which was recrystallized (CH_3OH) to give 0.01 g (61%) of the deuterated analogue of **1c**′: mp 239–240 °C; *m/e* 393.1395 (M^+; calcd 393.1380).

1,2,6-Triphenyl-3,3,5,5-tetradeuteriophosphorinan-4-one 1-Sulfide. Ketone **6** (0.0376 g 0.0001 mol) was dissolved in dry dioxane (3 mL), and to this were added 0.5 mL of deuterium oxide and sodium methoxide (0.0064 g, 0.12 mmol). The mixture was boiled with stirring under N_2 for 24 h. Upon cooling, the mixture was extracted with $HCCl_3$ (3 × 10 mL). The $HCCl_3$ layer was washed with deuterium oxide (1 mL) and dried (Na_2SO_4). The solvent was evaporated to leave a solid mass which was recrystallized (CH_3OH) to give 0.035 g (92.1%) of the deuterated analogue of **6**: mp 239–240 °C; *m/e* 380.1289 (M^+; calcd 380.1301).

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Registry No. **1a**′, 76173-27-8; **1b**′, 76173-28-9; **1c**′, 76173-29-0; **1d**′, 76173-30-3; **1e**′, 76173-31-4; **1f**′, 76173-32-5; **2a**, 14164-67-1; **2b**, 42124-16-3; **3**, 76173-33-6; **5**, 76173-34-7; **6**, 76156-75-7; **11**, 76173-35-8; bis(hydroxymethyl)phenylphosphine, 3127-08-0; phenylphosphine, 638-21-1; **1c**′ deuterated derivative, 76190-19-7.

Restricted Rotation in Hydroxyphenyl Ketones and Formaldehydes

William G. Antypas, Jr., Leila V. M. Siukola, and Daniel A. Kleier*[1]

Thompson Chemical Laboratory, Williams College, Williamstown, Massachusetts 01267, and Theoretical Division, Los Alamos Scientific Laboratory, Los Alamos, New Mexico 87545

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Barriers to rotation about the carbonyl carbon to phenyl carbon bond in phenyl ketones and formaldehydes are determined by a detailed line-shape analysis of the proton magnetic resonances which arise from hydroxyl groups substituted at the 2- and 6-positions of the phenyl ring. Enthalpies of activation for 2,4,6 derivatives of benzaldehyde and acetophenone are determined to be 8.0 and 6.9 kcal/mol, respectively. Although full line-shape analyses were not possible for the 2,6-dihydroxy derivatives of benzaldehyde and acetophenone, activation enthalpies are estimated to have upper limits of 6 kcal/mol. The effects of intermolecular exchange on the hydroxyl resonances are also reported as a function of water concentration. The experimental barriers to internal rotation are then compared with those obtained by using molecular orbital theory at the PRDDO level of approximation. Theoretical barriers are higher than experimental ones by at least 50%, suggesting significant solvent effects on the barriers.

In the absence of exchange the proton magnetic resonance (^1H NMR) spectrum of 2,4,6-trihydroxybenzaldehyde (III) or 2,4,6-trihydroxyacetophenone (IV) should contain three separate hydroxyl peaks. Under standard conditions, however, such peaks are either extremely broad or distinct peaks are not observed at all.[2]

The line broadening is due to the exchange of hydroxyl protons between various magnetic environments and can be slowed by using a dry solvent and/or by lowering the temperature of the sample. The former procedure lowers the rate of intermolecular exchange, while the latter lowers the rates of both intermolecular and intramolecular exchange.[3]

In this work we take advantage of the large chemical shifts associated with hydrogen bonding to study the kinetics of intramolecular exchange in compounds such as III and IV. At low temperature, two widely separated peaks are observed for the *o*-hydroxyls due to their different magnetic environments, one hydrogen-bonded the other not. As expected, an increase in sample temperature broadens and merges the *o*-hydroxyl peaks. Analysis of the exchange-broadened spectra yields rates and activation parameters for the exchange process. In order to gain insight concerning the details of this exchange process, we used approximate MO theory to explore the potential energy surface for intramolecular rearrangements in these and similar compounds.

