

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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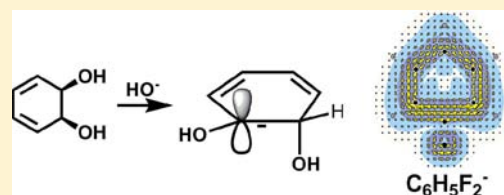
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S Supporting Information

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 with $\rho = 3.2$. 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

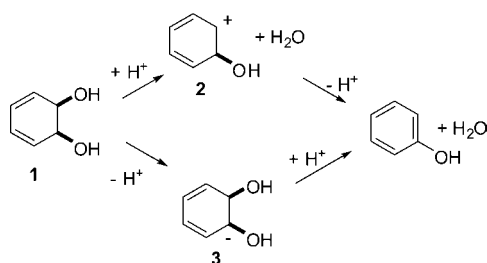
measurements are consistent with reaction via a carbanion intermediate or a concerted reaction with a “carbanion-like” transition state. These and other experimental results confirm that the reaction proceeds by a stepwise mechanism, with a change in rate-determining step from proton transfer to the loss of hydroxide ion from the intermediate. Hydrogen isotope exchange accompanying dehydration of the parent benzene *cis*-1,2-dihydrodiol was not found, and thus, the proton transfer step is subject to internal return. A rate constant of $\sim 10^{11} \text{ s}^{-1}$, 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 $10^{11}\text{--}10^{12} \text{ s}^{-1}$. From these limiting values and the measured rate constant for hydroxide-catalyzed dehydration, a $\text{p}K_{\text{a}}$ of 30.8 ± 0.5 was 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 this proposal is supported by additional experimental evidence and by computational results, 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.^{1–3} As shown in Scheme 1 for the example of benzene *cis*-1,2-dihydrodiol (**1**), it is believed to proceed

Scheme 1



through a carbocation intermediate **2**. The occurrence and mechanism of the reaction are understandable by analogy with the dehydration of alcohols and vicinal diols of nonaromatic 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 to form 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 fluorenyl group.⁵ It is quite unexpected that a cyclohexadienide anion

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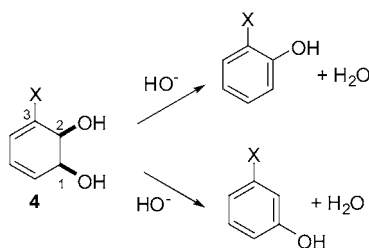
such as **3** would be a viable reactive intermediate under such mildly basic conditions. In principle, the reaction could proceed in a concerted manner, and this possibility is considered below, but to our knowledge, there is no example of a dehydration reaction in solution that proceeds by such a mechanism.

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} s^{-1}) to the loss of hydroxide ion from the carbanion intermediate has allowed the derivation of a $\text{p}K_{\text{a}}$ value for the carbanion, leading 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^{6–8} from the presence of a β -OH group, and this is supported by MP2 calculations on carbanion **3**, the structure of which corresponds to a Meisenheimer intermediate of nucleophilic aromatic substitution. Calculations also confirmed that the corresponding β -difluoro-substituted carbanion supports a diatropic (“aromatic”) ring current.

RESULTS

Kinetic Measurements. Rate constants for the reaction in aqueous sodium hydroxide at 25 °C were measured for 3-substituted benzene *cis*-1,2-dihydrodiols **4** with X = Br, Cl, I, CN, H, Ph, CF₃, MeSO, and EtSO₂ (Scheme 2). The reactants

Scheme 2



were obtained as the products of oxidative biotransformations 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 spectroscopy. 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 the formation of a carbanion intermediate at the 1-position of the ring should 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 meta isomer as the product. Thus Cl and I substituents should have product ratios similar to that for Br, while electron-withdrawing EtSO₂ and MeSO should yield the meta product exclusively. The product ratio for

the 3-carboxylate derivative was taken to be identical to that for the 3-phenyl derivative (25% *ortho*) on the basis of their similar σ values.

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 in Figure 1 for the 3-cyano-substituted reactant. As

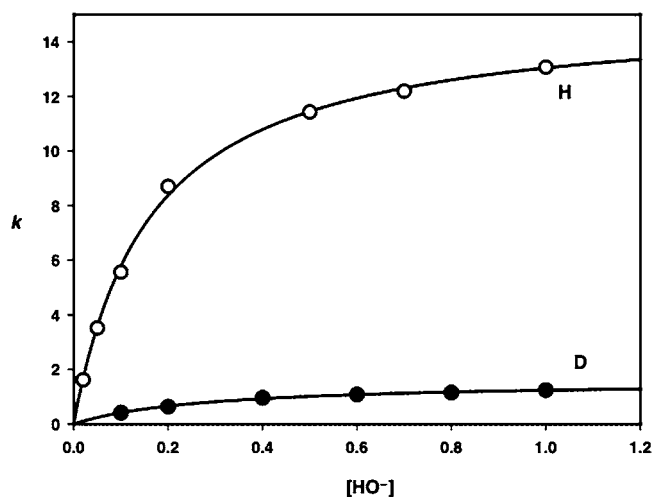
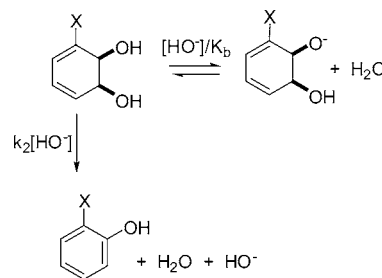


Figure 1. Plots of rate constants (in $\text{s}^{-1} \times 10^4$) for dehydration of 3-cyanobenzene *cis*-1,2-dihydrodiol (O, H) and its pentadeuterated analogue (●, D) in aqueous sodium hydroxide at 25 °C. The lines represent the best fits of the H and D rate constants to eq 1.

Scheme 3



shown in Scheme 3, this 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 given by eq 1, in which k_2 is the rate constant for dehydration of the unionized diol and $K_{\text{b}} = K_{\text{w}}/K_{\text{a}}$ is the base dissociation constant of the hydroxyl group.

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

The ionization was assumed to yield a species that would be unreactive because of 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. The rate constants and apparent $\text{p}K_{\text{a}}$ values for the two hydroxyl groups are listed in Table 1. These are apparent $\text{p}K_{\text{a}}$ values for ionization of one of the OH groups, and each is actually a function of the microscopic $\text{p}K_{\text{a}}$ values of both OH groups. The

Table 1. Second-Order Rate Constants (k_2 , in $M^{-1} s^{-1}$) and Acid Dissociation Constants of Hydroxyl Groups (pK_a) for the Dehydration of 3-Substituted Benzene *cis*-1,2-Dihydrodiols **4 in Aqueous Sodium Hydroxide at 25 °C**

base/ solvent	3- substituent	k_2^a	% <i>m</i> - phenol in product ^b	pK_a	
				kinetic ^c	equilib. ^d
HO ⁻ / H ₂ O	EtSO ₂	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 (4- <i>d</i> ₅)	4.52×10^{-6}		14.12	
	CN (4- <i>d</i> ₅)	5.61×10^{-4}	100	13.45	
	Cl (4- <i>d</i> ₅) ^g	1.22×10^{-6}	^f	in 1 M NaOH	14.0
	I (4- <i>d</i> ₅) ^g	1.82×10^{-6}	^f	in 1 M NaOH	
	DO ⁻ / D ₂ O	Cl	$(2.8 \times 10^{-5})^h$	^f	ⁱ
	CN	1.70×10^{-2}	100	13.05	13.5

^aCalculated as the measured k_2 value multiplied by the percentage of *m*-phenol product. ^bProduct analyses were also carried out for Me (89% meta) and Bu^t (87% meta), 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 in the Supporting Information). ^eFormation of 100% *m*-phenolic product was assumed. ^fFormation of 89% *m*-phenolic product was assumed. ^gThe rate constant was extrapolated from a single measurement as explained in the text. ^hThe limited amount of data added to uncertainty of this measurement (see Figure S3 in the Supporting Information). ⁱThe data were unsuitable for obtaining a measurement of pK_b (see the discussion of Figure 3). ^jTaking $pK_w = 14.85$ for D₂O.

