Substituent Effects in the Keto–Enol Tautomerism of Fused 1,4-Naphthalenediols

Myrna S. Pearson,* Barbara J. Jensky,[1a] Francis X. Greer,[1b] Janice P. Hagstrom,[1a,b] and Nancy M. Wells[1a]

Department of Chemistry, Wheaton College, Norton, Massachusetts 02766

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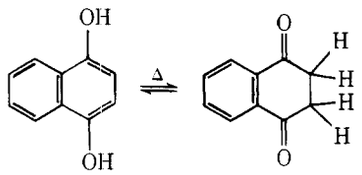
Using NMR the equilibrium constants and thermodynamic parameters for keto–enol tautomerism have been determined when a series of substituted 1,4-naphthalenediols are fused. Pure samples of single tautomers were sealed in ampules on a vacuum line, fused at a constant temperature, and then immersed in liquid nitrogen to freeze the equilibrium. After dissolving each equilibrium mixture in a suitable solvent, under a nitrogen atmosphere, the relative amounts of the tautomers were measured by NMR integration. By determining the equilibrium constants at three different temperatures, $\Delta G°$, $\Delta H°$, and $\Delta S°$ values at 220 °C were calculated. Significant amounts of the 1,4-diketo tautomers were measured in the equilibrium mixtures when 1,4-dihydroxynaphthalene, 2-methyl-1,4-dihydroxynaphthalene, 2,3-dimethyl-1,4-dihydroxynaphthalene, 2-ethyl-1,4-dihydroxynaphthalene, and 1,2,3,4-tetrahydro-5-hydroxynaphthalene-1,4-dione were fused. The substitution of an alkyl group in the 2 and/or 3 positions of 1,4-dihydroxynaphthalene was found to favor the enolic form. Substitution of a hydroxyl group in the 5 position favored the diketo form while no tautomerism was detected when 5-methoxy-1,4-dihydroxynaphthalene, 5,8-dimethoxy-1,4-dihydroxynaphthalene, 2-acetyl-1,4-dihydroxynaphthalene, and 1,2,3,4-tetrahydro-5,8-dihydroxynaphthalene-1,4-dione were fused. In each of these systems the favored tautomer was the one most effectively stabilized by intramolecular hydrogen bonding.

Keto–enol tautomerism has been observed when 1,4-dihydroxynaphthalene and a number of substituted 1,4-naphthalenediols are fused in vacuo.[2] Using infrared and ultraviolet spectroscopy, Thomson and Bruce[3] elucidated the diketo structure of the tautomers. Further substitution of hydroxyl groups in the 5 and 8 positions of 1,4-dihydroxynaphthalene was found to favor the 1,4-diketo compound over the enolic tautomer, and the preferential stabilization of the carbonyl compound was attributed to intramolecular hydrogen bonding. Their conclusions concerning the relative stabilities of the keto and enol compounds were based upon a comparison of the yields of the two tautomers isolated from the fusion mixtures.

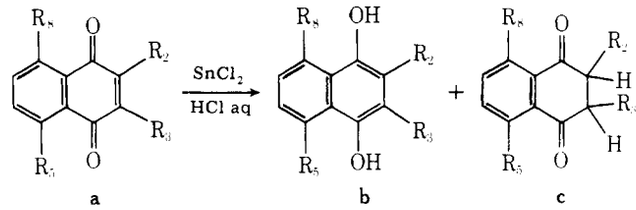


In an attempt to explain the observed variation in the keto–enol equilibria for a variety of aromatic hydroxy compounds, including 1,4-dihydroxynaphthalene, 1,4,5-trihydroxynaphthalene, and 1,4,5,8-tetrahydroxynaphthalene, Forsén and Nilsson[2b] resorted to molecular orbital calculations. Using the Hückel approximation, Forsén and Nilsson calculated the π energies of the tautomers and then compared their total delocalization energies (TDE). Qualitatively the calculations of the ΔTDE for the keto and enol tautomers appeared to correlate with the relative order of stabilities that Thomson reported. However, the ΔTDE values favored an enol form in all cases including those in which Thomson reported the keto tautomer to be the more stable. As a result of the approximations made in the TDE approach and in the absence of data for ΔS of enolization, the correlation between the free energies of enolization and ΔTDE values was only semiquantitative.

In order to obtain more precise data concerning the effect of structure on keto–enol equilibria in the 1,4-dihydroxynaphthalene system, we used nuclear magnetic resonance as a quantitative tool to measure the relative amounts of the tautomers present in fusion mixtures.[4] Analysis of the nuclear magnetic resonance spectra enabled us to measure equilibrium ratios without the necessity of isolating the tautomers, many of which were readily oxidized by exposure to air. By measuring the temperature dependence of the equilibrium constants for tautomerism, the thermodynamic parameters, $\Delta G°$, $\Delta H°$, and $\Delta S°$, were determined experimentally, and the importance of hydrogen bonding in preferentially stabilizing the diketo tautomers was investigated.

