The Double Hydrogen Bonding Ability of 4,5-Dinitro-1,8-biphenylenediol[1]

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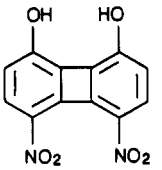
The equilibrium constants for hydrogen bonding of 4,5-dinitro-1,8-biphenylenediol to dimethyl sulfoxide, tetramethylene sulfoxide, 2,6-dimethyl-γ-pyrone, hexamethylphosphoramide, and 1,2,6-trimethyl-4-pyridone were determined in chloroform solution at 25 °C. The values obtained increased in the order the bases are listed, by about 1200-fold over the entire range of the series. Values for the same bases were also determined for 1,8-biphenylenediol, 4-nitro-3-(trifluoromethyl)phenol, and *m*-nitrophenol, which was also studied with tetrahydrofuran. Equilibrium constants were also determined for complexing of *p*-fluorophenol with dimethyl sulfoxide, tetramethylene sulfoxide, and hexamethylphosphoramide. All these values were found to be smaller and to vary over a narrower range than did the values for 4,5-dinitro-1,8-biphenylenediol. The values for 4-nitro-3-(trifluoromethyl)phenol, whose acidity is about the same as that of the dinitrobiphenylenediol per hydroxy group, varied by only 40-fold over the range of compounds and were from 7-fold to 200-fold smaller per hydroxy group. Such results show that both 1,8-biphenylenediol and its 4,5-dinitro derivative form two hydrogen bonds to a given basic atom. As expected, the more acidic dinitro derivative is the stronger hydrogen bonder.

1,8-Biphenylenediol has a molecular geometry that was expected to make it effective at forming two acidic hydrogen bonds to the same basic atom. X-ray crystal structure studies of several of its adducts with bases[2] and measurements of its catalytic activity[3] and of its equilibrium constants for hydrogen bonding in cyclohexane solution[4] showed that it does form such double hydrogen bonds. Because the hydrogen bonding ability of structurally similar acids increases with their increasing acidity,[5] more acidic derivatives of 1,8-biphenylenediol are of interest. Symmetrically substituted derivatives would have two hydroxylic protons of identical acidity, which would simplify a study of the quantitative relationship between acidity and hydrogen bonding strength.[6] Since ortho and para nitro substituents are among the strongest electron withdrawers of common substituents and since an ortho nitro substituent could give complications from internal hydrogen bonding, we have studied 4,5-dinitro-1,8-biphenylenediol (**1**).[7]



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Experimental Section

Equilibrium Constants. Equilibrium constants were measured by a UV spectrophotometric method similar to that described previously.[4] The solubility of **1** in carbon tetrachloride or in cyclohexane was so low, however, that chloroform was used as the solvent instead. Most of the measurements on 1,8-biphenylenediol were made at 271 nm, but because of interference from absorption by the base those with 1,2,6-trimethyl-4-pyridone (TMP) and 2,6-dimethyl-γ-pyrone (DMP) were made instead at 303.6 and 338 nm, respectively. Ten-centimeter cells were used in these measurements and in those with 1; 1-cm cells were used in all the other cases. As a measure of the reliability of the K values, all the equilibria were followed to at least 85% transformation of phenol to complex, except in the case of the complexation of *m*-nitrophenol with 2,6-dimethylpyrone, which could be followed to only 57% transformation because of the solubility limit of the pyrone in chloroform. An average of 15 additions of base to the phenol and absorbance measurement were made per run. At least two runs were made for each determination of an equilibrium constant. The extinction coefficients of the complexes differed from those of the phenol by from 19% to 195% except in the cases of the complexes of **1** with dimethyl sulfoxide (Me_2SO) and tetramethylene sulfoxide (TMSO) where the differences were 8% and 10%, respectively. In the least-squares treatments the disposable parameters were the equilibrium constants and the extinction coefficients of the complex and the phenol. The values obtained for the phenol were always within 3% of values obtained from measurements on the phenol alone. The standard deviations of the calculated from the observed absorbances averaged about 0.003 and were never larger than 0.007. The constant minimized was the sum of the squares of the deviations of the calculated from the observed absorbances. The observed absorbances were between 0.2 and 0.8.