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_a values are only “apparent” because normally the ionization of two hydroxyls with different acidities is occurring. There is little correlation between the acidity and the electron-withdrawing character of the 3-substituent. Presumably this is partly because of uncertainty in separating the two parameters in eq 1 (k_2 and K_b). Measurements in some cases were also based on fairly small but consistent variations in the initial absorbances of kinetic measurements with [HO⁻], as reported in Table S2 in the Supporting Information. Of the two sets of measurements, these probably yield the more reliable pK_a values.

In the case of the carboxylate substituent, the reactant was the corresponding methyl ester of carbomethoxybenzene *cis*-1,2-dihydrodiol. This substrate showed a rapid hydroxide ion-catalyzed decrease in absorbance at 290 nm with a rate constant of $7.0 \times 10^{-2} M^{-1} s^{-1}$, which was attributed to hydrolysis of the ester group; this was followed by a much slower hydroxide ion-catalyzed reaction with a rate constant of $2.5 \times 10^{-5} M^{-1} s^{-1}$, consistent with dehydration to form predominantly the *m*-hydroxybenzoate anion and probably a lower concentration of its ortho isomer. Details of this and other kinetic measure-

ments, 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*-1,2-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 3 weeks. This implies a strong dependence of the rate of reaction on the stereochemistry, with $k_{cis}/k_{trans} > 50$. 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 acidic solution.

Isotope Effects. A number of measurements of isotope effects were undertaken utilizing biotransformation products of deuterated aromatic substrates. Hexadeuterated benzene, pentadeuterated chlorobenzene, and iodobenzene were commercially available. Pentadeutero 3-iodobenzene *cis*-1,2-dihydrodiol diacetate was converted to pentadeutero cyanobenzene *cis*-dihydrodiol diacetate by reaction with tributyltin 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. Figures 1 and 2 show

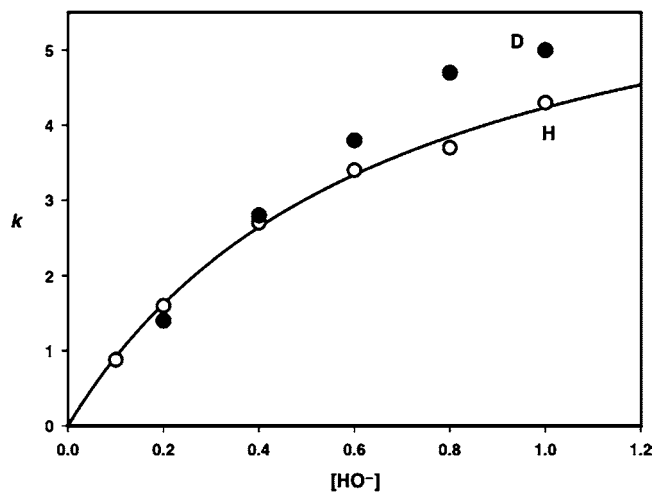


Figure 2. Plots of rate constants (in $s^{-1} \times 10^6$) for dehydration of benzene *cis*-1,2-dihydrodiol (O, H) and its hexadeuterated analogue (●, D) in aqueous sodium hydroxide at 25 °C. The line represents the best fit of the H rate constants to eq 1.

plots of first-order rate constants against hydroxide ion concentration for deuterated and undeuterated cyanobenzene *cis*-1,2-dihydrodiol and unsubstituted benzene *cis*-1,2-dihydrodiol, respectively.

It is apparent from Figure 1 that deuteration of 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 ionization of the hydroxyl groups of the reactant as the protio substrate. However, the rate constants are substantially smaller than for the undeuterated substrate at all base concentrations, with a limiting k_H/k_D value of 16.7 at low concentrations of hydroxide ion. In contrast, in the case of benzene *cis*-1,2-dihydrodiol, deuteration causes little change in the measured rate constants and yields a correspondingly small

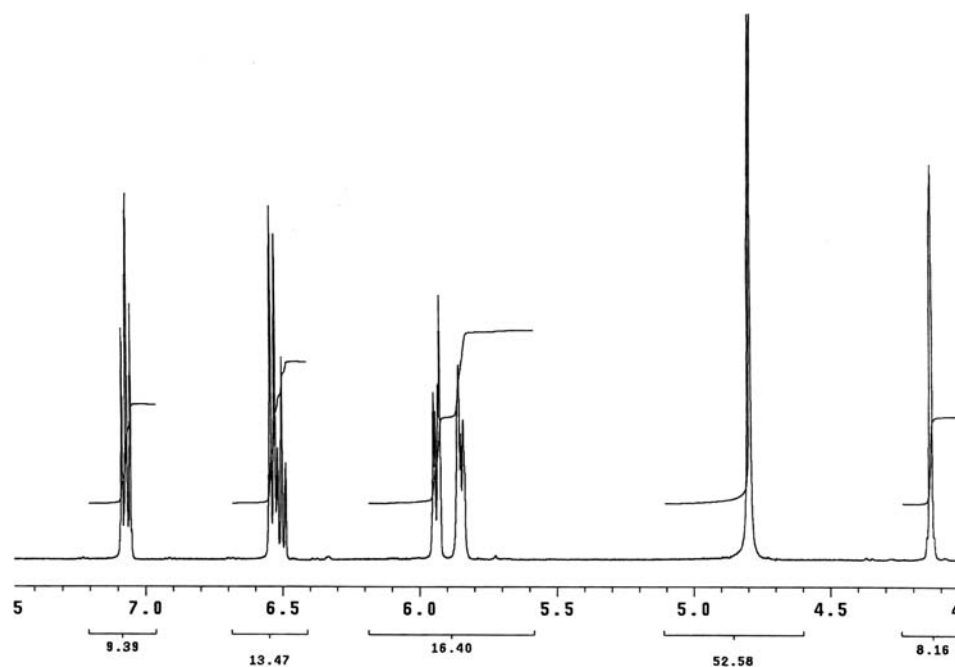


Figure 3. Partially reacted benzene *cis*-1,2-dihydrodiol in NaOD/D₂O at 25°. The peaks at 7.2 and 6.5 ppm correspond to the phenol product, and the peaks near 5.9 and at 4.15 ppm represent unreacted (and unexchanged) benzene *cis*-dihydrodiol. The peak at 4.8 ppm is assigned to an OH group.

isotope effect of $k_{\text{H}}/k_{\text{D}} = 1.16$. 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 $k_{\text{H}}/k_{\text{D}}$ decreasing to 0.8 at high concentrations of sodium hydroxide. This is because $k_{\text{H}}/k_{\text{D}}$ is based on its limiting value at low base concentration and the hydroxyl groups of deuterated benzene *cis*-1,2-dihydrodiol are less acidic than those of the undeuterated substrate (with $K_{\text{a}}^{\text{H}}/K_{\text{a}}^{\text{D}} = 1.9$). We infer from Figure 2 that the value of k_{H} will level off at a lower base concentration, leading to a lower limiting value for k_{H} than for k_{D} at high base concentrations.

The small isotope effect in the case of the perdeutero benzene *cis*-dihydrodiol was confirmed by a similar observation in the case of toluene *cis*-1,2-dihydrodiol and the corresponding perdeuterated substrate 3-CD₃C₆D₅ *cis*-1,2-dihydrodiol. These substrates reacted too slowly for conventional kinetic measurements, but repetitive scans of spectra for the reaction in 1 M NaOH over 30 h (Table S1 and Figure S5 in the Supporting Information) indicated the similarity of their rates. A crude estimate of the isotope effect gave $k_{\text{H}}/k_{\text{D}} \approx 1.5$.