Methods

2,4,6-Trihydroxybenzaldehyde (Pfaltz and Bauer) and 2,6-dihydroxyacetophenone (Pfaltz and Bauer) were obtained and used without further purification. 2,4,6-Trihydroxyacetophenone (Aldrich) was obtained as a monohydrate. It was dried by heating at 120 °C for 3 days. 2,6-Dihydroxybenzaldehyde was synthesized from 7-hydroxy-4-methylcoumarin (Aldrich) according to the method of Parikh and Thakor.[4]

Solutions of samples in deuterioacetone were placed in precision NMR tubes (Wilmad). NMR spectra were recorded at 60 MHz on a Perkin-Elmer R-12B spectrometer fitted with a variable-temperature probe. Temperature calibration was checked by recording the NMR spectrum of a methanol sample which possesses two signals whose chemical shift difference is temperature dependent.[5]

Rate constants for compounds III and IV were determined by fitting the experimental exchange-broadened spectra with theoretical spectra generated by using the classical two-site exchange theory.[6,7] From the low-temperature spectra the chemical shift difference $\Delta\nu$ between the *o*-hydroxyls of III was found to be very temperature dependent ($d(\Delta\nu)/dT = 0.70$ Hz/K). A linear extrapolation of $\Delta\nu$ was thus used in fitting the exchange-broadened spectra. Generally, the effective relaxation times were obtained from the line width of the *p*-hydroxyl resonance, except at higher temperatures where the *p*-hydroxyl signal was clearly broadened by intermolecular exchange (see

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[1] Camille and Henry Dreyfus Teacher-Scholar Grantee, 1979–1984. To whom correspondence should be addressed at Thompson Chemical Laboratory.

[2] Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co.: Milwaukee, WI, 1974; Vol. VI, p 34.

[3] Sternhell, S. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 163.

[4] Parikh, S. M.; Thakor, V. N. *J. Univ. Bombay* **1954**, *No. 36*, 37–8.

[5] Van Geet, A. L. *Anal. Chem.* **1970**, *42*, 679.

[6] Binsch, G. *Top. Stereochem.* **1969**, *3*, 97.

[7] Bell, H. *J. Chem. Educ.* **1976**, *53*, 665. Theoretical exchange-broadened spectra were generated by a slightly modified version of a computer program described in this reference.

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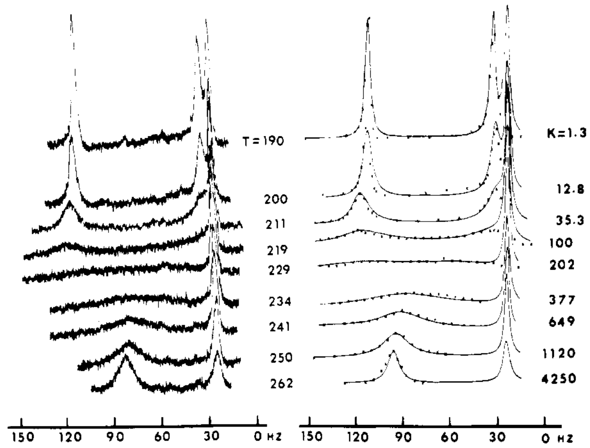


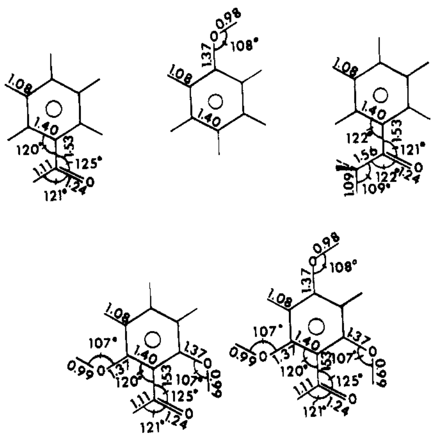
Figure 1. Experimental and theoretical exchange-broadened line shapes for 2,4,6-trihydroxybenzaldehyde. The peak furthest upfield is due to the hydroxyl group at the 4-position which is not broadened by the intramolecular exchange process and, hence, is simply superimposed on theoretical spectra. The points indicated by X on the theoretical plots represent the digitized experimental spectra used in the least-squares analysis.

Figure 1). At these higher temperatures we maintained the relaxation times for the *o*-hydroxyls at the values obtained from the *p*-hydroxyl resonance just prior to broadening. Arrhenius and Eyring parameters were calculated by using a weighted least-squares approach. Spectra near the "frozen" and exchange-averaged limits were given smaller weights than spectra at intermediate temperatures. The latter spectra were given heavier weights since their line shapes are more sensitive to small changes in the rate constant.

