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Acid-Catalyzed Dehydration of Naphthalene-*cis*-1,2-dihydrodiols: Origin of Impaired Resonance Effect of 3-Substituents

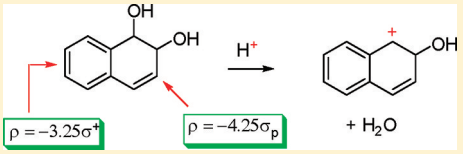
Jaya Satyanarayana Kudavalli,[†] Derek R. Boyd,[‡] Narain D. Sharma,[‡] and Rory A. More O'Ferrall*,[†]

[†]School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

[‡]School of Chemistry and Chemical Engineering, The Queens University of Belfast, Belfast BT9 5AG, Northern Ireland

Supporting Information

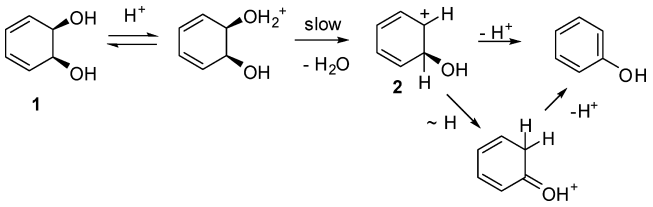
ABSTRACT: Acid-catalyzed dehydrations of substituted naphthalene-*cis*-1,2-dihydrodiols occur with loss of the 1- or 2-OH group to form 2- and 1-naphthols, respectively. Effects of substituents MeO, Me, H, F, Br, I, and CN at 3-, 6-, and 7-positions of the naphthalene ring are consistent with rate-determining formation of β-hydroxynaphthalenium ion (carbocation) intermediates. For reaction of the 1-hydroxyl group the 3-substituents are correlated by the Yukawa−Tsuno relationship with $\rho = -4.7$ and $r = 0.25$ or by σ_p constants with $\rho = -4.25$; for reaction of the 2-hydroxyl group the 3-substituents are correlated by σ_m constants with $\rho = -8.1$. The correlations for the 1-hydroxyl imply a surprisingly weak resonance interaction of +M substituents (MeO, Me) with a carbocation reaction center but are consistent with the corresponding correlation for acid-catalyzed dehydration of 3-substituted benzene-*cis*-1,2-dihydrodiols for which $\rho = -6.9$ and $r = 0.43$. Substituents at the 6- and 7-positions of the naphthalene rings by contrast are correlated by σ^+ with $\rho = -3.2$ for reaction of the 1-hydroxyl group and $\rho = -2.7$ for reaction of the 2-hydroxyl group. The unimpaired resonance implied by these substituent effects appears to be inconsistent with a previous explanation of the weak resonance of the 3-substituents in terms of imbalance of charge development and/or nonplanarity of the benzenium ring in the transition state. An alternative possibility is that the adjacent hydroxyl group interferes sterically with conjugation of +M substituents. "Hyperaromaticity" of the arenium ion intermediates does not appear to be a factor influencing this behavior.



INTRODUCTION

There is considerable evidence that arene 1,2-dihydrodiols, such as benzene dihydrodiol (**1**), undergo acid-catalyzed dehydration to give the corresponding phenol by the mechanism shown in Scheme 1, for which the rate-determining

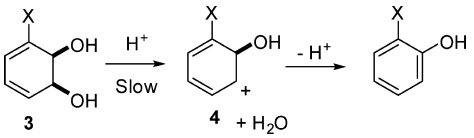
Scheme 1



step is formation of a β-hydroxy carbocation intermediate.[1,2] The carbocation may lose a proton or undergo a hydride ion rearrangement (NIH shift) as alternative pathways to product formation.[3] However, the product forming steps do not influence the effect of substituents on the rate of reaction.