The isotopic behavior of the *cis*-1,2-dihydrodiols of chlorobenzene and iodobenzene is intermediate between that of the cyano-substituted and unsubstituted (or methyl-substituted) benzene *cis*-1,2-dihydrodiols. The reactivities of pentadeutero chloro- and iodobenzene *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 h were undertaken. Details of these measurements are contained in the Supporting Information, but at the indicated base concentration, the values of $k_{\text{H}}/k_{\text{D}}$ were 8.5 for the chloro-substituted diol and 6.6 for the iodo-substituted compound. When the rate constant at 1 M was crudely corrected to its limiting value in dilute base using eq 1 and $\text{p}K_{\text{a}} = 14.0$, we obtained values of $k_{\text{D}} = 6.3 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{H}}/k_{\text{D}} = 6.3$ for the chloro compound.

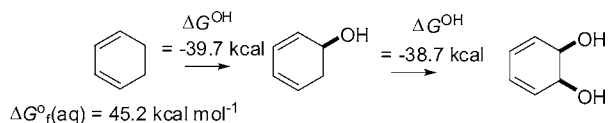
In addition to these substrate isotope effects, a solvent isotope effect of $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 1.2$ was measured for the chloro-substituted benzene *cis*-1,2-dihydrodiol. In principle, this is consistent with a solvent isotope effect on rate-determining proton transfer, for which $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ normally falls in the range 1.2–1.5.¹⁰ However, although the measurement was unchanged for hydroxide (or deuterioxide) ion concentrations between 0.3 and 0.9 M, it was not possible to separate accurately the effects on the kinetic and equilibrium steps. Thus, the greater rate in D₂O is consistent with the expectation that ionization of the hydroxyl groups of the *cis*-1,2-dihydrodiol reactant occurs more readily in H₂O than D₂O, and correspondingly, that the reverse of this equilibrium (which is fully expressed at higher base concentrations) is more favorable in D₂O. This makes it likely that the limiting rate constant for the dehydration reaction at low base concentrations is greater in H₂O than in D₂O, although the difference cannot be large (say, <1.5).

On the other hand, more extensive measurements for the 3-cyanobenzene *cis*-1,2-dihydrodiol could be extrapolated to dilute solution and yielded $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 1.8$. At higher base concentrations, the solvent isotope effects for cyano- and chloro-substituted substrates are similar, as may be seen by comparing Figures 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 fact that the isotope effect is nearly independent of the concentration of hydroxide ion suggests that the isotope effect on the equilibrium ionization 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 the rate-determining step (see below), but the similar isotope effect is not unreasonable.

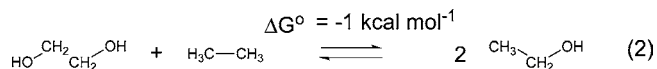
Isotope Exchange. The reaction of undeuterated benzene *cis*-1,2-dihydrodiol in D₂O was also monitored by NMR spectroscopy, and the occurrence of H for D isotope exchange in the reactant and phenolic product was examined. Remarkably, no exchange was detected. Figure 3 shows NMR spectra of the reactant and product after 60% reaction. The two low-field multiplets in the spectrum correspond to the phenoxide ion, and the peak at highest field corresponds to the potentially exchangeable methine hydrogen atoms adjacent to the hydroxyl groups of the dihydrodiol. It is apparent that there was no decrease in the 2:1 ratio of vinylic to methine hydrogens (4.3 ppm) in the unexchanged reactant, nor was there any sign of exchange in the product. The hydroxyl peak at 4.8 ppm decreased 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 the exchange remained undetected, the implication is that exchange is at least 10 times slower than the dehydration.

Equilibrium Constant for Dehydration. Of interest in connection with the mechanism of dehydration is the thermodynamic driving force for the reaction. As shown in Scheme 1, this is represented by the energy difference between the phenolic product and the *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 benzene hydrate (2,4-cyclohexadien-1-ol). As shown in Scheme 4, $\Delta G_f^\circ(\text{aq})$ for this

Scheme 4



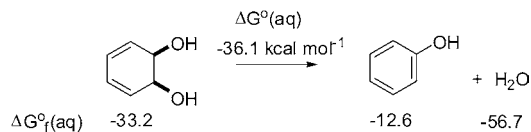
molecule was obtained from that for 1,3-cyclohexadiene by adding an increment representing the energy of replacing a hydrogen atom by a hydroxyl group.¹² In principle, the conversion of cyclohexadienol to benzene-1,2-dihydrodiol **1** (Scheme 4) should involve the same increment adjusted for any repulsion between the vicinal hydroxyl groups. This repulsion may be estimated from ΔG° for the bond separation equilibrium between ethylene glycol and ethanol (eq 2).⁸



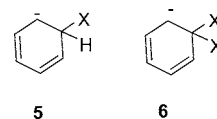
The derived value of $\Delta G^\circ(\text{aq}) = -33.2 \text{ kcal mol}^{-1}$ for benzene *cis*-dihydrodiol may be combined with the free energies of formation for water and phenol to give $\Delta G^\circ(\text{aq}) = -36.1 \text{ kcal mol}^{-1}$ for the dehydration reaction in Scheme 5. This translates to an equilibrium constant of $\log K = 36.1/1.364 = 26.5$.

Computed Energies and Geometries of Cyclohexadienide and Cycloheptadienide Anions. Energies of substituted cyclohexadienide and cycloheptadienide anions in the gas phase were obtained from G3MP2 and MP2 calculations. In Table 2, these are expressed as proton affinities (PAs) of the mono- and disubstituted anions C₆H₆X⁻ (**5**) and C₆H₅X₂⁻ (**6**) or C₇H₈X⁻ and C₇H₇X₂⁻, where the X

Scheme 5



substituents are at the 6-position of the cyclohexadienide anion or the 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 with respect to the unsubstituted cyclohexadienide anion, C₆H₇⁻. The effectiveness of the G3 method was demonstrated by showing that it gives proton affinities that correlate well with experimental values for 18 anionic bases: $\text{PA}_{\text{G3}} = 1.10\text{PA}_{\text{exptl}} + 5.2$ ($r^2 = 0.999$).¹³ This correlation is shown in Figure S8 in the Supporting Information on the basis of data summarized in Table S3 in the Supporting Information. More details of calculated energies, zero-point energies, and geometries of the cyclohexadienide and cycloheptadienide ions and their isomeric complexes and transition states are shown in Tables S4 (G3MP2) and S5 in the Supporting Information. Included in Table S4 (entry 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 the conjugate acids of the calculated anions are given in Table S8 in 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 C₆H₅X with X⁻, the intermediate C₆H₅X₂⁻ is the product of reaction at the ipso carbon of the aromatic ring. G3MP2 enthalpies and free energies of the nucleophiles and substrates in the nucleophilic substitutions are given in Table S3 in the Supporting Information.

When X is bound to the aromatic ring by a second-row element, as with F, OH, NH₂, and CH₃ (and CN or C≡CH), the cyclohexadienide anion exists as an energy minimum. Indeed, this Meisenheimer complex is more stable than the separated nucleophile (X⁻) and aromatic molecule. However, for third-row elements, only SiR₃ gives a stable monosubstituted anion with benzene, and the diphosphino anion is also stable. For the other third-row elements (SR and Cl), there is no energy minimum for mono- or disubstituted ions, and it appears that these are too reactive as leaving groups to maintain attachment to the benzene ring. The same was shown to be true for X = Br or NO₂. Previous work indicated that for these groups, the corresponding nucleophilic substitution reaction proceeds by a concerted mechanism without the formation of a Meisenheimer intermediate.¹⁴ As also shown previously, the