Results

In order to initiate the study of keto–enol tautomerism, a series of substituted 1,4-dihydroxynaphthalene compounds had to be prepared. With one exception, all of the compounds used in the fusion studies were synthesized by reducing the corresponding 1,4-naphthoquinones with stannous chloride in an aqueous acid medium. In agreement with the earlier reports of Thomson,[3] we found the 1,4-dihydroxy compound



a b c

1, R_2, R_3, R_5, R_8 = H
2, R_2 = CH_3; R_3, R_5, R_8 = H
3, R_2, R_3 = CH_3; R_5, R_8 = H
4, R_2 = C_2H_5; R_3, R_5, R_8 = H
5, R_2, R_3, R_8 = H; R_5 = OCH_3
6, R_2, R_3 = H; R_5, R_8 = OCH_3
7, R_2, R_3, R_8 = H; R_5 = OH
8, R_2, R_3 = H; R_5, R_8 = OH
9, R_2 = $COCH_3$; R_3, R_5, R_8 = H

to be the exclusive product from the reduction of quinones **1a–6a.** Reduction of 5-hydroxy-1,4-naphthoquinone (**7a**) yielded an equilibrium mixture in which the diketo tautomer **7c** was favored over the trihydroxy compound **7b,** while the reduction of 5,8-dihydroxy-1,4-naphthoquinone (**8a**) yielded only the diketo compound **8c.** One additional compound, 2-acetyl-1,4-dihydroxynaphthalene (**9a**), was synthesized by another route (see Experimental Section). The tautomers isolated from the reactions just described became the starting materials for the fusion studies. All tautomers appeared to oxidize readily to the quinone upon exposure to air, although the diketo tautomers appeared somewhat more stable than the hydroxy compounds. For this reason no attempt was made to calculate equilibrium constants based upon the quantities of the tautomers isolated from the reaction mixtures, and the

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Table I. Infrared Data for 1,4-Naphthalenediols Before and After Fusion at 220 °C

compd	registry no.	IR, cm^{-1} before fusion OH	before fusion C=O	after fusion OH	after fusion C=O
1b	571-60-8	3285		3285	1670
2b	481-85-6	3263		3257	1693
3b	38262-43-0	3320		3306	1685
4b	34987-32-1	3258		3238	1691
5b	61836-37-1	3361		3370	
		3295		3286	
6b	67597-83-5	3370		3366	
7c	6312-53-4	*a*	1693	3327	1677
			1645		1641
8c	4988-51-6	*a*	1633		1632
9b	40420-48-2	3270	1598	3270	1597

[a] The absence of the hydroxyl band resulting from intramolecular hydrogen bonding was reported by Thomson, ref 3a, and M. Flett, *J. Chem. Soc.*, 1441 (1948).

pure dry samples of the tautomers were always stored in sealed evacuated ampules.

Before investigating tautomerism resulting from the fusion of the 1,4-dihydroxynaphthalene and related compounds, an attempt was made to establish keto–enol equilibria in solution. None of the compounds studied gave evidence of equilibrating in dioxane, chloroform, acetone, or dimethyl sulfoxide. Nuclear magnetic resonance spectra of the compounds at ambient temperature (25 °C) were unchanged even after the solutions were allowed to stand for several weeks at room temperature under a nitrogen atmosphere. Therefore, all studies reported in this paper concern the equilibria established by the fusion of one of the tautomers.

In order to prevent oxidation of the tautomers during fusion, individual samples of the compounds listed in Table I were sealed in ampules which had been degassed on a vacuum line (<0.005 mmHg). Different ampules were immersed for 60 min in three constant temperature baths over a range of 170–239 °C, even though the equilibrium ratios remained unchanged after 30 min. As soon as the ampules were removed from the bath, the equilibria were frozen by plunging the tubes into liquid nitrogen. Initially, infrared spectroscopy was used to detect tautomerism by preparing KBr pellets from the fusion mixtures and comparing the spectra of the fusion mixtures with those of the starting materials. The appearance of a new absorption band in the region associated with the carbonyl group was observed after compounds **1b–4b** were fused. Compounds **5b, 6b, 8c,** and **9b** showed no change after fusion, and compound **7c** showed a new absorption band characteristic of the hydroxyl group. These results are presented in Table I. In all cases the infrared spectra of the fusion mixtures were compared with those of the quinones to assure that oxidation had not been mistaken for tautomerism. As a further check for the formation of the diketo tautomers, the fusion mixtures were extracted with carbon tetrachloride, a solvent in which the 1,4-naphthalenediols were insoluble. Analysis of the infrared and nuclear magnetic resonance spectra of the carbon tetrachloride extracts supported Thomson's original assignment of the diketo structures to the tautomers resulting from the fusion of 1,4-naphthalenediols.[3]

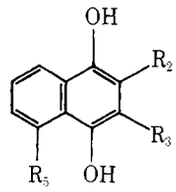
Nuclear magnetic resonance was used to measure the equilibrium distribution of tautomers resulting from the fusion for 60 min of compounds **1b, 2b, 3b, 4b,** and **7b** or **7c** at three temperatures over the range of 170–239 °C as shown in Table III. Table II shows the characteristic absorptions which were selected for the purpose of identifying and measuring the amount of each tautomer present. Each spectrum was integrated at least three times, and the average values for the relative number of hydrogens present were used in calculating the equilibrium constants. Deviations from the average were less than ±5%. In order to prevent air oxidation of the fusion products during analysis, the evacuated ampules were opened and maintained under a nitrogen atmosphere (e.g., in a dry-box) while the samples were completely dissolved in dioxane, deuterated acetone, or deuterated dimethyl sulfoxide. Tetramethylsilane was used as an internal standard. Whenever possible the concentrations of the tautomers were measured in more than one solvent. If two characteristic absorptions were available for a particular tautomer, the equilibrium constant was calculated from the integrations of each absorption as a check for internal consistency in the results. The integrations for the absorptions of the hydroxyl groups were not used to calculate the equilibrium constants in deuterated solvents because deuterium exchange can occur. However, when spectral grade dioxane was used as the solvent, it was possible to measure the relative amounts of 1,4,5-trihydroxynaphthalene (**7b**) and 1,2,3,4-tetrahydro-5-hydroxynaphthalene-1,4-dione (**7c**) using the integrations of the characteristic absorption of the hydroxyl group in the 5 position. Table III summarizes the equilibrium constants and the thermodynamic parameters calculated from the nuclear magnetic resonance spectra using a least-squares treatment of the data.[5]