Results and Discussion

Equilibrium Constants. The equilibrium constants obtained in chloroform for **1**, 1,8-biphenylenediol, 4-nitro-3-(trifluoromethyl)phenol, whose pK_a (6.07[8]) is near the value for **1** per hydroxy group (5.90[7]), *m*-nitrophenol, whose pK_a (8.36[9]) is very near the value for 1,8-biphenylenediol per hydroxy group (8.31[10]), and *p*-fluorophenol are listed in Table I.

In Figure 1 is a log–log plot of the other equilibrium constants per hydroxy group vs. the values for 4-nitro-3-(trifluoromethyl)phenol, the most strongly acidic monophenol that was studied. For the other two monophenols the slopes of the plots increase with increasing acidity; for *p*-fluorophenol, which is the least acidic (pK_a 9.90[9]), the slope (standard deviation) of 0.54 (0.03) is the smallest, for *m*-nitrophenol, which is more acidic, but less acidic than 4-nitro-3-(trifluoromethyl)phenol, the slope of 0.63 (0.05)

(1) This investigation was supported in part by Grant No. CHE-8114770 from the National Science Foundation. Abstracted in part from the Ph.D. Dissertation of K. Ahn, The Ohio State University, 1986.
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Table I. Equilibrium Constants for Hydrogen Bonding of Phenols to Various Bases[a] and pK_a Values for the Phenols

	$10^{-3}K$, M^{-1}				
base	4,5-dinitro-1,8-biphenylenediol	1,8-biphenylenediol	4-nitro-3-(trifluoromethyl)phenol	*m*-nitrophenol	*p*-fluorophenol
1,2,6-trimethyl-4-pyridone (TMP)	1910	49	4.4	0.29	
	(220)	(8)	(0.2)	(0.02)	
$(Me_2N)_3PO$ (HMPA)	470	42	2.4	0.19	0.069
	(70)	(1)	(0.1)	(0.01)	(0.003)
2,6-dimethyl-γ-pyrone (DMP)	4.3	1.04	0.24	0.048[b]	
	(0.2)	(0.06)	(0.02)	(0.012)	
$(CH_2)_4SO$ (TMSO)	2.3[b]	1.85	0.173	0.030	0.018
	(0.4)	(0.08)	(0.017)	(0.004)	(0.001)
Me_2SO (Me_2SO)	1.60[b]	1.03	0.102	0.031	0.012
	(0.24)	(0.08)	(0.009)	(0.011)	(0.001)
$(CH_2)_4O$ (THF)				0.012	
				(0.001)	
pK_a[c]	5.90	8.31	6.07	8.36	9.90

[a] In chloroform at 25 ± 1 °C. The figures in parentheses are estimated standard deviations. [b] Value relatively unreliable, see text. [c] In water per hydroxy group. This means that the experimental K_a values for the diols have been divided by 2.

Table II. Extinction Coefficients of Phenols and Their Hydrogen-Bonded Complexes with Various Bases[a]

	$10^{-3}\epsilon$, M^{-1} cm^{-1}				
base	4,5-dinitro-1,8-biphenylenediol 327 nm	1,8-biphenylenediol 271 nm	4-nitro-3-(trifluoromethyl)phenol 335 nm	*m*-nitrophenol 360 nm	*p*-fluorophenol 290 nm
none[b]	8.10	21.1	2.07	0.720	1.10
1,2,6-trimethyl-4-pyridone (TMP)	10.9	1.89[c]	5.92	1.22	
	(0.1)	(0.01)	(0.08)	(0.02)	
$(Me_2N)_3PO$ (HMPA)	9.95	40.4	4.78	1.18	1.80
	(0.07)	(0.8)	(0.01)	(0.01)	(0.03)
2,6-dimethyl-γ-pyrone (DMP)	9.62	1.68[d]	4.12	1.07	
	(0.03)	(0.01)	(0.02)	(0.10)	
$(CH_2)_4SO$ (TMSO)	8.95	38.1	3.70	1.06	1.70
	(0.03)	(0.2)	(0.05)	(0.09)	(0.02)
Me_2SO (Me_2SO)	8.81	36.7	3.55	1.02	1.69
	(0.07)	(0.1)	(0.04)	(0.06)	(0.02)
$(CH_2)_4O$ (THF)				0.93	
				(0.01)	