Table 2. G3MP2-Calculated Proton Affinities of 6-Substituted Cyclohexadienide Anions $C_6H_5XY^-$, Enthalpies ΔH_{add} and Activation Enthalpies $\Delta H_{\text{add}}^\ddagger$ for Addition Reactions of the Elimination Products ($C_6H_5X + Y^- \rightarrow C_6H_5XY^-$),^a and Calculated Proton Affinities of Selected 7-Substituted Cyclohexadienide Anions

entry	X, Y (point group) ^b	PA (kcal/mol) ^c	Δ PA (kcal/mol) ^d	elimination products	ΔH_{add} (kcal/mol)	$\Delta H_{\text{add}}^\ddagger$ (kcal/mol)
Cyclohexadienide Anions						
1	H, H (C_s)	374.3 ^e	0	benzene + H^-	-17.0	+6.6
2	CH₃ , 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	-CH₂-CH₂- (C_s) ^f	369.7	4.6	C_6H_5 -CH ₂ -CH ₂ ⁻	4.3	-
5	NH₂ , 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	OH_{ax} , H (C_s) ^g	357.7 ₅	16.5	benzene + OH^-	-6.9	-6.6
8	OH_{eq} , H (C_s) ^g	364.0	10.3	benzene + OH^-	-0.6	-
9	OH, OH (C_1)	356.9	17.4	phenol + OH^-	-15.1	-12.9
10	F , H (C_s) ^h	350.9	23.4	benzene + F^-	+3.7	-3.7
11	F, F (C_{2v})	345.8	28.5	fluorobenzene + F^-	-10.7	-4.9
12	SiH₃ , H (C_s)	369.2	5.1	benzene + SiH_3^-	+5.8	+12.1
13	SiH ₃ , SiH ₃ (C_s)	363.8	9.5	silylbenzene + SiH_3^-	-0.9	+4.2
14	(CH₃)₃Si , H (C_s)	371.8	2.5	benzene + $(CH_3)_3Si^-$	-7.2	-
15	PH₂ , H (C_s) ⁱ	-	-	benzene + PH_2^-	-5.1	-
16	PH ₂ , PH ₂ (C_s) ^j	359.5	14.9	phosphinobenzene + PH_2^-	-6.2	+5.6
17	HC≡C , H (C_2)	368.8	5.5	benzene + $HC\equiv C^-$	+3.1	+13.1
18	CN , H (C_s)	359.5	14.8	benzene + CN^-	+18.4	+23.5
Cycloheptadienide Anions						
19	H, H (C_2)	371.6	2.7			
20	F, H (C_1)	362.4	11.9			
21	F, F (C_1)	355.8	18.5			
22	OH, H (C_1)	360.5	13.7			
23	OH, OH (C_1)	360.3	14.0			

^aInitial step of nucleophilic aromatic substitution. ^bThe pseudoaxial group is indicated in bold type. Geometries are outlined in the main text. ^cPA = $-\Delta H_{\text{rxn}}$ for protonation of the anion to give the corresponding 1,3-cyclohexadiene. ^d Δ PA = $PA_{\text{HH}} - PA_{\text{XY}}$, where PA_{HH} is the PA for cyclohexadienide anion, $C_6H_7^-$. Thus, a positive Δ PA value indicates that the anion is less basic (more stable) than $C_6H_7^-$ relative to their respective protonation products. ^eThe experimental PA for $C_6H_7^-$ 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. In entry 8, the OH group was made equatorial by constraining dihedral angles to ensure C_s symmetry. ^hA covalent addition complex with a bond-length extension of 0.193 Å relative to its conjugate acid was found at the G3MP2 level. However, at the MP2/6-311+G** level, this structure optimized to a H-bonded benzene–fluoride⁻ complex. ⁱOptimization at the G3MP2 or MP2/6-311+G** level gave a H-bonded benzene– PH_2^- complex. ^jAt the G3MP2 level with MP2/6-31G* frequencies, a stable covalent adduct was formed. At the MP2/6-311+G** level, the structure became a transition state ($\nu = 117$ cm^{-1}).

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-row leaving groups, although a stable Meisenheimer complex with a highly extended fluoride bond was found at the G3 level, it was not found at the MP2/6-311+G** level. 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 kcal mol⁻¹) is in satisfactory agreement with that found by Glukhotsev et al. [-2.2 and -3.7 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 carbons 1, 2, 4, and 5 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 with low electronegativity (e.g., H and CH₃) to smaller values for electronegative groups (e.g., 6° for OH). The 3-

carbon is 15–18° out of plane. All of the X substituents occupy pseudoaxial positions with C–X bonds that 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 in the Supporting Information.

DISCUSSION

The dehydration of benzene *cis*-1,2-dihydrodiol shows a first-order dependence on the hydroxide ion concentration, albeit modified by partial ionization of a hydroxyl group as shown in Scheme 3. This observation, coupled with a positive ρ value of 3.2 and the correlation of the effect of 3-substituents by the σ^- values (Figure 4), is clearly consistent with reaction that occurs 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 favor a concerted mechanism.

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

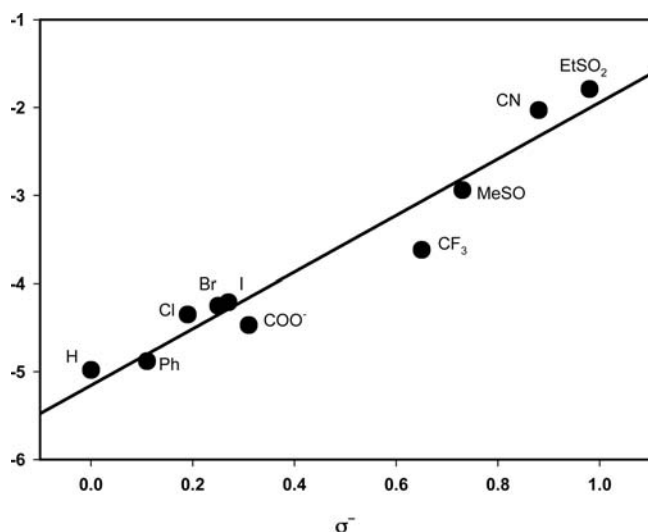
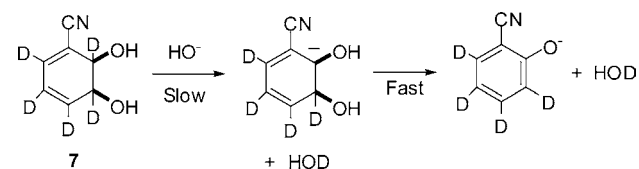


Figure 4. Plot of $\log k$ ($M^{-1} s^{-1}$) vs σ^- for the dehydration of 3-substituted benzene *cis*-1,2-dihydrodiols in aqueous NaOH at 25 °C: $\log k = -5.16 + 3.21\sigma^-$.

reaction. The much greater reactivity of the *cis*-1,2-dihydrodiol of benzene relative to that of naphthalene is consistent with this possibility. Also consistent with a concerted mechanism is the much greater reactivity of a *cis*-dihydrodiol compared with a *trans*-dihydrodiol. In the case of the *cis*-dihydrodiol, the OH leaving group and the β -carbon–hydrogen bond can achieve an *antiperiplanar* arrangement, which is normally considered optimum for a concerted reaction. This is not possible for the *trans*-dihydrodiol.

However, the measurements of hydrogen isotope effects for deuterated reactants appear to be decisive in indicating reaction via a carbanion intermediate. For pentadeutero cyanobenzene *cis*-dihydrodiol (7), the measured value of k_H/k_D is 16.7, 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 substituent is changed

Scheme 6



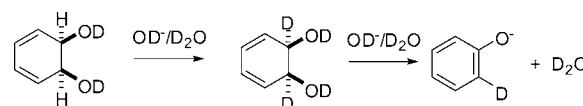
from cyano to chloro, the primary isotope effect is reduced to ~ 6.3 , and when the substituent is changed to deuterium (i.e., for the *cis*-1,2-dihydrodiol of hexadeuterobenzene), the isotope effect disappears altogether. For benzene *cis*-1,2-dihydrodiol, $k_H/k_D = 1.2$, which is a normal magnitude for a secondary isotope effect.