Molecular orbital calculations were performed by using a minimum basis of Slater orbitals and the partial retention of diatomic differential overlap (PRDDO) approximation.[8] All computations assumed a fixed hexagonal ring (r_{CC} = 1.40 Å, r_{CH} = 1.08 Å) for the phenyl group. The coordinates of the reference configurations were then obtained as follows. The internal coordinates of the C(phenyl)–CRO moiety (R = H, CH_3) of benzaldehyde and acetophenone and the internal coordinates of the hydroxyl group of phenol were optimized, and the results are shown in Figure 2. Internal coordinates for the acyl and hydroxyl groups of *p*-hydroxybenzaldehyde and *p*-hydroxyacetophenone were then transferred from benzaldehyde, acetophenone, and phenol. The internal coordinates for the hydroxyl groups in the 2- and 6-positions of I and III were obtained from the optimized coordinates of the hydroxyl hydrogen in *o*-hydroxybenzaldehyde while the internal coordinates of the *p*-hydroxyl in III were held fixed at values transferred from phenol. Finally, the internal coordinates of the formyl group in I and III were transferred from benzaldehyde.

Experimental Results

^{1}H NMR spectra were obtained for both 2,6-dihydroxybenzaldehyde (I) and 2,6-dihydroxyacetophenone (II) at temperatures as low as −90 °C in deuterioacetone. Clear broadening of the hydroxyl peak of I was observed at −70 °C, and we predict coalescence at about −100 °C. However, the hydroxyl peak of II remained a sharp singlet down to −80 °C. On the assumption that the chemical shift difference, $\Delta\nu$, between the *o*-hydroxyl protons is the same for compounds I and III at their respective coalescence temperatures, $\Delta H^{\ddagger}$ for I is estimated to be about 6 kcal/mol.[9] $\Delta H^{\ddagger}$ for compound II is similarly estimated to be 6 kcal/mol or less.



I III

Figure 2. Internal coordinates for benzaldehyde, phenol, acetophenone, 2,6-dihydroxybenzaldehyde (I), and 2,4,6-trihydroxybenzaldehyde (III). The following internal coordinates were optimized [C(Ph) = C(phenyl), C′ = C(carbonyl), C(Me) = C(methyl)]: benzaldehyde, C(Ph)–C′, C′–O, C′–H, ∠C(Ph)–C′–O, ∠C(Ph)–C′–H; phenol, C(Ph)–O, O–H, ∠(Ph)–O–H; acetophenone, C′–C(Me), ∠C(Ph)–C′–C(Me), ∠C(Ph)–C′–O. Other coordinates listed either were transferred from previous calculations (see methods section) or were assumed idealized values.

Figure 1 depicts the spectra of 2,4,6-trihydroxybenzaldehyde (III) in deuterioacetone as well as the spectra generated from the classical two-site exchange theory. At −83 °C the hydroxyl region consists of three singlets (δ_a 12.59, δ_b 11.09, and δ_c 10.84). These chemical shifts were observed to move upfield with increasing temperature (i.e., $d\delta_i/dT < 0$). Since the exchange-broadened spectra clearly indicate that hydroxyl c is uninvolved in the intramolecular exchange, it is assigned to the 4-position. On the basis of the well-known downfield shift associated with hydrogen bonding, the resonance which appears furthest downfield is assigned to the *o*-hydroxyl proton which is involved in hydrogen bonding. The peak at 11.09 ppm is then assigned to the remaining *o*-hydroxyl proton. The smaller temperature coefficient observed for the chemical shift of the hydroxyl involved in hydrogen bonding (δ_a) gives rise to the positive coefficient for $\Delta\nu = \delta_a - \delta_b$ as noted in Methods.

As the temperature increases, the two-site exchange broadens the *o*-hydroxyl peaks as expected, and coalescence occurs at about −44 °C. Thereafter only a single exchange-averaged peak is observed for the *o*-hydroxyls. In addition to the effects of intramolecular exchange, the effects of intermolecular exchange become important above −25 °C. This is clearly evidenced by the broadening of the *p*-hydroxyl peak above this temperature. Due to this intermolecular exchange, the *o*-hydroxyl peak begins to broaden again at 0 °C, and the *p*-hydroxyl resonance disappears at temperatures near 30 °C.

Three distinct hydroxyl resonances (δ_a 14.28, δ_b 11.16, and δ_c 10.83) were also observed for IV at low temperature, and a similar exchange broadening accompanied an increase in temperature.

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[8] (a) Halgren, T. A.; Lipscomb, W. N. *J. Chem. Phys.* **1973**, *58*, 1569. (b) Halgren, T. A.; Kleier, D. A.; Hall, J. H.; Brown, L. D.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1978**, *100*, 5681.