[a] In chloroform at 25 ± 1 °C. The parenthesized figures are estimated standard deviations. [b] ε values for the phenol. [c] Measured at 303.6 nm, where ε for the diol is 1380 M^{-1} cm^{-1}. [d] Measured at 338 nm, where ε for the diol is 1340 M^{-1} cm^{-1}.

is greater. For the 1,8-biphenylenediol derivatives, however, the results are different. Although 1,8-biphenylenediol itself is less acidic, per hydroxy group, by more than 100-fold, than 4-nitro-3-(trifluoromethyl)phenol, the log–log plot of its equilibrium constants, also on a per hydroxy group basis, has a slope of 1.15 (0.15) that is probably larger than 1.0. And the slope of 1.96 (0.10) of the plot for 1 is clearly much larger.

If the 1,8-diol derivatives were forming only single hydrogen bonds to the bases, their equilibrium constants per hydroxy group should be about the same as those of a monohydroxy phenol of the same acidity. Instead, the values for 1,8-biphenylenediol are seen to be from 11 to 110 times as large as those for *m*-nitrophenol and even from 2 to 9 times as large as those for 4-nitro-3-(trifluoromethyl)phenol, even though the latter is more than 100 times as acidic. Similarly, the values for 1 per hydroxy group are 7 to 220 times as large as those for 4-nitro-3-(trifluoromethyl)phenol. Since the individual constants should be about the same for 1,8-biphenylenediol and *m*-nitrophenol, the slope of the lines in Figure 1 should be about the same. Instead the line for 1,8-biphenylenediol is 83% steeper. Analogously, the line for 1 should have a slope of about 1.00, instead of 1.96.

The preceding deviations from the expectations of only single hydrogen bonding are just what would be expected if double hydrogen bonding was occurring. Since it would have to be occurring in addition to single hydrogen bonding the observed total equilibrium constants would be larger than the values for single hydrogen bonding alone. If we take the monohydroxy phenols of similar acidity as models for single hydrogen bonding, we may estimate that the extent of double hydrogen bonding by 1,8-biphenylenediol increases from 94% for dimethyl sulfoxide to 98.8% for 1,2,6-trimethyl-4-pyridone. The estimated extent for 1 increases from 87% for dimethyl sulfoxide to 99.5% for 1,2,6-trimethyl-4-pyridone.

If the two individual hydrogen bonds in a double hydrogen bond were independent of each other, the line in Figure 1 for 1,8-biphenylenediol should have a slope about twice that of the line for *m*-nitrophenol, and the slope of the line for 1 should be about 2.0. However, the formation of a hydrogen bond to one unshared pair of electrons on an oxygen atom must markedly decrease the basicity of the other unshared pair. To a considerably smaller extent, hydrogen bonding by one hydroxy hydrogen atom should decrease the acidity of the other one. In addition, the rigid structure of 1,8-biphenylenediol would probably prevent either hydrogen bond in its double hydrogen bonded adducts from having its optimum geometry. These reasons lead us to expect that the slopes of the lines for 1,8-biphenylenediol derivatives in Figure 1 would be less than twice what would be expected from single hydrogen bond formation. They are indeed less but probably by no more than the experimental uncertainty.