Such a large change in the magnitude of the isotope effect for a relatively small change in reactivity between cyano, chloro, and deuterio substituents would be unprecedented for a proton transfer reaction not subject to a change in mechanism or rate-determining step. What the behavior suggests is that there is a change from rate-determining proton transfer for the cyano substituent to pre-equilibrium proton transfer for the

unsubstituted *cis*-1,2-benzene dihydrodiol, within an overall E1cB mechanism for the dehydration reaction.

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

Scheme 7



benzene *cis*-1,2-dihydrodiol with NaOD in D_2O should lead to exchange of a hydrogen for deuterium in two C–H bonds in the dihydrodiol reactant and one in the phenolic product.

Remarkably, when the reaction was monitored by NMR spectroscopy, no exchange was observed in the reactant or product over a period that implied that the rate of exchange was at least 10 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., the formation of a carbanion that is 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 as H–Ar–OH or H–Ar–OD (in D_2O) and phenol as Ar. The H–Ar bond of the reactant is the carbon–hydrogen bond that undergoes ionization 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 into 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 D_2O 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 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 in Figure 5, in which the initial diffusion step has been omitted, and further simplified in Scheme 9, in which only the pre-equilibrium and rate-determining steps for the dehydration reaction 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

Scheme 8

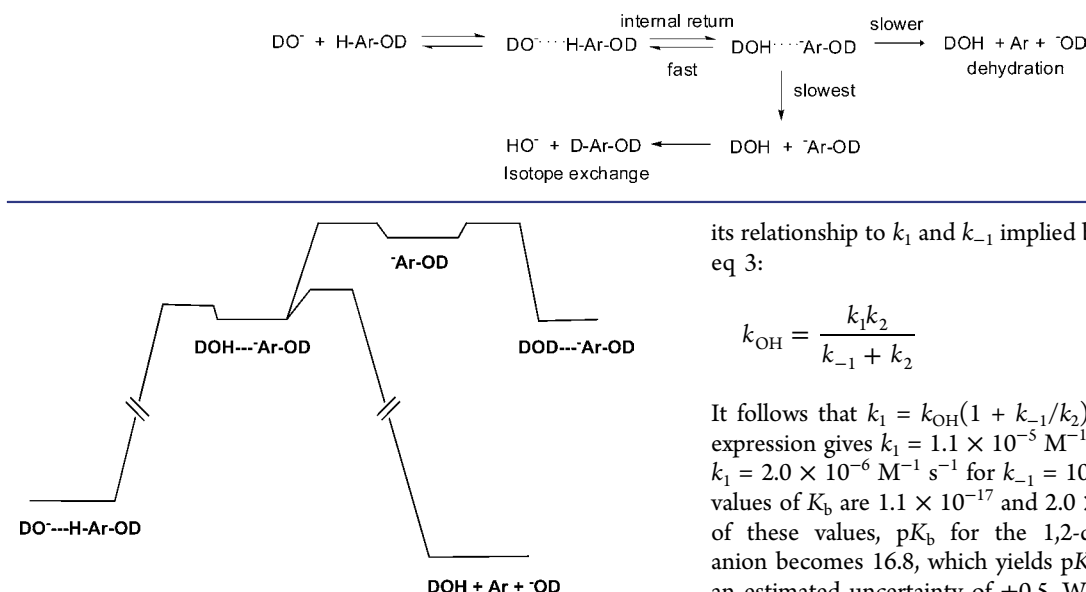
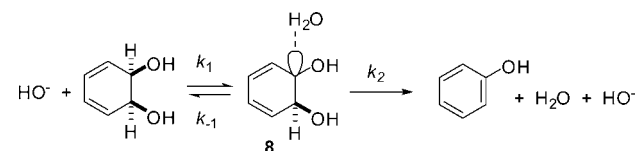


Figure 5. Schematic plot of free energy against reaction coordinate for base-catalyzed dehydration and isotope exchange of benzene *cis*-1,2-dihydrodiol. The deuteron transfer step completing the exchange reaction has been omitted.

Scheme 9



diffusion step) and a rate constant for the reaction of this complex.

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 $k_2 \approx 10^{11} \text{ s}^{-1}$.^{22–24} 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 of 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} s^{-1} if the thermodynamic driving force for the protonation of the carbanion is sufficiently great. The size of this driving force can be determined by deriving the equilibrium constant K_b for protonation of the carbanion intermediate. This is given by k_1/k_{-1} , 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. 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 3:

$$k_{\text{OH}} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (3)$$

It follows that $k_1 = k_{\text{OH}}(1 + k_{-1}/k_2)$, and with $k_2 = 10^{11}$, this expression gives $k_1 = 1.1 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ for $k_{-1} = 10^{12} \text{ s}^{-1}$ and $k_1 = 2.0 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ for $k_{-1} = 10^{11} \text{ s}^{-1}$. The 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, which yields $\text{p}K_a = 14.0 + \text{p}K_b \approx 31$ with an estimated uncertainty of ± 0.5 . We consider it possible that k_2 is somewhat less than 10^{11} , as HOD hydrogen bonded to the carbanion could impose a barrier to reorganization. If so, k_{ex} would be even smaller.

A more detailed argument regarding the limiting rate constant values focuses on the possible relative magnitudes of k_{-1} and k_2 in Scheme 9 and k_r , which for purposes of this analysis we will call the rate constant for solvent relaxation (or solvent reorganization) within the hydrogen-bonded $\text{DOH}\cdots\text{Ar}\cdots\text{OD}$ complex (Scheme 8 and Figure 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 large. 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 that 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 in $\text{DOH}\cdots\text{Ar}\cdots\text{OD}$, even though it is between C and O, will make solvent reorganization slower than in the solvent itself, by perhaps as much as 2 orders of magnitude; thus, $10^9 \text{ s}^{-1} < k_r < 10^{11} \text{ s}^{-1}$. This implies that $10^{10} \text{ s}^{-1} < k_2 < 10^{12} \text{ s}^{-1}$. 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 in 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 the limiting value of the barrier for solvent relaxation depends on the intrinsic barrier to the reaction. Without entering into a full discussion of the point here, we note that for proton transfer to a hydroxide ion from carbon activated by a series of carbonyl, carboxy, amido, and carboxylate groups, Richard has shown that the intrinsic barrier is 10 kcal mol^{-1} and that the reaction becomes diffusion-controlled as the $\text{p}K_a$ of the carbon acid approaches a value of 30.²⁶ Our assignment of a limiting rate constant to the reaction between water and a 1,2-dihydroxycyclohexadienyl anion for

which the pK_a of its conjugate acid is 30.8 is therefore reasonable.

A difference between the study by Richard and Williams²¹ and the present work is that they used hydrogen isotope exchange of nitriles to measure their rates of ionization to form anions. When reprotonation of the anion is sufficiently exothermic, the isotope exchange ceases to be catalyzed by buffer base, and Richard supposed 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



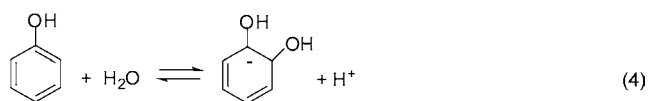
Richard assumed a k_{reorg} value of $\sim 10^{11} \text{ s}^{-1}$, which corresponds to rotational relaxation of the solvent.^{16–19} In our case, however, a rate constant corresponding to rotational relaxation is assigned to the loss of hydroxide ion from a dihydroxycyclohexadienide anion intermediate. Loss of hydroxide occurs at least 2 orders of magnitude more rapidly than the isotope exchange reaction. This implies that the isotope exchange cannot be controlled by solvent relaxation.

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

Is the thermodynamic driving force for the expulsion of hydroxide ion from the dihydroxycyclohexadienide anion sufficient to ensure that this occurs at the limiting rate of solvent relaxation? Bernasconi showed that the intrinsic barrier to loss of a β -hydroxide ion to form a double bond is significantly greater than that for protonation of the same carbanion.²⁸ The magnitude of the exothermicity (strictly, the reaction free energy) 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 is 26.5. To arrive at the value of $\log K$ for the conversion of the carbanion intermediate to product, we must add to this the pK_b value of 16.8; this gives an overall value of $\log K = 43.3$; which corresponds to $\Delta G = -59 \text{ kcal mol}^{-1}$ at 25 °C. This is an overwhelmingly large thermodynamic driving force, which leaves little doubt that the rate of expulsion of hydroxide ion must indeed occur at the limit of solvent relaxation.