The influence of 3-substituents on dehydration of benzene-*cis*-1,2-dihydrodiols **3**, in which the 1-OH acts as a leaving group (Scheme 2), was described some years ago.[2] Surprisingly, despite the formation of a carbocation intermediate **4** in which the substituent is directly conjugated with the positive charge, the reaction is quite insensitive to +M resonance effects. Thus, application of the Yukawa−Tsuno relationship (eq 1) was

Scheme 2



reported to yield a ρ value of −7.0, which is of a magnitude expected of a carbocation reaction, but a value of r, which is a sensitive indicator of resonance, with the surprisingly low value of 0.3. This implied that resonance effects of MeO, EtO, and alkyl substituents (e.g.) are not much greater than their effects on the ionization of benzoic acids, with $r = 0.27$.[4] Indeed, a reasonable correlation was obtained when logs of rate constants were plotted against σ_p, the substituent constant based on the ionization of (*p*-substituted) benzoic acids.[2]

$$\log k = \rho(\sigma_0 + r(\sigma^+ - \sigma_0)) \quad (1)$$

It is perhaps worth remarking that the substituent X in structures **3** and **4** formally occupies a "meta" position with respect to the site of reaction and at first sight might not have been expected to be in conjugation with it. However, we may recognize that carbocation **4** corresponds to the Wheland intermediate of an electrophilic hydroxylation reaction in which

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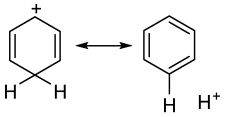
the X-substituted benzene is attacked by OH^+. The structure of **4** implies that attack of the electrophile has occurred ortho to X and that conjugation of X with the positive charge is indeed expected.

The anomalous resonance behavior for the dehydration of benzene-*cis*-1,2-dihydrodiols is of interest partly because it has been proposed that the carbocation intermediate **4** is unusual in possessing aromatic character[1] as a consequence of hyperconjugation between the methylene group and π-delocalized positive charge within arenium ions.[5] This character is most simply expressed in terms of valence bond resonance structures illustrated for the benzenium ion (**5a** ↔ **5b**) in which the no-bond structure associated with hyperconjugation is subject to exceptional stabilization arising from its aromatic character. Experimental evidence for this behavior has been summarized in a number of papers and includes the very large difference in reactivity between isomeric *cis*- and *trans*-benzene-1,2-dihydrodiols, k_{cis}/k_{trans} = 4500.[1,6,7] This difference can be understood in terms of formation of carbocation intermediates in which the C−H and C−OH bonds respectively at the 2-position are oriented in pseudoaxial positions favorable for hyperconjugation and the much greater ("positive") hyperconjugative ability of the C−H than the C−OH bond.



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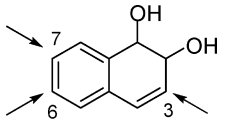
The question thus arises: is the anomalous lack of resonance contribution in the dehydration of 3-substituted benzene-*cis*-1,2-dihydrodiols a reflection of the unusual "hyperaromatic" character of the carbocation intermediate? To help answer this question, we describe here the acid-catalyzed dehydration of naphthalene-*cis*-1,2-dihydrodiols substituted at the 3-, 6-, and 7-positions shown arrowed in **6**.[8]



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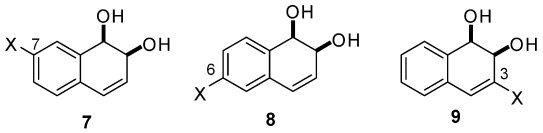
Insofar as reactions of OH leaving groups at both the 1- and 2-positions of the naphthalene ring of structure **6** may be monitored, the reactions yield a considerable amount of additional information on substituent effects for the dehydration reactions of dihydrodiols. As shown below, the 3-substituted naphthalene dihydrodiols follow a similar pattern to those of the benzene-1,2-dihydrodiols, with a notably restricted resonance contribution, whereas the 6- and 7-substituents show the full degree of resonance expected of direct conjugation with a carbocationic charge.

RESULTS

The naphthalene-*cis*-1,2-dihydrodiols used in this study were obtained as products of bacterial oxidation of the corresponding 2-substituted naphthalene substrates by dioxygenase enzymes present in cultures of *Pseudomonas putida* UV4. The structure and absolute stereochemistry of the isolated metabolites **7**−**9** have been described earlier.[9] The compounds were generally obtained as mixtures of 3-, 6-, and 7-substituted regioisomers which were separated by chromatography and characterized by NMR and other spectroscopic methods. In the case of the 6-methyl-, 7-cyano-, and 7-methoxy-substituted metabolites the yields obtained were too small for kinetic studies.