Discussion

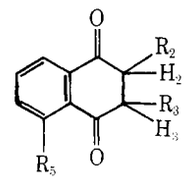
The equilibrium and thermodynamic data in Table III verify the earlier reports that a number of 1,4-naphthalenediols tautomerize to an appreciable degree when heated above their melting points and that the position of the equilibrium varies with the nature of the substituents in the 2, 3, 5, and 8 positions on the naphthalene ring system. From a comparison of the equilibrium constants for the tautomerization of compounds **1b, 2b, 3b,** and **4b** reported in Table III with the equilibrium constants estimated from Thomson's percent yield data,[3] it is apparent that he underestimated the less stable tautomer in each case. This discrepancy is not surprising in light of the susceptibility of these compounds to oxidation during the isolation process.

Since substitution of a methyl or ethyl group in the 2 position of 1,4-dihydroxynaphthalene results in a shift in the equilibrium in favor of the enol form, it is reasonable that the addition of a second methyl group in the 3 position favors the enol to an even greater degree. Analysis of the data in Table III shows that the $\Delta H°$ values for the tautomerization of compounds **1b, 2b,** and **3b** are the same, and it is the entropy term, $\Delta S°$, which is responsible for the difference in the equilibrium ratios observed for the substituted and unsubstituted 1,4-naphthalenediols. In each case the enol form is favored thermochemically while the entropy term favors the keto form. Surprisingly, the exchange of an ethyl group for a hydrogen atom or a methyl group in the 2 position of 1,4-dihydroxynaphthalene has a significant effect on the $\Delta H°$ and $\Delta S°$ values. The difference between the $\Delta H°$ values for the tautomerization of compounds **2b** and **4b** is greater than 4 kcal/mol, with the result that the keto form (**4c**) is more stable thermochemically than the enol form (**4b**). It is only as a result of the large favorable $\Delta S°$ value for the enolization that the free energy difference $\Delta G°$ remains negative. A simple explanation for the dramatic change in $\Delta H°$ and $\Delta S°$ of tautomerism with the simple substitution of an ethyl group is not apparent. If steric repulsion between the ethyl group and the hydroxyl group was sufficiently large to destroy the planar structure of the naphthalenediol system, then interference with the resonance stabilization of the compound could account for the difference in $\Delta H°$ values. However, Allinger and co-workers[6] have shown that the phenolic hydroxyl group is coplanar with the benzene ring even for 2,6-di-*tert*-butyl-

Table II. NMR Data Used in Calculating Equilibrium Constants[a]



b



c

	chemical shifts, Hz							
	enol			ketone				
	R_2	R_3	R_5	R_2	R_3	H_2	H_3	R_5
1 (R_2, R_3, R_5 = H)								
CD_3COCD_3	406 (s, 2 H)			184 (s, 4 H)				
Me_2SO-d_6	410 (s, 2 H)			186 (s, 4 H)				
2 (R_2 = CH_3; R_3, R_5 = H)								
CD_3COCD_3	142 (s, 3 H)	405 (s, 1 H)		74 (d, J = 6 Hz, 3 H)				
Me_2SO-d_6	141 (s, 3 H)	405 (s, 1 H)		72 (d, J = 6 Hz, 3 H)				
3 (R_2, R_3 = CH_3; R_5 = H)								
CD_3COCD_3	142 (s, 6 H)			66 (d, J = 6 Hz, 6 H)[b]				
				74 (d, J = 6 Hz, 6 H)[c]				
4 (R_2 = Et; R_3, R_5 = H)								
Me_2SO-d_6	74 (t, J = 8 Hz, 3 H, CH_3)	408 (s, 1 H)		54 (t, J = 7 Hz, 3 H, CH_3)				
7 (R_2, R_3 = H; R_5 = OH)								
CD_3COCD_3	402 (AB, 2 H)				188 (AA′, BB′, 4 H)			732 (s, 1 H)
p-dioxane	394 (s, 2 H)		576 (s, 1 H)					727 (s, 1 H)

[a] All chemical shifts reported in this table are distinctly separated from other bands. [b] Protons on equatorial CH_3 groups. [c] Protons on axial CH_3 groups.

