisons do not demonstrate that the hyperconjugative effect confers aromaticity. Evidence on this point comes from a comparison between *p*- and *o*-substituted phenyl anions.

As illustrated in **16**, for the *o*-anion hyperconjugative stabilization but not aromaticity can be envisaged. Moving a cyano group from a *p*- to an *o*-position reduces the proton affinity of the ion by only about 2 kcal/mol. In contrast, moving a fluorine atom reduces the affinity by over 7 kcal/mol.³² This suggests that there is some contribution from hyperconjugative stabilization. However, the effect is much smaller than the stabilization estimated above for the 6-fluorocyclohexadienide anion (**14**, X = F). Hyperconjugative interactions in **16** may be limited to some extent by the implied contribution from a high energy benzyne resonance structure, but the large difference (19 versus 7 kcal mol⁻¹) suggests that the cyclohexadienide anions are experiencing added stabilization of up to 12 kcal mol⁻¹ from hyperaromaticity in **14**.

Figure 7. Plot of Computed Cyclohexadienide PAs vs. *p*-Phenyl Anion PAs.

A further way of estimating the aromatic contribution to the hyperconjugation is to compare the proton affinities of the F and OH substituted cyclohexadienide ions in Table 4 and Table 2 with

those of the corresponding unsubstituted and substituted cycloheptadienide anions **17** - **19**. Values of Δ PA relative to the unsubstituted cyclohexadienide ion are shown under the structures. From Table 2 we see that the unsubstituted cycloheptadienide ion and the 6-methylcyclohexadienide ion have practically the same proton affinities. The difference between these values and that for unsubstituted cyclohexadienide ion is about 2.8 kcal/mol, an increment which can be assigned to the polarizability effect of having an additional carbon in the seven-carbon ring anions. The PA difference between the monofluoro cyclohexadienide and monofluoro cycloheptadienide ions is 11.5 kcal/mol which, allowing for the effect of the extra carbon in the latter, gives a corrected difference of about 14 kcal/mol. The same analysis using 7-hydroxycycloheptadienide (**19**) shows the OH to confer an extra stabilization of about 6 kcal mol⁻¹. It is likely that the fluorinated and hydroxylated cycloheptadienides are somewhat stabilized by hyperconjugation as indicated by the extended bond lengths of their pseudoaxial C-F and C-OH bonds relative to those in their conjugate acids. To that extent the exalted stabilities of the fluorinated and hydroxylated cyclohexadienides reveal the additional ‘aromatic’ stabilizing effect over and above the ‘non-aromatic’ hyperconjugative stabilization of the seven-membered model ions. In the case of the fluoro substituent the magnitude of the stabilization (14 kcal mol⁻¹) agrees satisfactorily with that estimated above based on the *o*-fluorophenyl anion model (12 kcal mol⁻¹).

Finally we mention that this aromaticity differs from that inferred for transition states of nucleophilic aromatic substitution reactions proceeding in a concerted manner without formation of a Meisenheimer complex, as is characteristic of most third or higher period nucleophiles. Uggerud and Frenkel attribute the relatively low activation energies of these reactions to loose binding of a nucleophile and leaving group which allows a fraction of the aromaticity of the reactants to be retained at the transition state.¹⁴

Orbital Interactions and Ring Current Calculations.

A calculation of the ‘ipsocentric’³⁴ type confirms that there is a ring current associated with the gem-difluoro substituted cyclohexadienide anion **20**. A current-density map was calculated for this system with the distributed-gauge CTOCD-DZ^{35,36} method at the RHF/6-31G** level of theory, for a height of $1a_0$ above the median plane, using the SYSMO and GAMESS packages^{37,38} with a structure optimised at the B3LYP/6-31G** level with GAUSSIAN 09.³⁹ This map is shown as structure **20**. It shows the summed contributions of all occupied molecular orbitals of π symmetry, which in qualitative terms captures both the contributions from the conventional π system of the ring, and any contribution that may arise from the antisymmetric combinations of CF bonds, and of F ‘lone-pairs’ of the CF₂ group. The main observation is that there is a clear indication of a global π ring current passing above and below all carbon centres, with the same sense of circulation as in benzene itself. This is fully consistent with an attribution of aromatic character deriving from hyperconjugative participation of the fluorine atoms.

20

21

Incidentally, the map also shows a pronounced but tightly localised diamagnetic circulation associated with the hyperconjugating CF₂ group, which is a reflection of the presence of a closed octet valence shell on the fluorine atom and is not connected with the global aromaticity of the ring. There is no equivalent in the benzenium ion **21**, where of course the H centres do not carry

these extra valence electrons. An estimate of the intensity of the ring currents in these systems is available from the maximum magnitude of the current density per unit inducing field taken over the 1-bohr plotting plane. For benzene itself, in a calculation of the present type, the value of this quantity is 0.079 a.u., and in **20** and **21** the corresponding values are 0.056 a.u. and 0.046 a.u., respectively. Hence, the π ring current in the benzenium cation has a little under 60 per cent of the strength of the full π current of benzene, and this increases to about 70 per cent in the difluoro anionic species, confirming both ions, and in particular the gem difluoro substituted cyclohexadienide anion **20**, as aromatic on the magnetic criterion.