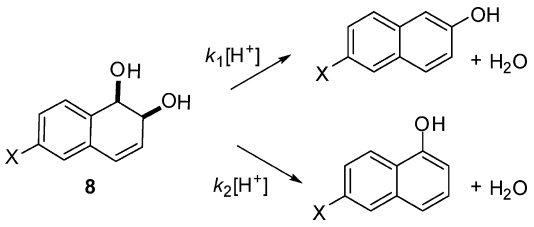
7 X = H, Me, MeO, F, Br, I, CN

8

9 X = H, Me, F, Br, I, OMe

First-order rate constants k_{obs} for dehydration were measured spectrophotometrically in aqueous $HClO_4$ at 25 °C. Second-order rate constants were obtained from the slopes of linear plots of the first-order constants against acid concentration or, for slower reactions for which the use of concentrated acid was necessary, from the intercepts of plots of $\log(k_{obs}/[H^+])$ against the acidity parameter X_0.[10] Because, normally, both 1- and 2-naphthols were found as products, the rate constants were partitioned on the basis of product fractions for the two reaction paths as shown in Scheme 3, in which k_1 and k_2

Scheme 3



represent rate constants for reaction of the 1- and 2-hydroxyl groups, respectively, and correspond to rate-determining formation of 1- and 2-(β-hydroxy)naphthalenium ion intermediates (cf. Scheme 1). The measured rate constant corresponds to $k_1 + k_2$ and the ratio of product fractions ([2-naphthol]/[1-naphthol]) to k_1/k_2. The product fractions were determined by HPLC or proton NMR analysis. They are shown together with the conditions of measurement in the Supporting Information (Table S1). Measured first-order rate constants are shown in Table S2. The factored second-order rate constants (k_1 and k_2) are listed in Table 1.

Analysis of the kinetic data is based chiefly on application of the Yukawa−Tsuno relationship.[4,11] This makes use of substituent constants σ^+ and σ_0, convenient compilations of which have been provided by Exner,[12] Leffler and Grunwald,[13] and Tsuno and Fujio.[14]

DISCUSSION

The first question that may be asked is: do substituents at the 3-position of the naphthalene-*cis*-1,2-dihydrodiols **9** experience the same impairment of resonance interactions with the developing positive charge in the transition state for the acid-catalyzed dehydration reaction (Schemes 3 and 4) as 3-substituents in benzene-*cis*-1,2-dihydrodiols **3**?

In Scheme 4, reaction of the C-1 hydroxyl group is shown. This is favored by the resonance interaction with a +M 3-substituent and the less unfavorable inductive effect from a −I substituent than for reaction of the C-2 hydroxyl group adjacent to the substituent. In the case of the benzene-*cis*-1,2-dihydrodiols **3** reaction occurs very predominantly at the C-1 position, and rate constants for reaction at the 2-position were deemed too unreliable to justify application of Yukawa−Tsuno free energy relationship.[2]

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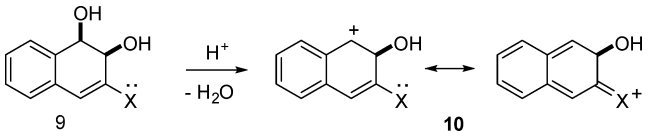
Table 1. Second-Order Rate Constants (L mol^{-1} s^{-1}) for Acid-Catalyzed Dehydrations of 3-, 6-, and 7-Substituted Naphthalene-*cis*-1,2-dihydrodiols for Loss of 1- and 2-Hydroxyl Groups (k_1 and k_2, Respectively) in Aqueous $HClO_4$ at 25 °C

	3-X		6-X		7-X	
X	k_1	k_2	k_1	k_2	k_1	k_2
H	7.00×10^{-5}	1.41×10^{-3}	7.00×10^{-5}	1.41×10^{-3}	7.00×10^{-5}	1.41×10^{-3}
Me	7.35×10^{-4}	1.36×10^{-3}			9.2×10^{-4}	7.47×10^{-3}
OMe	1.81×10^{-3}	5.6×10^{-5}	0.113	2.32×10^{-3}		
F	7.20×10^{-6}	1.27×10^{-7}	2.10×10^{-4}	7.0×10^{-5}	1.59×10^{-5}	1.57×10^{-3}
Br	3.57×10^{-6}	8.94×10^{-7}	2.85×10^{-5}	1.35×10^{-4}		3.62×10^{-4}
I	4.78×10^{-6}	2.05×10^{-6}	3.6×10^{-5}	1.44×10^{-4}	3.88×10^{-5}	3.5×10^{-4}
CN	6.9×10^{-8}	4.6×10^{-8}	2.0×10^{-6}	1.80×10^{-5}		

Scheme 4



In the case of the naphthalene dihydrodiols, however, the substituent preference for reaction at the C-1 position is compensated by an intrinsically greater reactivity of the C-2 than C-1 hydroxyl group. For the unsubstituted naphthalene dihydrodiol **6**, the C-2 hydroxyl group is more reactive by a factor of 20. For other X substituents ratios of reactivity range from this value to 32 in the opposite direction for a 3-methoxy group which strongly activates reaction of the 1-hydroxyl, as expected of the resonance interaction illustrated in Scheme 4. Thus, substituent effects can be determined with similar precision for reactions of both hydroxyl groups.