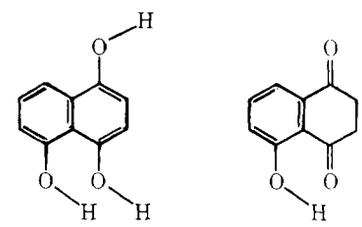
Table III. Thermodynamic Data for the Fusion of 1,4-Naphthalenediols (220 °C)

compd	T, °C	$K = \frac{[\text{enol}]}{[\text{ketone}]}$	$\Delta G°$,[a] kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$, eu
1b	200	1.98 ± 0.05	−0.567 ± 0.013	−2.3 ± 0.4	−3.4 ± 0.9
	220	1.75 ± 0.02			
	239	1.65 ± 0.03			
2b	198	4.74 ± 0.10	−1.43 ± 0.01	−2.0 ± 0.3	−1.1 ± 0.6
	220	4.24 ± 0.04			
	239	4.01 ± 0.07			
3b	209	6.36 ± 0.09	−1.76 ± 0.01	−2.5 ± 0.1	−1.5 ± 0.3
	220	6.10 ± 0.16			
	239	5.47 ± 0.11			
4b	200	3.62 ± 0.09	−1.37 ± 0.01	+2.6 ± 0.2	+8.0 ± 0.5
	219	4.08 ± 0.02			
	239	4.45 ± 0.04			
7c	170	0.24 ± 0.02	+1.01 ± 0.02	+3.3 ± 0.2	+4.7 ± 0.6
	190	0.29 ± 0.01			
	211	0.33 ± 0.01			
8c	200, 220, 240	<0.05			
5b, 6b, 9b	200, 220, 240	>20			

[a] $\Delta G°$ was determined for each system using the computed value of ln K at 220 °C, which resulted from the least-squares fit of the experimental data.[5]

phenol. There is no reason to expect the situation to be different with the naphthols. With acyclic ketones anomalous changes in the equilibrium constants for tautomerization have been reported[7a] with changes in the chain length of the alkyl substituents. However, Allinger and co-workers[7b] have questioned the significance of these results, and without further data it is not appropriate to make any comparison of substituent effects. The observed differences may simply represent a solvent effect.

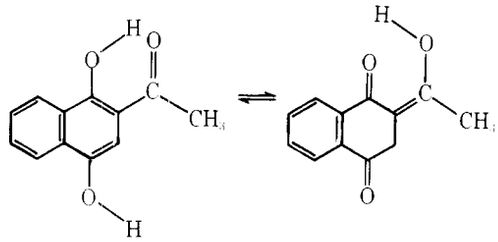
The substitution of a hydroxyl group in the 5 and 8 positions of 1,4-dihydroxynaphthalene has a significant effect on the tautomeric equilibrium. The addition of a single hydroxyl group in the 5 position is sufficient to shift the equilibrium in favor of the keto form; $\Delta G°$ is equal to 1 kcal/mol as shown. The keto form is the more stable thermochemically by 3 kcal/mol and more than compensates for the entropy term which favors the enol. The greater thermochemical stability of the keto tautomer compared to the enol is attributed to the difference in the strength of the hydrogen bonds in the two tautomers which must be significant from a comparison of the $\Delta H°$ values for the tautomerism of 1,4,5-trihydroxynaphth-



alene with 1,4-dihydroxynaphthalene. In this case, the $\Delta H°$ term is more important than $\Delta S°$. With the addition of a second hydroxyl group in the 8 position, the amount of enol is too small to measure. Thus, K must be less than 0.05. As further evidence for the effectiveness of hydrogen bonding in controlling the equilibrium ratios, samples of 5-methoxy- and 5,8-dimethoxy-1,4-dihydroxynaphthalenes were fused. In both cases the amount of keto tautomer was too small to be detected ($K > 20$). In these two cases hydrogen bonding with the methoxyl group was only possible for the enol.

In their theoretical treatment of the relative stability of the keto–enol tautomers cited above, Forsén and Nilsson[2b] ignored $\Delta S°$ as well as differences in the strengths of hydrogen bonds in the keto and enol forms. Since the data in Table III show that the $\Delta S°$ values have a significant effect on the equilibrium distribution and that the differences in the strength of intramolecular hydrogen bonds are sufficiently important to determine which tautomer dominates in the equilibrium, the difference between these results and Forsén's predicted distribution can be understood.

As a further test of the relative importance of hydrogen bonding and substituent effects, 2-acetyl-1,4-dihydroxynaphthalene was fused with the intention of measuring the relative amounts of tautomers. Although both forms could be



stabilized by hydrogen bonding, no evidence of tautomerization was detected. In this case the difference between the stability of an exocyclic double bond compared with an endocyclic double bond which is part of an aromatic ring system is too great to allow for a detectable amount of the ketone. This result is consistent with the work of Brown, Brewster, and Shechter[8] on the stability of endo and exo double bonds in five- and six-membered ring compounds.

Experimental Section

Melting points were determined using a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 grating infrared spectrophotometer and a Perkin-Elmer Infracord 137-B. Using a Varian T-60 spectrometer, the chemical shifts were measured at ambient temperature with tetramethylsilane as an internal reference. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Starting Materials. 1,5-Dinitronaphthalene, 2-ethylnaphthalene, and 5-hydroxy-1,4-naphthoquinone were obtained from Aldrich Chemical Co. 1,4-Naphthoquinone was obtained from Eastman Organic Chemicals (white label). Matheson Coleman and Bell supplied the 2,3-dimethylnaphthalene and 2-methyl-1,4-naphthoquinone. The chemicals were purified by standard procedures when the physical constants did not agree with the values in the literature. All other naphthols except 2-acetyl-1,4-dihydroxynaphthalene were prepared by the reduction of the appropriately substituted naphthoquinones.