In Figure 2 are plots of log *K*, per hydroxy group, for hydrogen-bonded complex formation for the three bases that were studied with all five phenols vs. the pK_a values,

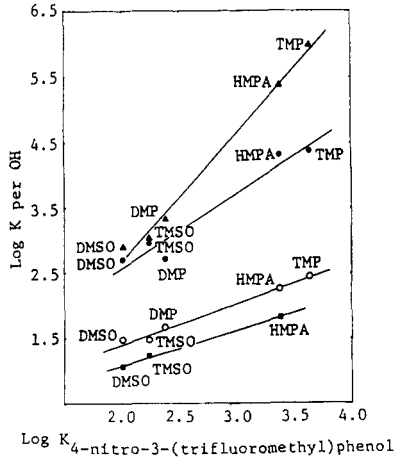

Figure 1. log–log plots of K values for hydrogen bonding of phenols to various bases vs. K values for hydrogen bonding of 4-nitro-3-(trifluoromethyl)phenol to the same bases: dinitro diol (▲), 1,8-biphenylenediol (●), *m*-nitrophenol (○), *p*-fluorophenol (■).

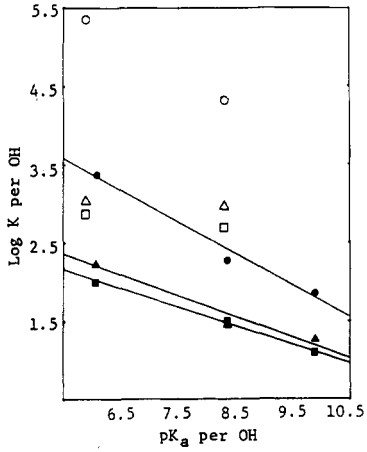

Figure 2. Plots of log K for hydrogen bonding of bases to various phenols vs. the pK_a values for the phenols. Circular points are for hexamethylphosphoramide, triangular points for tetramethylene sulfoxide, and square points for dimethyl sulfoxide. Solid points are for meta- and para-substituted derivatives of phenol. Open points are for 1,8-biphenylenediol and its 4,5-dinitro derivative.

per hydroxy group, for the phenols. In each case the points for the monohydroxy phenols fall moderately near a straight line and the points for the 1,8-biphenylenediol derivatives lie well above this line. The slopes of the lines for hexamethylphosphoramide (HMPA), tetramethylene sulfoxide, and dimethyl sulfoxide are −0.41, −0.26, and −0.24, respectively. The steepness of the lines thus tends to increase with the increasing hydrogen bonding basicity of the bases. The two-point line (not shown) for the diols with hexamethylphosphoramide has a steeper slope than the corresponding three-point line for monophenols, as might be expected. The two-point lines for the diols with the sulfoxides have less steep slopes than the corresponding three-point lines, but it should be remembered that the equilibrium constants for complexing of the sulfoxides with the dinitro diol are relatively unreliable.

Figure 3 contains log–log plots of the equilibrium constants in chloroform vs. the values previously determined in cyclohexane.[4,11] The values in chloroform are smaller

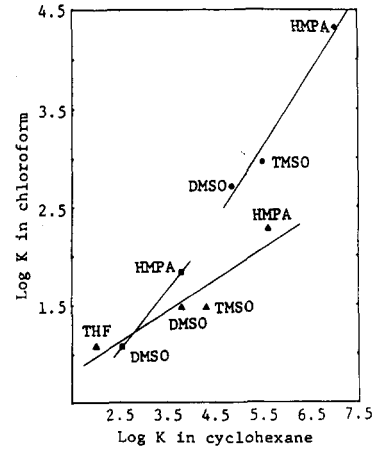

Figure 3. log–log plots of equilibrium constants for hydrogen bonding in chloroform vs. values in cyclohexane: 1,8-biphenylenediol (●), *m*-nitrophenol (▲), *p*-fluorophenol (■).