Cycle of Equilibrium Constants. The value of $\log K$ corresponds to $\log K_c$, the logarithm of the equilibrium constant for addition of hydroxide ion to an ortho position of phenol. Values of $\log K_c$ for the addition of hydroxide ion to various electrophiles have been discussed by Hine.²⁹ They may be converted to values of pK_R by recognizing that K_R and K_c are related in a manner comparable to that $K_R/K_c = K_w$, where $K_w = 10^{-14}$ is the autoprotolysis constant of water.³⁰ The value of pK_R for phenol, which refers to the equilibrium shown in eq 4, is $43.3 + 14 = 57.3$.

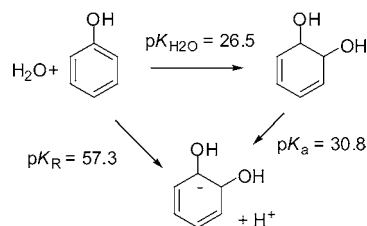
Normally, pK_R refers to carbocations and has a negative value, implying that hydrolysis of the carbocation ($\text{R}^+ + \text{H}_2\text{O} \rightarrow \text{ROH}$



+ H^+) is a favorable reaction; for example, $pK_R = -16$ for the *tert*-butyl cation.³¹ Hydrolysis becomes unfavorable and pK_R positive for weaker electrophiles such as aldehydes or ketones. In the case of benzaldehyde, for which the resonance form PhCH^+-O^- may be considered to represent a highly stabilized carbocation, $pK_R = 14.7$. 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 also reflected 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 $K_{\text{H}_2\text{O}}$ for addition of water to phenol, which corresponds to the reciprocal 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 the reaction to which each equilibrium constant refers.

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 stabilize the carbanion and increase the barrier for reprotonation. This renders the proton transfer rate-determining, insofar as the much greater exothermicity of the loss of hydroxide ion ensures that the rate constant for this reaction step remains close to its limiting value of 10^{11} s^{-1} . This is illustrated schematically in Figure 6, in which the upper free energy profile corresponds to

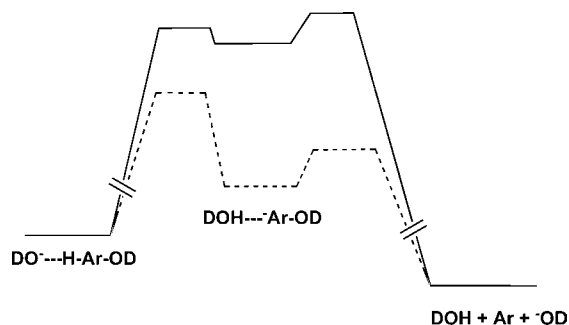
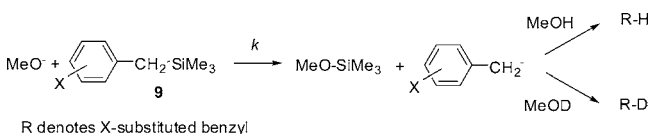


Figure 6. Schematic free energy profiles for hydroxide ion-catalyzed dehydration of unsubstituted (upper profile, from Figure 4) and 3-cyano-substituted (lower profile) benzene *cis*-1,2-dihydrodiol.

the unsubstituted benzene *cis*-1,2-dihydrodiol and the lower (dashed) profile to its 3-cyano-substituted derivative. The sharp change in isotope effect in going from the chloro ($k_{\text{H}}/k_{\text{D}} \approx 6.3$) to the cyano compound ($k_{\text{H}}/k_{\text{D}} = 16.7$) suggests that the isotope effect may be reduced in the case of the chloro substituent because the proton transfer step is only partially rate-determining.

A similar dependence of the isotope effect on the substituent was observed by Eaborn in the cleavage of benzyltrimethylsilanes **9** in methanolic sodium methoxide (Scheme 12).³² The

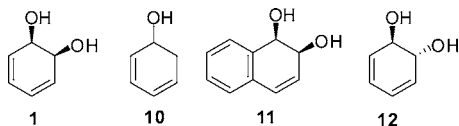
Scheme 12



isotope effect was measured as the ratio of H to D in the toluene product, $[R\text{-H}]/[R\text{-D}]$, following the reaction of the benzylic anion intermediate in a mixed MeOH/MeOD solvent. Table 3 shows values of $[R\text{-H}]/[R\text{-D}]$ for various substituents along with values of $\log k_{\text{rel}}$, where k_{rel} is the relative rate constant for generating the anion from the benzyltrimethylsilane precursor.

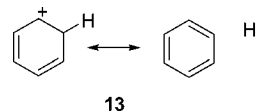
One question that remains is why does the reaction proceed so readily for so apparently unstable an intermediate as a cyclohexadienide anion? The following may provide at least a partial answer.

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 when the benzene *cis*-1,2-dihydrodiol reactant is replaced by benzene hydrate [2,4-cyclohexadien-1-ol (**10**), i.e., the dihydrodiol lacking a 2-hydroxyl group], naphthalene-*cis*-1,2-dihydrodiol (**11**), or benzene *trans*-1,2-dihydrodiol (**12**). The structures of these potential reactants are compared below.



The more than 50-fold greater reactivity of the benzene *cis*-dihydrodiol relative to the *trans* isomer in particular recalls the behavior observed for the *acid*-catalyzed dehydration, a reaction for which the reactivity difference amounted to $k_{\text{cis}}/k_{\text{trans}} = 4500$.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 center of charge and the β -C–OH bond in a pseudoequatorial position. It was argued that although this occurred for the reaction of the *cis*-dihydrodiol, the carbocation of the *trans* isomer was formed with a pseudoaxial β -C–OH bond and a

pseudoequatorial β -C–H bond, a geometry that is much less favorable for hyperconjugation. The large magnitude of the effect was attributed to the aromatic character of the no-bond resonance structure associated with the hyperconjugation, as illustrated in structure **13**; it is further magnified by good electron-donating groups (e.g., silyl) at the β -carbon.



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* favorable than a C–H bond. The preferential formation of carbanions with C–OH and C–H bonds in β -pseudoaxial positions from the reactions of *cis* and *trans* reactants, respectively, is illustrated in Scheme 13 (hydrogen bonding between the newly formed water and the carbanion has been omitted). An important assumption is that the proton transferred from the reactant benzene dihydrodiol departs from a pseudoaxial position. This should optimize the overlap between the developing negative charge and the π orbitals of the cyclohexadienyl ring.

Calculated Stabilities of Cyclohexadienide Anions.

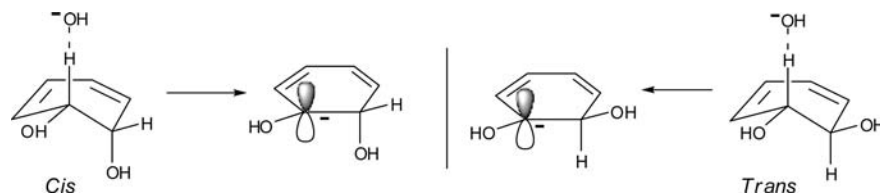
Support for the concept of negative hyperaromaticity was provided by MP2 calculations on substituted cyclohexadienide anions in the gas phase. As noted above, these ions have the structure of Meisenheimer intermediates in nucleophilic aromatic substitution reactions. Thus the 2-hydroxycyclohexadienide 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 the aromatic substrate and the nucleophile in the gas phase.^{14,15} They have emphasized 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 assessed the 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 the 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 canceled with the cyclohexadiene reactant.