Considering first the reaction of the C-1 hydroxyl group, which may be directly compared with the corresponding reaction of the benzene-dihydrodiols, application of the Yukawa–Tsuno relationship to rate constants for the 3-substituted naphthalene-*cis*-1,2-dihydrodiols gives values of $\rho = -4.7$ and $r = 0.25$ (Figure 1). These values may be compared

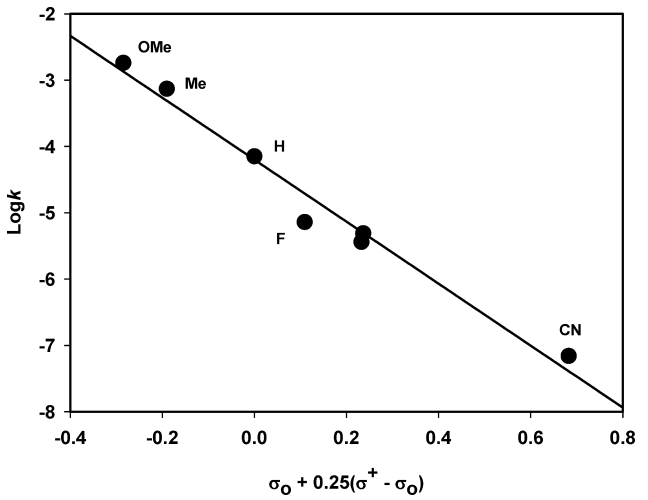


Figure 1. Yukawa–Tsuno plot for the acid-catalyzed dehydration of 3-substituted naphthalene-*cis*-1,2-dihydrodiols **9** in aqueous solution at 25 °C; log $k = -4.20 - 4.67\{\sigma_0 + 0.25(\sigma^+ - \sigma_0)\}$, Rsqr = 0.977.

with $\rho = -6.9$ and $r = 0.43$ for dehydration of the benzene dihydrodiols.[2] The value of r for the benzene dihydrodiols differs from that previously reported (0.3)[2] and represents a redetermination based on 11 substituents. Despite its larger value, it still implies that resonance interaction of 3-substituents is impaired for these acid-catalyzed dehydration reactions compared with a "normal" carbocation reaction. This conclusion is endorsed by the even smaller value of 0.25 for the 3-substituted naphthalene-*cis*-1,2-dihydrodiols. By comparison, for the solvolysis of cumyl chlorides, the defining reaction for σ^+, $\rho = -4.84$ and by definition $r = 1.0$.

It is possible that the smaller resonance interaction for the naphthalene dihydrodiols reflects a longer path between substituent and reaction site and sacrifice of the resonance stabilization of a benzene ring (Scheme 4, structures **10**) when compared with the carbocations formed from benzene dihydrodiols. This may also be reflected in the further reduction in the effect of +M substituents implied by the smaller ρ value. It is perhaps surprising at first that the ρ value is smaller, insofar as this is based on inductive effects and that the distance between the substituent and the reaction site is the same for benzene and naphthalene dihydrodiols. The difference presumably arises as a result of a reduction in effective charge sensed by a –I substituent because of partial delocalization into the second benzene ring. However, a caveat for over-interpreting magnitudes of these ρ and r values is noted below.

The most important conclusion from these measurements is that 3-substituents in the naphthalene-*cis*-1,2-dihydrodiols are experiencing similar or indeed greater impairment of resonance interactions than that observed for the benzene-*cis*-1,2-dihydrodiols. This is confirmed by (a) the good linear correlation with slope 0.745 when logs of rate constants for 3-substituted naphthalene dihydrodiols are plotted against corresponding values for 3-substituted benzene dihydrodiols as shown in Figure 2 and (b) by a satisfactory correlation (with $\rho = -4.25$) when logs of rate constants for 3-substituted naphthalene dihydrodiols are plotted agains σ_p constants based on the ionization of *p*-substituted benzoic acids, for which the resonance contribution is small.