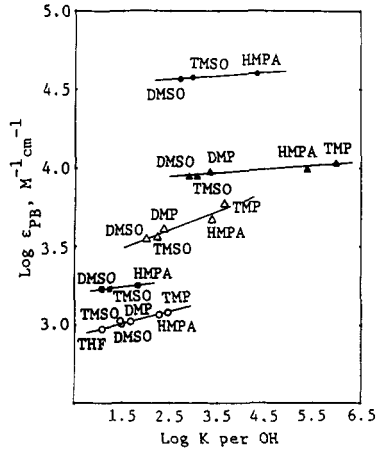

Figure 4. log–log plot of extinction coefficients of hydrogen-bonded complexes vs. K values for their formation in chloroform: dinitro diol (▲), 1,8-biphenylenediol (●), 4-nitro-3-(trifluoromethyl)phenol (△), *m*-nitrophenol (○), and *p*-fluorophenol (■).

than those in cyclohexane, probably mainly because of hydrogen bonding of the bases to the chloroform.[12] Although deviations from the best line through the points as a whole would be rather large, the correlations for a given phenol are better.[13] For *m*-nitrophenol there are five points that describe, not too well, a line of slope 0.32. There are only three points for 1,8-biphenylenediol and two for *p*-fluorophenol. Lines through these points have slopes of 0.76 and 0.61, respectively. In other words, the sensitivity of the equilibrium constants to changes in the structure of the bases is greater in cyclohexane than it is in chloroform, where the equilibrium constants are smaller.

The extent of formation of complexes of two molecules of base with one molecule of diol was estimated by the method described previously.[4] The maximum estimated extents of transformation of diol to 2:1 complex, which occur at the highest base concentrations, are 4% for the complex of 1 with dimethyl sulfoxide and 15% for the complex of 1 with tetramethylene sulfoxide. For the latter this may significantly increase the uncertainty in the K value that already exists because of the relatively small

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(12) Cf. Christian, S. D.; Johnson, J. R.; Affsprung, H. E.; Kilpatrick, P. J. *J. Phys. Chem.* **1966**, *70*, 3376–3377. Buchowski, H.; Devaure, J.; Huong, P. V.; Lascombe, J. *Bull. Soc. Chim. Fr.* **1966**, 2532–2535.

(13) Cf. Joris, L.; Mitsky, J.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 3438–3442.

change in apparent extinction coefficients that accompanies complex formation.

In Table II are the extinction coefficients obtained for the complexes. For a given complex at a given wavelength, these extinction coefficients tend to change monotonically with increasing strength of complexation. This is shown by the log-log plots of extinction coefficients vs. equilibrium constants per hydroxy group for formation of the complexes shown in Figure 4. This sort of observation has been made previously.[14] It suggests that there is more proton transfer in the complexes formed with larger equilibrium constants. Because of the different ways in which the hydroxy group is linked to the chromophore that is responsible for the UV absorption, no simple relationship is expected between the slopes of the lines for the different phenols.

We do not wish to imply that all the relationships suggested in the figures would describe the results adequately over an indefinite range of the variables. This would require such improbable constants as smaller equilibrium constants for more acidic phenols than for closely related phenols of weaker acidity. The straight lines shown are presumably just approximations to the long gradual curves that would be required to describe the results over an infinite range of the variables.

(14) Cf. Joesten, M. D.; Schaad, L. J. *Hydrogen Bonding*; Marcel Dekker: New York, 1974, Section 4.IV. Vinogradov, S. N.; Linnell, R. H. *Hydrogen Bonding*; Van Nostrand Reinhold: New York, 1971; Sections 3-5, 4-8, 5-10.