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
$[R\text{-H}]/[R\text{-D}]$	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

Scheme 13

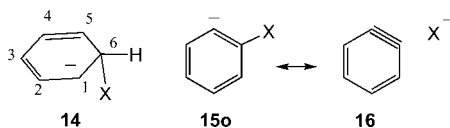
Table 4. Proton Affinities (PA) and Relative Proton Affinities (Δ PA) of 6-Monosubstituted Cyclohexadienide Ions 11^a

	substituent							
	H	CH ₃	NH ₂	OH	F	SiH ₃	C≡CH	CN
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; all values are in kcal mol⁻¹.

Calculated PAs of monosubstituted cyclohexadienide ions and Δ PA values relative to the unsubstituted cyclohexadienide ion are summarized 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 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, the electronegative substituents 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 for CH₃ or SiH₃.

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 when the dihedral angle formed by 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 for assessing the stabilization derived from hyperconjugation is to compare the proton affinities of 6-substituted cyclohexadienide ions with those of carbanions that cannot profit from hyperconjugation. For this comparison, we chose para-substituted phenyl anions 15p. A plot of the

computed proton affinities of the *p*-phenyl anions³³ against the proton affinities of the correspondingly substituted stable cyclohexadienide anions is given in Figure 7. Groups that are

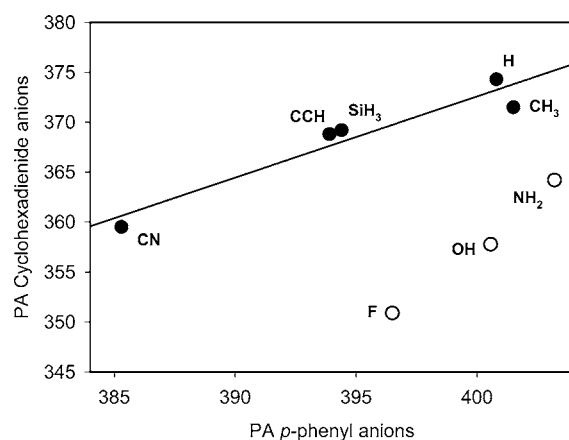


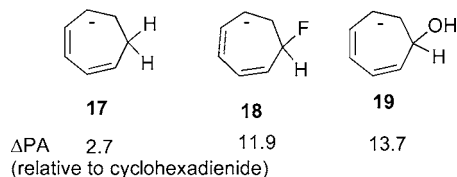
Figure 7. Plot of computed cyclohexadienide PAs vs *p*-phenyl anion PAs.

not expected to have a strong contribution from hyperconjugation give a reasonable correlation line with a slope of 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 of the cyclohexadienide relative to the phenyl anion. The magnitude of the implied stabilization is large, amounting 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 for negative hyperconjugation.

These comparisons do not demonstrate that the hyperconjugative effect confers aromaticity. Evidence regarding this point comes from a comparison between para- and ortho-substituted phenyl anions. As illustrated by 15o and 16, hyperconjugative stabilization but not aromaticity can be envisaged for the ortho anion. Moving a cyano group from a para to an ortho position reduces the proton affinity of the ion by only ~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 vs 7 kcal mol⁻¹) suggests that the cyclohexadienide anions experience added stabilization of up to 12 kcal mol⁻¹ due to hyperaromaticity in **14**.

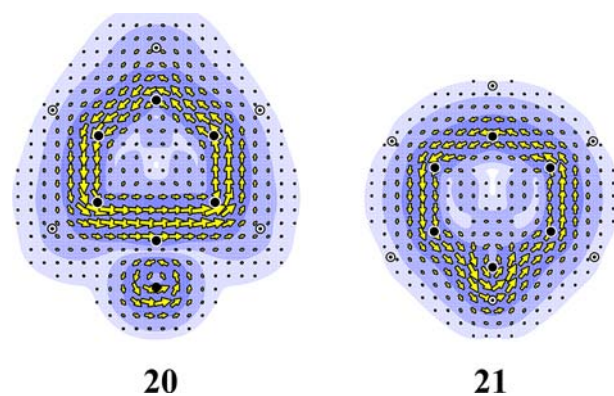
A further way of estimating the aromatic contribution to the hyperconjugation is to compare the proton affinities of the F- and OH-substituted cyclohexadienide ions in Table 4 and Table 2 with those of the corresponding unsubstituted and substituted cycloheptadienide anions **17**–**19**. Values of Δ 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 PA. The difference between these values and that for unsubstituted cyclohexadienide ion is \sim 2.8 kcal/mol, an increment that can be assigned to the polarizability effect of having an additional carbon in the seven-carbon-ring anions. The difference between the PAs of the monofluorocyclohexadienide and monofluorocycloheptadienide ions is 11.5 kcal/mol, which, allowing for the effect of the extra carbon in the latter, gives a corrected difference of \sim 14 kcal/mol. The same analysis using 7-hydroxycycloheptadienide (**19**) shows that OH confers an extra stabilization of \sim 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 increased stabilities of the fluorinated and hydroxylated cyclohexadienides reveal the additional “aromatic” stabilizing effect over and above the “nonaromatic” hyperconjugative stabilization of the seven-membered-ring model ions. In the case of the fluoro substituent, the magnitude of the stabilization (14 kcal mol⁻¹) agrees satisfactorily with that estimated above on the basis of 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 *n*th-row nucleophiles with $n \geq 3$. 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 in the transition state.¹⁴

Orbital Interactions and Ring Current Calculations. A calculation of the “ipsocentric”³⁴ type confirmed that there is a ring current associated with the *gem*-difluoro-substituted cyclohexadienide anion **20**. A current density map at a height of $1a_0$ above the median plane was calculated for this system with the distributed-gauge CTOCD-DZ method^{35,36} at the RHF/6-31G** level of theory using the SYSMO³⁷ and GAMESS³⁸ packages and a structure optimized at the B3LYP/6-31G** level with GAUSSIAN 09.³⁹ This map is shown as structure **20**. It displays 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 contributions that may arise from the antisymmetric combinations of CF bonds and of the 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 of the carbon centers, 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.

Incidentally, the map also shows a pronounced but tightly localized 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 centers do not carry these extra valence electrons. Estimates of the intensities of the ring currents in these systems were available from the maximum magnitudes of the current density per unit inducing field taken over the $1a_0$ plotting plane. For benzene itself, in a calculation of the present type, the value of this quantity is 0.079 au, and in **20** and **21**, the values are 0.056 au and 0.046 au, respectively. Hence, the π ring current in the benzenium cation has a little under 60% of the strength of the full π current of benzene, and this increases to \sim 70% in the difluoro anionic species, confirming that both ions, and in particular the *gem*-difluoro-substituted cyclohexadienide anion **20**, are 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 a stable double bond with close to zero activation energy for loss of both the proton and the leaving group from the intermediate suggests an unusual potential energy surface for the reaction. Ab initio quantum chemical calculations^{40,41} are currently underway to explore this surface and the balance between the concerted and stepwise pathways. The results will be reported in a later paper.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on 300 or 500 MHz instruments. Kinetic measurements utilized 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 a function of time for subtraction from the measured values for the sample(s). HPLC measurements normally employed a dual-pump instrument, usually under isocratic conditions. Standard reagents such as sodium hydroxide, tributyltin cyanide, and

ethyl phenyl sulfide were purchased and used without further 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 *P. putida* UV4.^{42a–c} The structures 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, carboxy, trifluoromethyl, and methylsulfoxy were reported previously.⁴² Proton NMR spectra are included in the Supporting Information. Deuterated *cis*-1,2-dihydrodiols were prepared by similar biotransformations of hexadeuterobenzene, pentadeutero bromobenzene, pentadeutero chlorobenzene and perdeuterated toluene. They were identified from their *R*_f values on silica preparative layer chromatography plates, which were identical to those of their undeuterated analogues, and similarly identical reactant and product UV spectra before and after hydroxide ion-catalyzed dehydration. The perdeutero 3-cyanobenzene *cis*-dihydrodiol was prepared from the corresponding 3-iodo-substituted *cis*-dihydrodiol by reaction with tributyltin cyanide and Pd(Ph₃P)₄ for 4 h in THF solvent, as described by Boyd et al.^{42a} for the corresponding undeuterated compound.