[9] If $\Delta\nu$ for I at its coalescence temperature of 173 K is assumed to be the same as $\Delta\nu$ for III at its coalescence temperature of 229 K, then the rate constants at these two temperatures should also be equal. Assuming equal activation entropies, we have $\Delta H^{\ddagger}(\text{III})/229\text{ K} = \Delta H^{\ddagger}(\text{I})/173\text{ K}$. Using $\Delta H^{\ddagger}(\text{III})$ = 8.0 kcal/mol (see text), we estimate $\Delta H^{\ddagger}(\text{I}) \approx 6$ kcal/mol.

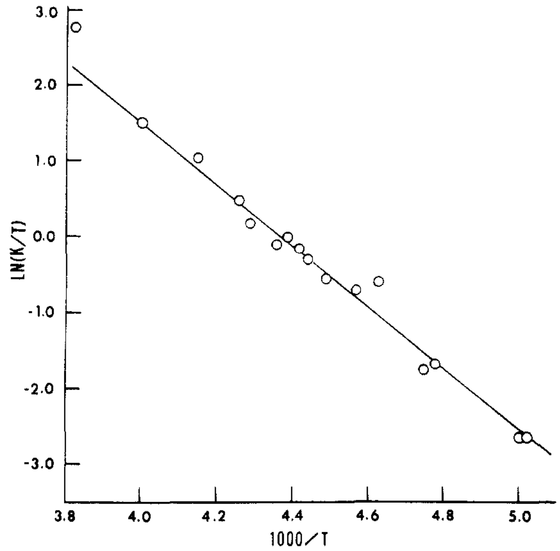


Figure 3. Eyring plot for 2,4,6-trihydroxybenzaldehyde.

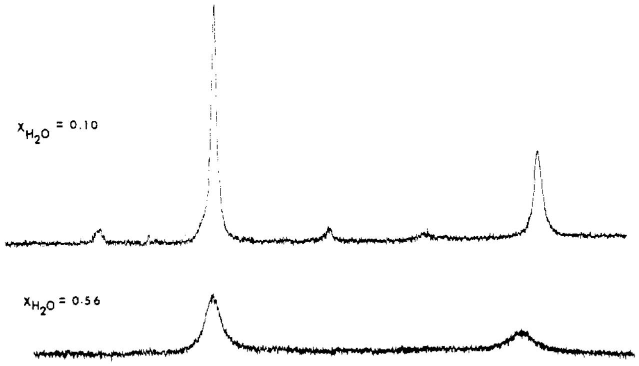


Figure 4. Hydroxyl region of ^1H NMR spectrum for IV at ambient temperature. X_{H_2O} is the molar ratio of water to IV.

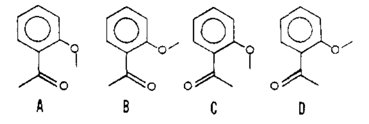
Weighted least-squares analysis of the Arrhenius plots for compounds III and IV yields activation parameters of E_a = 8.4 ± 0.3 kcal/mol and log A = 10.4 ± 0.3 for III and E_a = 7.3 ± .3 kcal/mol and log A = 10.3 ± 0.4 for compound IV. Analyses of the Eyring plots gave $\Delta H^{\ddagger}$ = 8.0 ± 0.4 kcal/mol and $\Delta S^{\ddagger}$ = −12 ± 2 cal/mol K for III and $\Delta H^{\ddagger}$ = 6.9 ± 0.3 kcal/mol and $\Delta S^{\ddagger}$ = −13 ± 2 cal/mol K for IV. A typical Eyring plot is illustrated in Figure 3.

In reasonably dry solvents intermolecular exchange does not significantly broaden the hydroxyl peaks until coalescence due to intramolecular exchange has been well established. In our samples, broadening due to intermolecular exchange is clearly evident for both the *p*- and *o*-hydroxy groups at temperatures about 25 °C above the coalescence temperatures for intramolecular exchange. By use of suitably dry solvents, it thus appears feasible to obtain kinetic information for intramolecular rearrangements involving hydroxyl groups by a line-shape analysis of the hydroxyl region of the ^1H NMR spectrum.

The rate of intermolecular exchange can be increased by the addition of water to the deuterioacetone solvent. This is most clearly illustrated in Figure 4 where the ambient-temperature spectra of IV are depicted at two different water concentrations. We note that addition of water broadens the resonance due to the *p*-hydroxyl group relatively more than that of the *o*-hydroxyl groups.