Notes

Bakers' Yeast Mediated Synthesis of 4-Deoxy-D-*lyxo*-hexopyranose (4-Deoxy-D-mannose)

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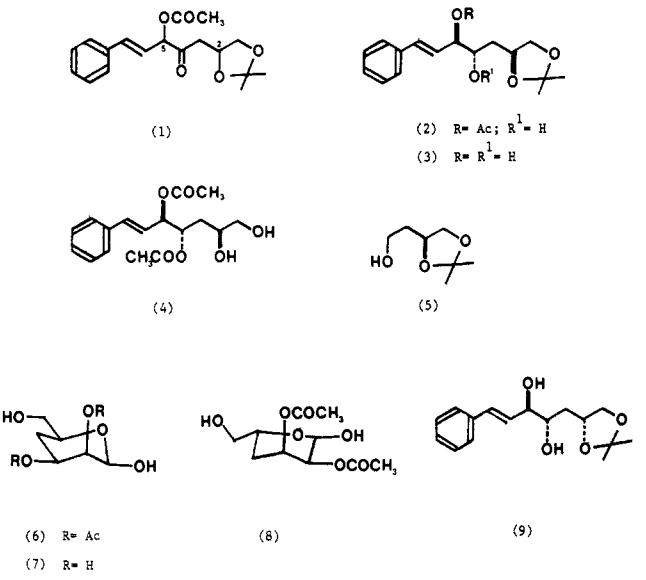
Recently,[1] in a study of the substrate specificity of the multienzymatic conversion by bakers' yeast of C_6–C_3 aromatic α,β-unsaturated aldehydes to C_6–C_5, 2*S*,3*R* methyl 2,3-diols, we obtained from a series of racemic α-hydroxy ketones, a set of synthetically useful anti and syn chiral diols. We observed high stereospecificity in the carbonyl reduction, but the ratios of the two diastereoisomers, as the result of a kinetic resolution, were strongly dependent on structural features of the substrate. In order to obtain more information on the acceptability of nonnatural substrates by synthetically useful enzymes[2] we extended our investigation to diastereoisomeric α-acetoxy ketones bearing in β'- and γ'-positions of the alkyl side chain two oxygen substituents, and we now report on the results that eventually led to a straightforward synthesis of 4-deoxy-D-*lyxo*-hexopyranose (**7**) and of the 4,7-dideoxy-D-heptose derivative **15**.

Thus, yeast treatment of the racemic α-acetoxy ketone **1**, obtained as a ca. 1:1 mixture of diastereoisomers starting from protected 3-bromopropane-1,2-diol, 1,3-dithiane, and cinnamaldehyde,[3] afforded the 2*S*,4*S*,5*R* carbinol **2** as a major transformation product in ca. 20% yield, 70% of starting material being recovered. The stereochemical assignment of product **2** was made as follows (Chart I). Basic hydrolysis of the carbinol fraction gave crude material from which crystalline **3**, mp 111–112 °C, separated in 85% yield. The latter on HIO_4 oxidation followed by

Chart I



$NaBH_4$ reduction afforded optically pure **5**, characterized as the crystalline 3,5-dinitrobenzoate.[4] Furthermore, the diacetate diol **4**, prepared in 80% yield from **3** on acetylation followed by controlled acidic hydrolysis, afforded on ozonolysis and Ph_3P treatment the diacetate **6**, converted in turn into 4-deoxy-D-*lyxo*-hexopyranose (**7**), $[\alpha]^{20}_D$ +28° (*c* 1, H_2O) (lit.[5] $[\alpha]^{20}_D$ +29.5°), in ca. 47% overall yield from **4**.

The minor diastereoisomer (10%) which accompanied **2** in the yeast treatment of **1** was assigned the 2*R*,4*S*,5*R* stereochemistry depicted in **9**. This compound from the mother liquors of crystalline **3** was also converted into a diacetate diol and afforded on ozonolysis 2,3-diacetyl-4-deoxy-D-*lyxo*-hexopyranose (**6**) and a ribo isomer **8**, $[\alpha]^{20}_D$ −18° (*c* 1, MeOH), in ca. 1.5:1 ratio. The latter 4-deoxy sugar was assigned the L absolute configuration because the *S* alcohol **5** from the mixture eventually yielding **6** and **8** resulted of ca. 0.3% ee.[6]

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