Product Analyses. Products of the reactions of substituted benzene *cis*-1,2-dihydrodiols in sodium hydroxide were analyzed by NMR spectroscopy, HPLC, or GC–MS to identify and determine the ratio of ortho- to meta-substituted phenols formed. The following analysis for *cis*-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 15 h at 25 °C. The pH of the reaction mixture was adjusted to 6–7 with saturated aqueous sodium bicarbonate, and this was followed by extraction with ethyl acetate and evaporation of the solvent under reduced pressure. The ¹H NMR spectrum was recorded, and the ratio of products was 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 the ortho isomer in the mixture. Analyses of the products from the reaction of the 3-methylbenzene- and 3-trifluoromethylbenzene *cis*-dihydrodiols were carried out in the same way as for the bromo compound.

Kinetic Measurements. Kinetic measurements 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 reaction. 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 at an absorption maximum of the substituted benzene *cis*-dihydrodiol reactant or phenoxide ion product. Measurement wavelengths and first-order rate constants measured at different concentrations of sodium hydroxide or deuterioxide are reported in the Supporting Information.

■ ASSOCIATED CONTENT

■ Supporting Information

Complete ref 39; details of kinetic measurements, including UV–vis spectra of reactants and products (Figures S1 and S2); isotope effects (Table S1 and Figures S3–S5); product analyses (Figure S7); measurements of ionization constants (Table S2); computational results (Tables S3–S7); observed and calculated absorbances as a function of [HO[−]] for cyanobenzene 1,2-dihydrodiol (Figure S6); plot of computed versus experimental proton affinities for various anions (Figure S8); and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Boyd, D. R.; Blacker, J.; Byrne, B.; Dalton, H.; Hand, M. V.; Kelly, S. C.; More O’Ferrall, R. A.; Rao, S. N.; Sharma, N. D.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1994**, 313–314.
- (2) Boyd, D. R.; Coyne, D.; Keeffe, J. R.; Lawlor, D. A.; MacCormac, A. C.; More O’Ferrall, R. A.; Rao, S. N.; Sharma, N. D. *Org. Lett.* **2010**, *12*, 5550–5553.
- (3) Lawlor, D. A.; Bean, D. E.; Fowler, P. W.; Keeffe, J. R.; Kudavalli, J. S.; More O’Ferrall, R. A.; Rao, S. N. *J. Am. Chem. Soc.* **2011**, *133*, 19729–19742.
- (4) (a) Schubert, W. M.; Keeffe, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 4048–4050. (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383. (c) Modena, G.; Rivetti, F.; Scorrano, G.; Tonellato, U. *J. Am. Chem. Soc.* **1977**, *99*, 3392–3395.
- (5) (a) Fishbein, J. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 5074–5086. (b) Fedor, L. R. *J. Am. Chem. Soc.* **1969**, *91*, 908–913. (c) More O’Ferrall, R. A.; Slae, S. *J. Chem. Soc. B* **1970**, 260–268.
- (6) Saunders, W. H., Jr. *J. Org. Chem.* **1999**, *64*, 861–865.
- (7) Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 1434–1445.
- (8) Keeffe, J. R.; Gronert, S.; Colvin, M. E.; Tran, N. L. *J. Am. Chem. Soc.* **2003**, *125*, 11730–11745.
- (9) Boyd, D. R.; Bugg, T. H. *Org. Biomol. Chem.* **2006**, *4*, 181–192.
- (10) Kresge, A. J.; More O’Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1986; Vol. 5.
- (11) Guthrie, J. P. *Can. J. Chem.* **1992**, *70*, 1042–1054.
- (12) Dey, J.; O’Donoghue, A. C.; More O’Ferrall, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 8561–8574.
- (13) Bartmess, J. E. In *NIST Standard Reference Database Number 69*; Mallard, W. G., Linstrom, P. J., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, 2003; <http://webbook.nist.gov>.
- (14) Fernández, I.; Frenking, G.; Uggerud, E. *J. Org. Chem.* **2010**, *75*, 2971–2980.
- (15) Glukhotsev, M. N.; Bach, R. D.; Laiter, S. *J. Org. Chem.* **1997**, *62*, 4036–4046.
- (16) Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*; Organic Nitro Chemistry Series; VCH: New York, 1991; Chapter 1.2.
- (17) Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430–6437.
- (18) Kim, Y.; Mohrig, J. R.; Truhlar, D. G. *J. Am. Chem. Soc.* **2012**, *132*, 11071–11082.
- (19) Buncl, E.; Dust, J. M. *Carbanion Chemistry: Structures and Mechanisms*; Elsevier: New York, 2003.
- (20) Koch, H. F.; Biffinger, J. C.; Mishima, M.; Mustanir; Lodder, G. *J. Phys. Org. Chem.* **1998**, *11*, 614–617.

- (21) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715–726.
- (22) Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718–3725.
- (23) Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371–374.
- (24) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017–6020.
- (25) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.
- (26) Richard, J. P.; Williams, G.; O'Donoghue, A. C.; Amyes, T. L. *J. Am. Chem. Soc.* **2002**, *124*, 2957–2968.
- (27) Koch, H. F.; Dahlberg, D. G.; Lodder, G.; Root, K. S.; Touchette, N. A.; Solaky, R. L.; Zuck, R. M.; Wagner, L. J.; Koch, N. H.; Kuzemko, M. A. *J. Am. Chem. Soc.* **1983**, *103*, 2394–2398.
- (28) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **2010**, *44*, 223–324.
- (29) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701–3708.
- (30) Bunting, W. J. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.
- (31) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434–11445.
- (32) Alexander, R.; Asomaning, R. A.; Eaborn, C.; Jenkins, D.; Walton, D. R. M. *J. Chem. Soc. Perkin Trans. 2* **1974**, 490–494.
- (33) Bouchoux, G. *Chem. Phys. Lett.* **2011**, *506*, 167–174.
- (34) Steiner, E.; Fowler, P. W. *J. Chem. Soc., Chem. Commun.* **2001**, 2220–2221.
- (35) (a) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223–231. (b) Coriani, S.; Lazzeretti, P.; Malagoli, M.; Zanasi, R. *Theor. Chim. Acta* **1994**, *89*, 181–192. (c) Steiner, E.; Fowler, P. W. *J. Phys. Chem.* **2001**, *105*, 9553–9562.
- (36) Steiner, E.; Fowler, P. W.; Jenneskens, L. W. *Angew. Chem., Int. Ed.* **2001**, *40*, 362–366.
- (37) Lazzeretti, P.; Zanasi, R. SYSMO; University of Modena: Modena, Italy, 1980. With extra mapping and orbital contribution routines by E. Steiner, P. W. Fowler, R. W. A. Havenith, and A. Soncini and an interface to GAMESS by R. W. A. Havenith.
- (38) Guest, M. F.; Bush, I. J.; van Dam, H. J. J.; Sherwood, P.; Thomas, J. M. H.; van Lenthe, J. H.; Havenith, R. W. A.; Kendrick, J. *Mol. Phys.* **2005**, *103*, 719–747.
- (39) Frisch, M. J.; et al. *Gaussian 09*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.
- (40) Kamerlin, S. C. L. *J. Org. Chem.* **2011**, *76*, 9228–9237.
- (41) Kamerlin, S. C. L.; Florian, J.; Warshel, A. *ChemPhysChem* **2008**, *9*, 1767–1773.
- (42) (a) Boyd, D. R.; Hand, M. V.; Sharma, N. D.; Chima, J.; Dalton, H.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1991**, 1630–1632. (b) Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935–1943. (c) Boyd, D. R.; Sharma, N. D.; Byrne, B. E.; Shepherd, S. D.; Ljubez, V.; Allen, C. C. R.; Kulakov, L. A.; Larkin, M. L.; Dalton, H. *Chem. Commun.* **2002**, 1914–1915.