Theoretical Results

Rigid rotation of the acyl group in benzaldehyde and in acetophenone yielded calculated barrier heights of 6.1 and 5.6 kcal/mol, respectively. Similar rigid rotation in *p*-hydroxybenzaldehyde and in *p*-hydroxyacetophenone gave slightly enhanced barrier heights of 6.4 and 5.8 kcal/mol, respectively. The calculated barrier height for rigid rotation of the hydroxyl group in phenol was 6.3 kcal/mol.



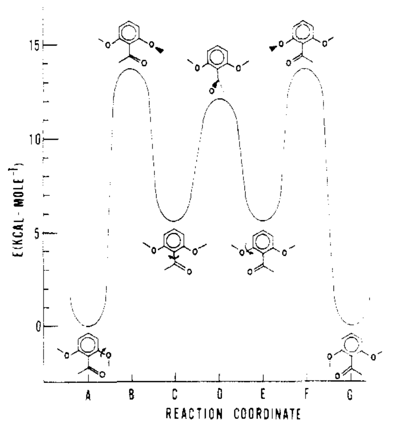


Figure 5. Potential energy curve for rotation of the formyl group in 2,6-dihydroxybenzaldehyde. Energies for structures A–G were calculated by using the PRDDO approximation.

Before investigating the rotation barriers in the 2,6-dihydroxy compounds, we performed calculations on the conformations of *o*-hydroxybenzaldehyde shown in Chart I. The relative energies of conformations A and B give an intramolecular hydrogen bond strength of 5.1 kcal/mol. Rotation of the formyl group by 180° from its position in reference conformation A yields conformation C. Due to the loss of the hydrogen bond and the steric repulsion between the formyl and hydroxyl hydrogens, conformation C is 12.2 kcal/mol higher in energy than reference conformation A. Rotating the hydroxyl group of conformation C by 180° to give D relaxes the steric repulsions, and the energy drops to 4.2 kcal/mol relative to reference conformation A.

Conformation D can be obtained from conformation A by simultaneous rotation of the hydroxyl and formyl groups. Even though simultaneous rotation in opposite senses helps to preserve the intramolecular hydrogen bond along the initial part of the pathway, simultaneous loss of π overlap with the aromatic ring by both groups makes this motion prohibitively expensive.[10] Thus, the lowest energy path connecting structures A and D is a two-step process (i.e., rotation of the hydroxyl group followed by rotation of the formyl group).

The results for *o*-hydroxybenzaldehyde suggest that the exchange of hydroxyl environments in compounds I–IV is a three-step process involving consecutive 180° rotations of the 2-OH, formyl, and 6-OH groups. The calculated potential energy curve for this process in I is shown in Figure 5, and the relative energies for conformations A–G are given in Table I. The rate-determining step for the

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(10) The 90° out-of-plane rotation of phenol's hydroxyl group costs 6.3 kcal/mol (Table II) and is accompanied by a decrease of 0.025 e in the overlap population[34] between the hydroxyl oxygen and the ring carbon. This decrease in atomic overlap population is largely due to the loss of overlap between the p_π orbitals on the two centers. Passage from planar to perpendicular phenol decreases the p_π atomic overlap population by 0.043 e, and this decrease is only partially compensated by increases in the overlap between atomic orbitals lying in the plane of the aromatic ring.

Table I. Energetic Results[a] of PRDDO Calculations on Compounds I and III

compd	structure[b] A (G)	B (F)	C (E)	D
I	0.0	13.6	5.6	12.1
III	0.0	14.7	6.5	13.3

[a] All results in kilocalories/mole. [b] Refer to Figure 5.

Table II. Summary of Computed Barrier Heights

compd	barrier height, kcal/mol
benzaldehyde	6.1
acetophenone	5.6
phenol	6.3[a]
p-hydroxybenzaldehyde	6.4[b]
p-hydroxyacetophenone	5.8[b]
2,6-dihydroxybenzaldehyde (I)	13.6[c] (6.5)[d]
2,4,6-trihydroxybenzaldehyde (III)	14.7[c] (6.8)[d]

[a] Barrier height for rotation of hydroxyl group. [b] Barrier for rotation of the acyl group. [c] Barrier for rotation of the *o*-hydroxyl which is initially hydrogen bonded to the carbonyl oxygen (process A → C in Figure 5). [d] Value in parentheses is for a rotation of the acyl group following the 180° rotation of the hydroxyl group to which it is potentially hydrogen bonded (process C → E in Figure 5).