2-Ethyl-1,4-naphthoquinone (4a). The method of preparation was similar to that of Sah.[9a] A solution of 40 g (0.4 mol) of chromic anhydride in 75 mL of 80% acetic acid was added dropwise to a solution of 6.0 g (0.038 mol) of 2-ethylnaphthalene in 100 mL of glacial acetic acid while cooling the reaction mixture to maintain a temperature of 20–25 °C during the addition. The resulting mixture was poured over 500 mL of crushed ice with continuous stirring. After 1 h, the crystals were separated by filtration and recrystallized from methanol to give 2.6 g (37% yield) of yellow needles: mp 87.5 °C (lit.[9b] mp 86–87 °C); IR (KBr) 1665 cm^{-1} (C=O); NMR (CCl_4) δ 1.23 (t, J = 3.5 Hz, 3 H), 2.60 (q of d, J = 3.5 and 0.5 Hz, 2 H), 6.75 (t, J = 0.5 Hz, 1 H), 7.42–7.90 and 7.90–8.25 (2 m, 4 H).

2,3-Dimethyl-1,4-naphthoquinone (3a). Using the above procedure, 2,3-dimethylnaphthalene was oxidized to 2,3-dimethyl-1,4-naphthoquinone in greater than 50% yield. Recrystallization from methanol gave yellow needles: mp 127 °C (lit.[10] mp 127 °C); IR (KBr) 1660 cm^{-1} (C=O); NMR (CCl_4) δ 2.12 (s, 6 H), 7.45–7.85 and 7.85–8.33 (2 m, 4 H).

5,8-Dihydroxy-1,4-naphthoquinone (8a). The method of preparation was similar to that of Fieser.[11] A solution of 5.0 g of sulfur in 75 mL of 23% fuming sulfuric acid was added dropwise with stirring to a suspension of 10 g (0.046 mol) of 1,5-dinitronaphthalene in 46 mL of concentrated sulfuric acid. The reaction mixture was maintained between 50–60 °C, initially by cooling and finally by external heating. After cooling to room temperature, the dark red solution was poured over 400 mL of crushed ice; the resulting solution was dark blue. Following filtration, the solution was heated until the filtrate became dark red and a thick mass formed. The red solid was separated by filtration and dried. The crude product was obtained by repeated extraction of the red solid with benzene followed by evaporation of the solvent. Sublimation gave pure needles of **8a** with a green reflex in 15% yield: mp 234 °C dec; IR (KBr) 1612 cm^{-1} (C=O) and identical with the spectrum of an authentic sample; NMR (dioxane) δ 7.18 (s, 4 H, aromatic and quinoidal protons), 12.25 (s, 2 H, OH protons), and agrees with a reported spectrum.[12]

5,8-Dimethoxy-1,4-naphthoquinone (6a). The method of preparation was similar to that of Garden and Thomson.[13] A stirred solution containing 1.0 g (0.0053 mol) of 5,8-dihydroxy-1,4-naphthoquinone, 4 mL of methyl iodide, and 36 mL of chloroform was refluxed with 1.0 g of silver oxide for approximately 48 h until an aliquot from the reaction mixture failed to give a violet color with 5% sodium hydroxide. Additions of 2 mL of methyl iodide and 1.0 g of silver oxide were made after 2, 6, and 24 h. When the reaction was completed, the silver salt was removed by filtration and the filtrate was passed through a chromatographic column packed with alumina. Three distinct bands were observed and eluted with light petroleum ether (bp 90–120 °C). Evaporation of the solvent from the fraction containing the second band produced orange needles of 5,8-dimethoxy-1,4-naphthoquinone in 27% yield: mp 155 °C (lit.[13] mp 155 °C); IR (KBr) 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.97 (s, 6 H), 6.80 (s, 2 H), 7.37 (s, 2 H).

5-Methoxy-1,4-naphthoquinone (5a). Using a modification of the above procedure, 1.0 g (0.0057 mol) of 5-hydroxyl-1,4-naphthoquinone was methylated by continuous stirring and refluxing with 2.0 g of silver oxide, 1.5 mL of methyl iodide, and 25 mL of chloroform. Two additions of 1.0 g of silver oxide and 1.0 mL of methyl iodide were made at intervals of 1 h. Stirring and refluxing were maintained until an aliquot of the solution no longer gave a violet color with 5% sodium hydroxide. The mixture was filtered, the solvent evaporated, and the residue recrystallized from methanol to give orange needles of 5-methoxy-1,4-naphthoquinone in 90% yield: mp 185–186 °C (lit.[14] mp 186 °C); IR (KBr) 1655 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.03 (s, 3 H), 6.90 (s, 2 H), 7.15–7.52 (m, 1 H), 7.52–7.88 (m, 2 H).

2-Acetyl-1,4-dihydroxynaphthalene (9b). The method of preparation was a modification of the procedure for preparing acetylhydroquinone described by Reynolds, Cathcart, and Williams.[15] Aluminum chloride (1.0 g, 0.0041 mol) was ground with 1,4-dihydroxynaphthalene diacetate (0.6 g, 0.0025 mol), which was previously prepared by reacting 1,4-dihydroxynaphthalene with acetic anhydride using the procedure for preparing hydroquinone diacetate.[16] The mixture was maintained at 130–135 °C with continuous stirring until all fuming ceased and the mixture appeared yellow and powdery. The cooled reaction mixture was added with stirring to 10 g of crushed ice and 0.5 mL of concentrated hydrochloric acid. After stirring for 1 h, the resulting slurry was filtered and the solid was washed with cold water. The crude product was further purified by stirring with 8 mL of a 5% solution of hydrochloric acid in methanol. The resulting solution was poured with stirring into 5 mL of an ice–water mixture, and the solid was filtered, washed, and dried. Recrystallization from ethanol yielded yellow crystals, mp 203–204 °C with decomposition. The infrared spectrum was identical with that of an authentic sample of 2-acetyl-1,4-dihydroxynaphthalene.