A final puzzle concerns the nature of the potential energy surface for the dehydration reaction. Despite the experimental evidence that the reaction proceeds in a stepwise manner via formation of a carbanion intermediate, the exceptional stability of the aromatic double bond of the product makes it somewhat surprising that the reaction is not concerted, with simultaneous loss of a proton and HO^- leaving group. Indeed the combination of stable double bond with close to zero activation energy for loss of both the proton and leaving group from the intermediate suggests an unusual potential energy surface for the reaction. To explore the potential energy surface and the balance between concerted and step-wise pathways, we are undertaking *ab initio* calculations using Gaussian 03 based on initial structures obtained by gas phase geometry optimization using Becke's B3LYP hybrid functional, the 6-31+G* basis set and COSMO continuum model for solvation. The possible impacts of dynamics effects on the reactions will also be considered in these computations. Details of the method are given in previous publications,^{40,41} and the results of the calculations will be reported in a later paper.

EXPERIMENTAL

General. NMR spectra were recorded on 300 or 500 MHz instruments. Kinetic measurements utilised double beam or single beam UV-Vis spectrophotometers. For measurements over extended time periods a multiple cell changer was used and a reference absorbance recorded as function of time for subtraction from measurements for the sample(s). HPLC measurements normally employed a dual pump instrument, usually under isocratic conditions. Standard reagents such as sodium hydroxide, tributyl tin cyanide or ethyl phenyl

sulfide were purchased and used without purification. Reagents for kinetics were of AR or ARISTAR quality; the water used as a solvent was distilled. Concentrated solutions of NaOD in D₂O were purchased and diluted with 99.8% D₂O.

Reagents for Kinetic Measurements. The substituted benzene-*cis*-1,2-dihydrodiols studied kinetically in this work were prepared earlier by bacterial oxidation of the corresponding substituted benzene substrates by dioxygenase enzymes present in cultures of *Pseudomonas putida* UV4.^{42a-c} The structure and spectra of most of the dihydrodiol metabolites, including the unsubstituted benzene-*cis*-dihydrodiol and benzene-*cis*-dihydrodiols with 3-substituents chloro, bromo, iodo, phenyl, carbethoxy, trifluoromethyl, and methylsulfoxy have been reported earlier.⁴² Proton NMR spectra are included in the Supporting Information. Deuterated *cis*-1,2-dihydrodiols were prepared by similar biotransformations of hexadeuterobenzene, pentadeutero bromobenzene, pentadeuterochlorobenzene and perdeuterated toluene. They were identified from the identical R_f values on silica PLC plates as their undeuterated analogues and similarly identical reactant and product UV spectra before and after hydroxide ion-catalyzed dehydration. The 3-cyano perdeutero benzene *cis*-dihydrodiol was prepared from the corresponding 3-iodo substituted *cis*-dihydrodiol by reaction with tributyltin cyanide and Pd(Ph₃P)₄ for 4h in THF solvent as described by Boyd *et al* for the corresponding undeuterated compound.^{42a}

Product Analyses. Products of the reactions of substituted benzene-*cis*-1,2-dihydrodiols in sodium hydroxide were analysed by NMR spectroscopy, HPLC or GCMS to identify and determine the ratio of *o*- to *m*-substituted phenols formed. The following analysis for 1,2-dihydroxy-3-bromo-1,2-cyclohexa-3,5-diene is typical. The *cis*-dihydrodiol reactant (30 mg) in acetonitrile (5 mL) was treated with a solution of 1.0 M sodium hydroxide for 15h at 25 °C. The pH of the reaction mixture was adjusted to 6-7 with saturated aqueous sodium bicarbonate, followed by extraction with ethyl acetate and evaporation of the solvent under reduced pressure. A ¹H NMR spectrum was recorded and the ratio of products determined by HPLC. Comparison of the HPLC peaks with those of authentic samples of the isomeric products confirmed their identity and allowed correction of the measured peak intensities for a small difference in response factors (*m*-bromo/*o*-bromo = 0.9) to give 11% as the fraction of *o*-isomer in the mixture.

Analysis of the products from reaction of the 3-methylbenzene- and 3-trifluoromethylbenzene-*cis*-dihydrodiols was carried out in the same way as for the bromo compound.

Kinetic Measurements. Kinetic measurement in aqueous sodium hydroxide and NaOD/D₂O were based on UV spectra. The cell compartment of the spectrophotometer was thermostatted at 25 °C. Initially, for each substrate repetitive scans of spectra were recorded throughout the dehydration reactions reactions. Samples of the spectral changes are shown in the Supporting Information. Measurements of rate constants were based on kinetic measurements at a single wavelength, usually an absorption maximum of the substituted benzene-*cis*-dihydrodiol reactant or phenoxide ion product. Wavelengths of measurement and first order rate constants measured at different concentrations of sodium hydroxide or deuterioxide are recorded in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Details of kinetic measurements including UV-Vis spectra of reactants and products (Figs S1 and S2); isotope effects (Table S1 and Figs S3 – S5); product analyses (Fig S7); NMR spectra; measurements of ionization constants (Table S6); computational results (Tables S3 – S7); complete ref 34. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

This work was supported by the Science Foundation Ireland (Grant No. 04/IN3/B581). Financial support for DEB from EPSRC and the University of Sheffield (UK) is also gratefully acknowledged, as is a Royal Society Conference Travel Grant for PWF. Support for SG was provided by the National Science Foundation (CHE-0716147).

This paper is dedicated to the memory of Rory More O’Ferrall, colleague, collaborator and friend.

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