Table III. Free Energies of Activation at the Coalescence Temperature for Some Substituted Phenyl Ketones and Formaldehydes

substituents	$\Delta G^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/K mol	$\Delta H^{\ddagger}$, kcal/mol
	A. Benzaldehydes		
4-NMe_2	10.5,[b] 10.8,[a] 10.7,[d] 10.5[e]	1.7,[b] 1.9[d]	11.0,[b] 11.1[d]
4-OMe	8.7,[b] 9.2,[a] 9.4[e]		
4-Me	8.2,[b] 8.5[d]		
4-$CHMe_2$	7.8[b]		
4-F	8.4[d]		
4-Cl	7.8[b]		
4-H	7.6,[b] 7.9,[a] 7.7[f]	3.6[f]	8.3[f]
4-CF_3	6.8[b]		
2,6-OH (I)	~8[g]	~−12	~6
2,4,6-OH (III)	10.8[g]	−12	8.0
	B. Acetophenones		
4-NMe_2	8.3,[c,d] 8.5[e]		
4-OMe	6.7,[c] 6.6,[d] <7.3[e]	−3[c]	6.3[c]
4-Me	5.9[c]		
4-F	5.9[c]		
4-Cl	5.4[c]		
4-Br	5.4[c]		
4-H	5.4[c]		
4-CF_3	4.7[c]		
4-NO_2	4.4[c]		
2,6-OH (II)	8	−13	<6
2,4,6-OH (IV)	9.7[g]	−13	6.9

[a] Reference 11. [b] Reference 17. [c] Reference 18. [d] Reference 19. [e] Reference 12. [f] Reference 16. [g] This work.

overall process is thus predicted to be the 180° rotation of the hydrogen-bonded hydroxyl group. Similar results are also obtained for III. However, the additional hydroxyl group in the para position appears to increase all three rotation barriers along the reaction pathway (Table I). Calculations on compounds II and IV were complicated by additional degrees of freedom and are not reported here.

The theoretical barrier heights for all the compounds studied are summarized in Table II.

Discussion

Hindered rotation has been studied in a number of neutral benzaldehydes and acetophenones by using NMR line-shape analysis.[3,11-19] Previous ^1H NMR studies[3,11,12] have for the most part dealt with the effects of para substitution on the rotation barrier of the acyl group and have focused on the aromatic region of the spectrum. Due to the relatively low barriers for acyl rotation and the small chemical shift differences between the aromatic protons whose environments are exchanged, line-broadening effects cannot be observed over large temperature ranges, and, in many cases, a frozen spectrum is unattainable. Thus, activation parameters are difficult to measure from the ^1H NMR spectra of these compounds. Protonation of the carbonyl moiety raises the barriers into a range more accessible to NMR measurement.[13-15] Alternatively, the barriers in the neutral compounds can be studied by using ^{13}C as the observed nucleus,[16-19] thereby taking advantage of the inherently larger chemical shift differences between nonequivalent ^{13}C nuclei in the aromatic ring.

Our approach has been to take advantage of the large chemical shift differences associated with different degrees of hydrogen bonding of hydroxyl protons. To the best of our knowledge this is the first line-shape study of an intramolecular rearrangement which focuses on the hydroxyl region of the ^1H NMR spectrum. In the cases at hand, the chemical shift difference between the *o*-hydroxyl protons which exchange environments is between 1.5 and 3.0 ppm. For the purposes of determining accurate activation parameters, these large chemical shift differences are advantageous since line broadening can be studied over a large temperature range. However, the approach is complicated by large inherent temperature coefficients of the hydroxyl resonances, and accuracy is limited by the simplicity of the spectra. Fortunately, the anticipated complication associated with line broadening due to intermolecular exchange can be avoided in dry solvents because under these conditions the inter- and intramolecular exchange processes cause line broadening over distinct temperature ranges.

Our experimental results for activation parameters are compared with those of similar compounds in Table III. Our activation free energies are similar to those reported for other substituted benzaldehydes and acetophenones and show the expected barrier enhancement due to para substitution (e.g., compare the barriers for I and II with those for III and IV, respectively). However, in light of the theoretical calculations it is clear that the exchange

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[11] Anet, F. A. L.; Ahmad, M. *J. Am. Chem. Soc.* **1964**, *86*, 119.

[12] Klinck, R. E.; Marr, D. H.; Stothers, J. B. *Chem. Commun.* **1967**, 409.

[13] Sommer, J. M.; Jost, R. P.; Drakenberg, T. *J. Magn. Reson.* **1976**, *21*, 93.