General Procedure for Preparation of 1,4-Naphthalenediols. A modification of Thomson's procedure[3a] for the reduction of 5-hydroxy-1,4-naphthoquinone was used. A 0.0057-mol sample of quinone was added to 250 mL of 12% hydrochloric acid solution in aqueous ethanol containing 0.023 mol of stannous chloride. The mixture was refluxed for 1 h while being maintained under a nitrogen atmosphere. The resulting hot solution was filtered through a pad of Norit, allowed to cool to room temperature, and chilled in the refrigerator until crystallization was complete. All procedures were carried out under a nitrogen atmosphere (e.g., using a drybox). The

resulting crystals were filtered, washed with cold water, and dried in a vacuum desiccator in the dark. Minimal exposure to light and air was necessary in order to obtain white crystals with sharp melting points. When the products were exposed to air, the crystals became discolored and the melting points were variable. The physical constants and spectral data for the compounds are listed below.

1,4-Dihydroxynaphthalene (1b): mp 194–196 °C (lit.[17] mp 195 °C); IR (KBr) 3235 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 6.83 (s, 2 H, C_2 H and C_3 H), 7.30–7.67 (m, 2 H, C_6 H and C_7 H), 8.00–8.40 (m, 2 H, C_5 H and C_8 H), 9.38 (s, 2 H, 2OH).

2-Methyl-1,4-dihydroxynaphthalene (2b): mp 176–178 °C [lit.[18] mp 170 °C (178 °C)]; IR (KBr) 3263 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 2.35 (s, 3 H, CH_3), 6.75 (s, 1 H, C_3 H), 7.22–7.70 (m, 2 H, C_5 H and C_8 H), 7.93–8.43 (m with a spike at δ 8.27, 3 H, C_6 H, C_7 H, and C_1 OH), 9.4 (s, 1 H, C_4 OH).

2,3-Dimethyl-1,4-dihydroxynaphthalene (3b): mp 185 °C; IR (KBr) 3320 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 2.30 (s, 6 H, $2CH_3$), 7.20–7.55 (m, 2 H, C_6 H and C_7 H), 7.80–8.57 (m, 4 H, C_5 H, C_8 H, and 2OH).

2-Ethyl-1,4-dihydroxynaphthalene (4b): mp 147 °C (lit.[19] mp 143–144 °C); IR (KBr) 3258 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 1.20 (t, 3 H, CH_3), 2.73 (q, 2 H, CH_2), 6.73 (s, 1 H, C_3 H), 7.25–7.62 (m, 2 H, C_6 H and C_7 H), 7.92–8.33 (m, 3 H, C_5 H, C_8 H, and C_1 OH), 9.37 (s, 1 H, C_4 OH).

1,4,5-Trihydroxynaphthalene (7b). Using Thomson's procedure,[3a] the crystals that precipitated out of the cold reaction mixture were filtered, dried, and washed with $CHCl_3$. These cream-colored crystals of **7b** gave the following: mp 140–142 °C (lit.[20] mp 148 °C); IR (KBr) 3233 cm^{-1} (OH); NMR (dioxane) δ 6.57 (s, 2 H, C_2 H and C_3 H), 6.63–7.95 (m, 4 H, C_6 H, C_7 H, C_8 H, and C_1 OH), 9.03 (s, 1 H, C_5 OH), 9.60 (s, 1 H, C_4 OH). Upon exposure to air, the crystals of **7b** readily oxidized to **7a.**

1,2,3,4-Tetrahydro-5-hydroxynaphthalene-1,4-dione (7c). Following Thomson's procedure,[3a] 1.0 g (0.0057 mol) of 5-hydroxy-1,4-naphthoquinone was reduced by refluxing with stannous chloride in dilute hydrochloric acid. Repeated extraction of the cooled reaction mixture with $CHCl_3$ yielded 0.65 g (0.0037 mol) of **7c:** mp 97 °C (lit.[3a] mp 96–97 °C); IR (KBr) 1693 and 1645 cm^{-1} (2C=O); NMR (Me_2SO-d_6) δ 3.12 (s, 4 H, $2CH_2$), 7.20–7.97 (m, 3 H, aromatic H), 12.17 (s, 1 H, C_5 OH).

1,4-Dihydroxy-5-methoxynaphthalene (5b). Thomson's procedure[3a] for the preparation of **7c** was used to reduce 5-methoxy-1,4-naphthoquinone with two modifications. The reaction mixture was maintained under nitrogen at all times, and 6% HCl was used as the solvent. The resulting white crystals were stored in the dark in an evacuated dessicator: mp 183–185 °C; IR (KBr) 3361 sharp (OH), 3295 shoulder (OH) cm^{-1}; NMR (Me_2SO-d_6) δ 4.03 (s, 3 H, OCH_3), 6.53–7.88 (m, 5 H, aromatic H), 8.83 (s, 1 H, C_1 OH), 9.33 (s, 1 H, C_4 OH). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.36; H, 5.41.