Not much is added to the comparison by consideration of the effects of 3-substituents upon reaction of the C-2 hydroxyl group of the naphthalene-*cis*-1,2-dihydrodiols. Now resonance between the substituent and site for carbocation formation is precluded. Altough formally there appears to be an *o*-relationsip between the substituent and reaction site, it can be seen that if the intermediate was generated by electrophilic attack of OH^+ at the 1-position of a 3-substituted naphthalene, the substituent would be *m*- to the point of attack. Correspondingly, the logs of the measured rate constants show a good correlation with substituent constants σ_m based on the ionization of *m*-substituted benzoic acids (Figure S1). Significantly $\rho = -8.0$ is larger than for reaction of the 1-hydroxyl

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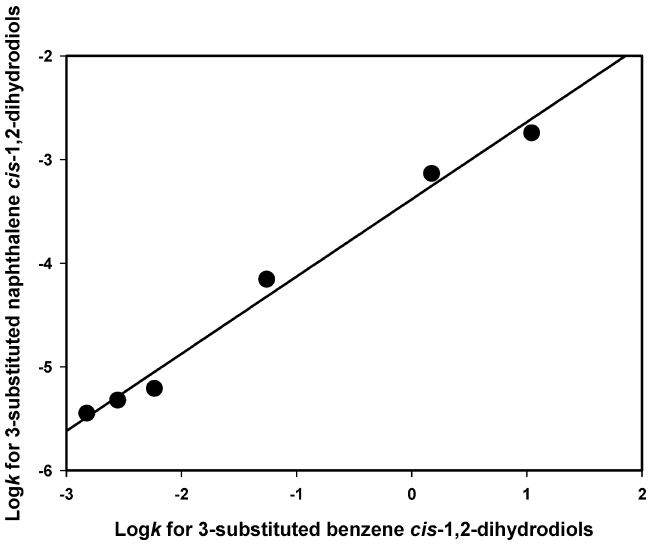


Figure 2. Plot of log *k* for dehydration of 3-substituted naphthalene-*cis*-1,2-dihydrodiols with loss of OH at the 1-position against log *k* for 3-substituted benzene-*cis*-1,2-dihydrodiols; from measurements in aqueous $HClO_4$ at 25 °C; slope = 0.745, intercept = −3.38, Rsqr = 0.984.

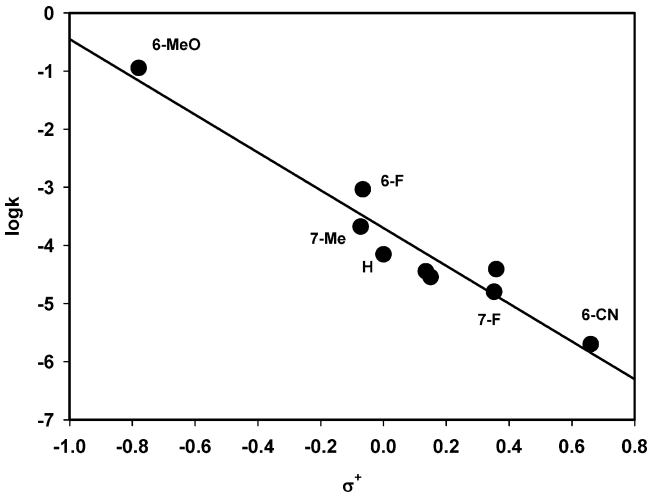


Figure 3. Plot of log *k* for the acid-catalyzed dehydration of 6- and 7-substituted naphthalene-*cis*-1,2-dihydrodiols (**7**, **8**) in aqueous perchloric acid at 25 °C with loss of the 1-hydroxyl group versus σ_p^+ for 7- and σ^+_m for 6-substituents; log *k* = −3.24 − 3.70σ^+, Rsqr = 0.934.

group, consistent with the closer proximity of substituent and reacting group in this case.

Turning to the 6- and 7-substituted naphthalene-*cis*-1,2-dihydrodiols, the obvious question arises, are resonance effects of these substituents similarly impaired to those of the 3-substituents? The answer is clearly negative. For these substituents, again we consider reactions of the 1- and 2-hydroxyl groups independently. However, for both leaving groups, 6- and 7-substituents may be combined within a Yukawa−Tsuno correlation. For reaction of the 1-hydroxyl +M substituents at the 6-position but not at the 7-position are capable of a resonance interaction with the reaction center, and *vice versa* for reaction of the 2-hydroxyl group.