[14] Barthelemy, J.; Jost, R.; Sommer, J. *Org. Magn. Reson.* **1978**, *11*, 438.

[15] Barthelemy, J.; Jost, R.; Sommer, J. *Org. Magn. Reson.* **1978**, 443.

[16] Lunazzi, L. *Tetrahedron Lett.* **1975**, 1205.

[17] Drakenberg, T.; Jost, R.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1974**, 1011.

[18] Drakenberg, T.; Sommer, J. M.; Jost, R. *Org. Magn. Reson.* **1976**, *8*, 579.

[19] Grindley, T. B.; Katritzky, A. R.; Topsom, R. D. *J. Chem. Soc., Perkin Trans. 2* **1975**, 443.

Table IV. Selected Bond Distances and Angles for Substituted Phenyl Ketones and Formaldehydes

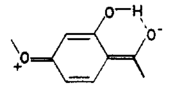
compd	C(phenyl)-C(carbonyl), Å	C(carbonyl)-O, Å	C(carbonyl)-C(methyl), Å	C(phenyl)-C(carbonyl)-O, deg
p-hydroxybenzaldehyde[29]	1.46	1.22		126
2-nitrobenzaldehyde[30]	1.51	1.20		122
2-hydroxy-3-methoxybenzaldehyde[31]	1.43	1.23		123
p-hydroxyacetophenone[32]	1.48	1.20	1.48	120
p-aminoacetophenone[33]	1.47	1.21	1.50	121

process in the *o*-hydroxyphenyl ketones and formaldehydes is more complicated than a simple rotation of an acyl group, and it is also clear that the rate-determining hydroxyl rotations predicted by the theory have barriers substantially exceeding those observed. Of course, the theoretical results refer to the gas phase, and the discrepancy between theory and experiment argues for rate enhancements caused by the solvent.

The deuterioacetone used as a solvent apparently competes successfully with the carbonyl moiety of the hydroxyphenyl ketone for the hydrogen bond given by the *o*-hydroxyls. Since structures B–F (Figure 5) are capable of forming one more intermolecular hydrogen bond than structures A and G, intermolecular hydrogen bonding would lower all barriers in Figure 5 as well as the energy of the intermediates B and E relative to A and G.

Of course, deuterioacetone is not expected to form a hydrogen bond that is significantly stronger than the intramolecular one and therefore will not firmly establish structures C and E as more stable than structures A and G (Figure 5). Drago et al.[20] have experimentally determined the enthalpy of formation for an acetone–phenol complex to be 3.3 ± 0.5 kcal/mol while our computed intramolecular hydrogen bond strengths are on the order of 5 kcal/mol. Thus, in the deuterioacetone solvent a potential energy diagram may be operative which is qualitatively similar to that in Figure 5, but with solvent-modified heights for the peaks and troughs. Structures B–F would be differentially stabilized relative to structures A and G, perhaps by as much as 3–5 kcal/mol. The solvent effect will thus bring the effective barrier heights more in line with those determined from the line-shape analysis. It is interesting to observe that the ordering of solvent as implied by its participation in the transition state described above is consistent with the negative activation entropy observed for the exchange process (Table III).

The observed enhancement of the activation enthalpy upon substitution of a third hydroxyl in the para position of the 2,6-dihydroxy compounds is consistent with the theoretically predicted increase of this barrier. (Compare the calculated barrier reported in Table II for I with that of III.) However, the usual explanation of this phenomenon in terms of a mesomeric increase in the double bond character for the C(phenyl)–C(carbonyl) bond may be only part of the story. Not only will the mesomeric interaction increase the double bond character of the C(phenyl)–C(carbonyl) bond but it should also increase the strength of the intramolecular hydrogen bond, thereby enhancing the barrier for the hydroxyl rotation as well as that for the acyl rotation:



Actually, the mesomeric effect on the barrier to simple acyl rotation is rather small. This is demonstrated by our theoretical values for the acyl rotational barrier with the *o*-hydroxyl groups "pinned back" in such a manner that intramolecular hydrogen bonding is not possible (see Table II, values in parentheses).