5,8-Dimethoxy-1,4-dihydroxynaphthalene (6b). Using the above procedure for the preparation of **5b,** white crystals of **6b** were collected: mp 165.5–166.5 °C; IR (KBr) 3370 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 4.00 (s, 6 H, $2OCH_3$), 6.75 (s, 2 H, C_2 H and C_3 H), 6.85 (s, 2 H, C_5 H and C_7 H), 9.15 (s, 2 H, 2OH).

1,2,3,4-Tetrahydro-5,8-dihydroxynaphthalene-1,4-dione (8c). A suspension of 0.2 g (0.0011 mol) of naphthazarin in dilute hydrochloric acid containing 1.2 g (0.0053 mol) of stannous chloride was refluxed for 1 h. The hot solution was filtered through a pad of Norit. The resulting filtrate yielded 0.14 g (0.0007 mol) of **8c:** mp 154 °C (lit.[21] mp 154 °C); IR (KBr) 1633 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 3.12 (s, 4 H, $2CH_2$), 7.35 (s, 2 H, aromatic H), 12.03 (s, 2 H, 2OH).

Isolation of the Keto Tautomers from Fusion Mixtures. The sealed ampules of the fused 1,4-naphthalenediols were opened in a drybox under nitrogen to minimize oxidation of the tautomers to the quinone. Each sample was extracted with several portions of carbon tetrachloride, a solvent in which the 1,4-naphthalenediol tautomers were known to be insoluble. After combining the extracts and concentrating the solutions by allowing the excess solvent to evaporate under a stream of nitrogen, IR and NMR spectra were recorded. Since the diketo tautomers were extremely susceptible to oxidation, melting points could not be obtained for all compounds. The following data were obtained.

1,2,3,4-Tetrahydronaphthalene-1,4-dione (1c): mp 95 °C (lit.[22] mp 94 °C); IR (CCl_4) 1695 cm^{-1} (C=O); NMR (CCl_4) δ 3.03 (s, 4 H, $2CH_2$), 7.60–8.16 (m, 4 H, aromatic H).

2-Methyl-1,2,3,4-tetrahydronaphthalene-1,4-dione (2c): mp 59–63 °C (lit.[3a] mp 60 °C); IR (CCl_4) 1702 cm^{-1} (C=O); NMR (CCl_4) δ 1.33 (d, J = 5 Hz, 3 H, CH_3), 2.67–3.33 (m, 3 H, CH_2 and CH), 7.60–8.12 (m, 4 H, aromatic H).

2,3-Dimethyl-1,2,3,4-tetrahydronaphthalene-1,4-dione (3c): IR (CCl_4) 1702 cm^{-1} (C=O); NMR (CCl_4) δ 1.20 and 1.35 (two doublets, J = 6 Hz, 6 H, axial and equatorial CH_3), 2.67–3.30 (m, 2 H, 2CH), 7.50–8.33 (m, 4 H, aromatic H).

2-Ethyl-1,2,3,4-tetrahydronaphthalene-1,4-dione (4c): IR (CCl_4) 1696 cm^{-1} (C=O); NMR (CCl_4) δ 1.00 (t, J = 7 Hz, 3 H, $-CH_3$), 1.40–2.00 (m, 2 H, CH_2), 2.55–3.30 (m, 3 H, CH and CH_2), 7.53–8.13 (m, 4 H, aromatic H).

Procedure for the Fusion of Samples Used in the Keto–Enol Equilibrium Studies. Individual samples were prepared by sealing 100-mg quantities of the 1,4-naphthalenediols or their pure tautomers in Pyrex tubes using a high vacuum line (<0.005 mmHg). The sealed ampules were immersed in an oil bath regulated and maintained to within 1° of the reported temperature. After heating, the samples were immediately immersed in liquid nitrogen and subsequently stored in a freezer.

Infrared Analysis of Fusion Mixtures. The sealed ampules of fused material were removed from the freezer and allowed to reach room temperature before being opened under a nitrogen atmosphere (e.g., in a drybox). Quantities of 1–3 mg of the mixtures were ground with anhydrous KBr and pressed into a pellet under vacuum. The infrared spectra were taken immediately.

Nuclear Magnetic Resonance Analysis of Fusion Mixtures. The sealed ampules of fused material were removed from the freezer and allowed to reach room temperature before being opened under a nitrogen atmosphere (e.g., in a drybox). Enough solvent was added to each ampule to completely dissolve the 100-mg sample. The resulting solution was transferred to an NMR tube and stoppered under nitrogen. All samples were analyzed immediately even though the mixtures were found to be stable over a period of several days if not exposed to air.

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Registry No.—**1c,** 21545-31-3; **2c,** 67597-84-6; **3a,** 2197-57-1; **3c,** 67597-85-7; **4a,** 5409-32-5; **4c,** 67597-86-8; **5a,** 4923-61-9; **6a,** 15013-16-8; **7b,** 481-40-3; **8a,** 475-38-7; 2-ethylnaphthalene, 939-27-5; 2,3-dimethylnaphthalene, 581-40-8; 1,5-dinitronaphthalene, 605-71-0; methyl iodide, 74-88-4; 5-hydroxy-1,4-naphthoquinone, 481-39-0; 1,4-dihydroxynaphthalene diacetate, 5697-00-7.