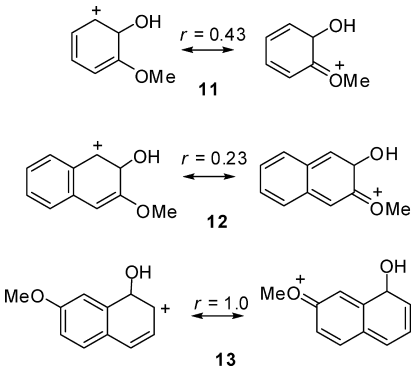
For reaction of the 1-hydroxyl group the importance of resonance can be seen qualitatively from the reactivity of the substrate with a 6-methoxy substituent. This is the only substituent for which the reactivity of the 1-hydroxyl is greater than the 2-hydroxyl. A Yukawa−Tsuno plot for reaction of the 1-hydroxyl leads to values of ρ = −3.25 and r = 1.0. This implies that an optimum correlation is achieved for a plot of log *k* against σ^+ with no contribution from σ_0. This plot is shown in Figure 3 with σ_m^+ values used for substituents at the 7-position. Both this plot and Figure 1 show a certain amount of scatter. Probably this reflects the presence of the charge center in a ring and a somewhat different molecular environment from the cumyl cation forming reaction for which σ^+ is defined. Limitations of σ^+ for correlating substituent effects in electrophilic aromatic substitutions have been discussed by Taylor.[15]

For reaction of the 2-hydroxyl group ρ = −2.9, and again there is a good correlation with σ^+ (Figure S2). In this case r is less well-defined than for reaction of the 1-hydroxyl because there is no 7-methoxy substituent, and the magnitude of r is effectively determined by Me and F substituents, for which resonance contributions to the substituent effects are smaller. The less negative ρ for reaction of the 2- rather than 1-hydroxyl group is consistent with the increased number of bonds between substituent and reaction site.

However, the main inference to be drawn from these results is the contrast between the strong resonance interactions of +M substituents at the 6- and 7-positions of the naphthalene ring and the weaker resonance from the 3-position.

The "normal" values of ρ and degree of resonance for the 6- and 7-positions strongly suggest that these are not substantially modified by "hyperaromatic" stabilization of the β-hydroxy arenium ion intermediate or transition state leading to it. In an earlier paper it was suggested that the impaired resonance of 3-substituents in the dehydration of benzene *cis*-1,2-dihydrodiols was the result of an imbalance between inductive and resonance effects at the transition state. This was suggested as arising because planarity of the five bonds between the electron pair of a +M substituent and the positive charge at the reaction site had not been achieved at the transition state with a detrimental effect on the resonance interaction shown for a methoxy substituent in structures **11** of Chart 1.

Chart 1



The resonance interaction of a 3-methoxy substituent with the reaction site in the dehydration of a naphthalene dihydrodiol is illustrated by structures **12** of Chart 1. In this case the distance between substituent and cation center is the same as for the benzene dihydrodiol, but arguably the fusion of a benzene ring could increase coplanarity of the π-bonds involved in the conjugation, favoring a normal resonance

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interaction for +M substituents. In practice, the resonance is even less favorable than for the benzene-*cis*-1,2-dihydrodiols. Moreover, if the bonds separating substituent and reaction site for 3- and 7-substituents are compared (Chart 1, **12** and **13**), it is hard to see why there should not be a similar impairment of resonance in the case of +M substituents at the 7-position as at the 3-position.

These considerations suggest that the reduction in resonance may stem less from the nonplanarity and/or imbalance of resonance and inductive effects in the transition state than steric hindrance, preventing the methoxy substituent itself achieving the planarity necessary for full expression of its resonance. This is most obviously due to the adjacent hydroxyl group. It is true that there is little evidence of steric hindrance to electrophilic aromatic substitution at an *ortho* position, which might have been considered a closely related reaction. However, both reactants and transition states for these reactions differ, and only the intermediates are strictly comparable in structure. For the dihydrodiols the steric influence of the adjacent hydroxyl on conjugation of a substituent is likely to be enhanced by a buttressing effect from the reacting hydroxyl group, an effect which is not present in the transition state for the electrophilic aromatic substitution reaction.

A caveat for these comparisons is that the precision with which *r* values may be determined is quite sensitive to experimental or "chemical" dispersion within a group of measurements. Optimization of values involves complementary changes in *r* and ρ, so that correlation coefficients are a relatively insensitive function of one parameter when the other can vary. Chart 2

Chart 2

r	0	0.43	1.0
ρ	−8.5	−6.9	−4.7
Rsqr	0.86	0.97	0.91

illustrates variation of these parameters between limiting and optimum combinations of σ_0 and σ^+ based on 11 substituents for the previously studied 3-substituted benzene *cis*-dihydrodiols.

Nevertheless, it is clear that the present results for naphthalene-*cis*-1,2-dihydrodiols reinforce the conclusion that resonance between substituent and reaction site is impaired in the dehydration of 3-substituted arene-1,2-dihydrodiols. The proposal that the lack of resonance is mainly steric in origin remains a tentative one, but it is difficult to envisage an alternative explanation. Importantly, it seems safe to rule out any explanation in terms of stabilization of the positive charge of the intermediate through hyperconjugation enhanced by the aromatic character of the benzenium (**4**) or naphthalenium (**10**) ion as reactive intermediates. Apart from their chemical interest, the results are significant in allowing a better understanding of factors influencing the stabilities under physiological conditions of an important class of aromatic metabolites.[9]

EXPERIMENTAL SECTION

Instrumentation and Chromatography. All the substituted naphthalene-*cis*-1,2-dihydrodiols **3**, **6**, and **7** were obtained as enantiopure metabolites of 2-substituted naphthalene substrates using whole cells of *Pseudomonas putida* UV4.

They were structurally and stereochemically characterized as described in an earlier paper.[8] For the work of the current paper NMR spectra were run on instruments operating at 300, 400, or 500 MHz. HPLC measurements were made with dual wavelength absorbance detection. UV−vis spectra and kinetic measurements were run on a spectrophotometer equipped with an automatic cell changer which was thermostated at 25 ± 0.1 °C. Column chromatography was performed on Merck-Kieselgel type 60 9250−400 mesh silica. Preparative TLC was carried out on glass plates coated with Merck-Kieselgel$_{PF254/366}$ silica (21 g in 60 mL of water).

Product Analyses. Product analyses were carried out for each of the 3-, 6-, and 7-substituted naphthalene-*cis*-1,2-dihydrodiols for which a rate constant for acid-catalyzed dehydration was determined. These involved identification of 1- and 2-naphthol products from reaction of the 2- and 1-hydroxyl groups of the dihydrodiols and determination of their ratio of concentrations (cf. Scheme 3). As a general procedure, 7−10 mg of reactant in acetonitrile was treated with dilute perchloric acid for at least seven half-lives of reaction. The reaction mixture was neutralized with saturated sodium bicarbonate followed by extraction with ethyl acetate and evaporation of the solvent under reduced pressure; a ^{1}H NMR spectrum of the mixture was recorded.

In general, the NMR spectrum revealed two products with two sets of peaks in the 6.5−8.5 ppm region corresponding to the 1- and 2-naphthols. The ratio of products was determined from integration of non-overlapping peaks. The major product was isolated by preparative TLC, and the structure was assigned by comparison of the spectrum with an authentic sample or spectrum reported in the literature. The minor product was presumed to have the complementary structure.

In the case of bromo- and iodonaphthol samples spectra were not available, and the mixtures of phenolic products were converted to a mixture of the unsubstituted 1- and 2-naphthols by reductive hydrogenation. The ratio of naphthol concentrations was determined by HPLC based on comparison with authentic samples.

The detailed procedure for hydrogenation and analysis of the iodo- and bromonaphthol products was as follows. The unpurified mixture of products from the dehydration reaction was dissolved in 5 mL of methanol and triethylamine (0.05 mL). Pd/C (10 mg) was added followed by stirring for 10 h under a H_2 atmosphere. The solution was filtered through Celite, and the filtrate was concentrated under vacuum. The products were analyzed by reverse phase HPLC on a C18 column with water and acetonitrile as eluants and a flow rate of 1 mL/min.

The spectrophotometric method for kinetic measurements is outlined in the Results section and Supporting Information and is described in more detail in previous publications.[16] The measured first-order rate constants are listed in the Supporting Information (Table S3).

ASSOCIATED CONTENT

Supporting Information

Details of product analyses, rate constants, and *m** values, including summary Tables S1−S3: graphical representations of free energy relationships, Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: rmof@ucd.ie.

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