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The True Course of the Solvolysis of 3β-Tosyloxy-5β-hydroxycholestan-6-one, or the S_N2 Inversion Rule Upheld

Vinod Dave and E. W. Warnhoff*

Department of Chemistry, University of Western Ontario, London, Canada N6A 5B7

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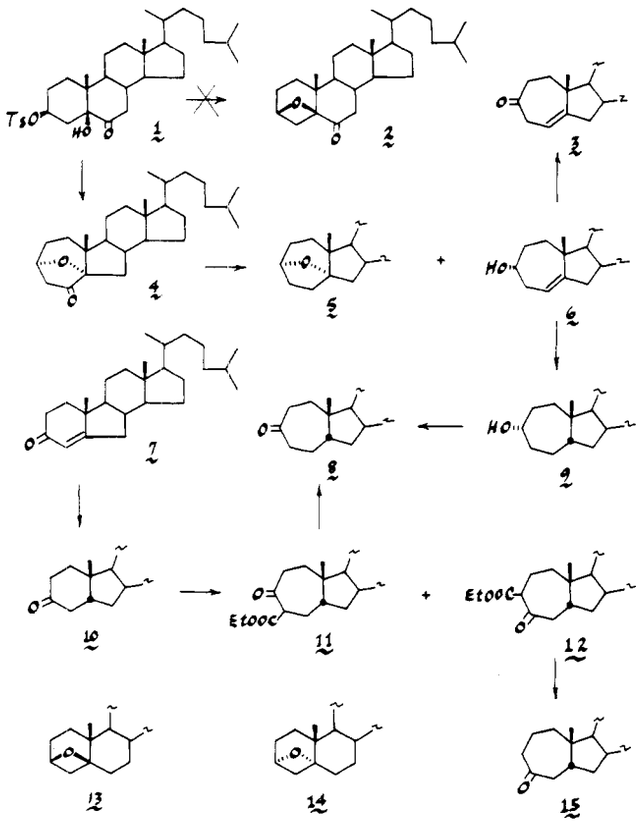
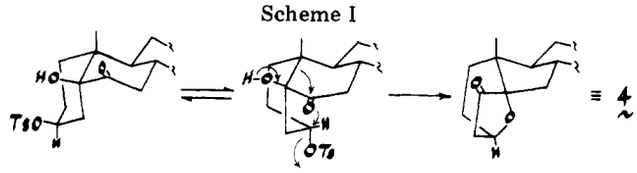
The product of solvolysis of 3β-tosyloxy-5β-hydroxycholestan-6-one (**1**) has been shown to be the *A*-homo-*B*-norketo oxide **4** by ^1H NMR spectroscopy and transformation into ketone **8**, which was synthesized by A-ring expansion of *cis*-*B*-norcholestan-3-one (**10**). The formation of **4** follows the rearrangement sequence in Scheme I with inversion at C-3. The rearrangement occurs in both the forward and reverse directions under a variety of conditions.

The requirement of inversion in the S_N2 reaction at carbon is one of the basic tenets of organic reaction mechanisms.[1] While theoretical calculations have predicted certain circumstances under which retention in an S_N2 reaction might be observed, the search for an actual example has so far met with failure.[1] In this regard, the report[2] some time ago of the solvolysis of 3β-tosyloxy-5β-hydroxycholestan-6-one (**1**) was



of more than passing interest. The product obtained from a variety of solvents was assigned the oxetanone structure **2**, and it was suggested that the reaction proceeded via a transition state involving "partial bonding from the oxygen [at C-5] to C-3 before significant carbonium ion character at C-3 is developed."[2a] Although the reaction caused raised eyebrows,[3,4]

Scheme I



it has not been challenged.[5,6] Our attention was attracted because such a transition state amounts to an unprecedented retention of configuration during an S_N2 substitution.[7] Also, if the reaction were really the simple displacement suggested, it is difficult to understand why the C-3 epimer of **1** with the correct stereochemistry for a normal S_N2 reaction with inversion was inert under the same conditions.[2a] When it is further considered that the carbonyl IR absorption (1757 cm^{-1} in CCl_4) of the solvolysis product is not appropriate for an α-alkoxycyclohexanone (expected[8] 1713–1724 cm^{-1} in CCl_4), it was clear that a more plausible rationalization of the reaction was required.

An alternative course for the solvolysis which would not require violation of the S_N2 inversion rule involves participation of the 6-carbonyl oxygen of **1** in a displacement at C-3 with concomitant stereoelectronically favorable A/B ring rearrangement as shown in Scheme I.[9] This reaction leads by inversion at C-3 to a different keto oxide **4** whose 3-oxotetrahydrofuranyl carbonyl group would absorb at about 1757 cm^{-1}.[10] Moreover, the mechanism of Scheme I accounts for the failure of the C-3 epimer of **1** to react since it could not do so with inversion.[11]

Structures **2** and **4** are readily distinguishable by ^1H NMR spectroscopy in conjunction with deuterium exchange experiments. While each structure has an H–C–O group with the hydrogen coupled to two adjacent methylene groups and each has a carbonyl α-methylene group, only **4** has the exchangeable α-methylene adjacent to the H–C–O group. In the preparation of the solvolysis product for these experiments, the use of anhydrous isopropyl alcohol gave the best yield in our hands. The compound incorporated two, and only two, deuterium atoms on exchange in NaOD–D_2O–dioxane with the disappearance of two protons from the δ 2–3 region of its ^1H NMR spectrum (Figure 1).[12] The pattern of the H–C–O signal in the d_2 solvolysis product was now much simplified (Figure 1), proving that the exchanged hydrogens had been

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