Returning to the parent compounds (benzaldehyde, acetophenone, and phenol), our theoretical value for the benzaldehyde rotational barrier (6.1 kcal/mol) is somewhat higher than the microwave[21] and infrared[22] values of 4.90 and 4.66 kcal/mol, respectively, but lower than the NMR values reported in Table III. For acetophenone, the theoretical barrier (5.6 kcal/mol) is once again significantly higher than that given by infrared studies[23] (3.1 kcal/mol) and is almost identical with the NMR results (Table III). Our theoretical barrier for rotation of the hydroxyl group in phenol is 6.3 kcal/mol, and this is larger than the experimental values of 3.28, 3.36 (microwave),[24,25] and 3.47 kcal/mol (infrared).[26]

The barrier heights computed by using the PRDDO approximation for benzaldehyde, acetophenone, and phenol (Table II) compare favorably with those obtained by using the STO-3G procedure.[27] For comparison, the STO-3G calculations yielded 6.6, 4.4, and 5.2 kcal/mol for the barriers in benzaldehyde, acetophenone, and phenol, respectively. The modest differences between the PRDDO and STO-3G results for acetophenone may result from the use of partially optimized geometries in the former case and standard geometries in the latter.

The partially optimized geometries for the molecules in Figure 2 can be compared with several geometries determined by diffraction techniques.[28-33] X-ray diffraction studies of phenol gave a C–O distance ranging from 1.35 to 1.40 Å in good agreement with our value of 1.38 Å.[28] In general, our calculated bond distances for the C(phenyl)–C(carbonyl), C(carbonyl)–O, and C(carbonyl)–C(methyl) bonds (Figure 2) are longer than those determined from diffraction studies for comparable compounds (Table IV). The values calculated for the C(phenyl)–C(carbonyl)–O bond angles are larger for the benzaldehydes

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(20) Drago, R. S.; Wayland, B.; Carlson, R. C. *J. Am. Chem. Soc.* **1963**, *85*, 3125.

(21) Kakar, R. K.; Rinehart, E. A.; Quade, C. R.; Kojima, T. *J. Chem. Phys.* **1970**, *52*, 3803.

(22) Fateley, W. G.; Harris, R. K.; Miller, F. A.; Witkowski, R. E. *Spectrochim. Acta* **1965**, *21*, 231.

(23) Miller, F. A.; Fateley, W. G.; Witkowski, R. E. *Spectrochim. Acta, Part A* **1967**, *23*, 891.

(24) Forest, H.; Dailey, B. P. *J. Chem. Phys.* **1966**, *45*, 1736.

(25) Pedersen, T.; Larsen, N. W.; Nygaard, L. *J. Mol. Struct.* **1969**, *4*, 59.

(26) Bist, H. D.; Williams, D. R. *Bull. Am. Phys. Soc.* **1966**, *11*, 826.

(27) Hehre, W. J.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 1496.

(28) Wyckoff, R. W. G. "Crystal Structures", 2nd ed.; Interscience: New York, 1969; Vol. 6.

(29) Iwasaki, F. *Acta Crystallogr., Sect. B.* **1977**, *B33*, 1646.

(30) Coppens, P. *Acta Crystallogr.* **1964**, *17*, 573.

(31) Iwasaki, F.; Tonaka, I.; Aihara, A. *Acta Crystallogr., Sect. B* **1976**, *B32*, 1264.

(32) Vainshtein, B. K.; Lobanova, G. M.; Gurskaya, G. V. *Kristallografiya* **1974**, *19*, 531.

(33) Haisa, M.; Kashino, S.; Yuasa, T.; Akigawa, K. *Acta Crystallogr., Sect. B* **1976**, *B32*, 1326.

than for the acetophenones, and this seems consistent with the experimental results given in Table IV. Where comparisons can be made with neutron diffraction results, the theoretically predicted positions of the hydrogen atoms agree quite well. Thus, for *o*-nitrobenzaldehyde[32] neutron diffraction gives C(carbonyl)–H = 1.12 Å and H–C(carbonyl)–O = 122°, while our theoretical optimization for benzaldehyde gives 1.11 Å and 121°, respectively.

Assignment of proton resonances in the 2,4,6-trihydroxy compounds was simplified by the nature of the exchange broadening. In both cases the upfield peak which was not broadened by the intramolecular exchange process could be assigned to the *p*-hydroxyl while the resonance furthest downfield could be assigned to the *o*-hydroxyl which is involved in the hydrogen bond. The latter assignment is based on the presumed deshielding of a proton involved in a hydrogen bond and is consistent with the Mulliken atomic charges[34] calculated for the hydroxyl hydrogens in the most stable conformation of III. The atomic charge for the hydroxyl hydrogen involved in the hydrogen bond is 0.240 e, which is to be compared with the less positive values of 0.206 and 0.202 e for the hydroxyl hydrogens in the para position and remaining ortho position, respectively. The near equality of charges on the latter two protons is consistent with the small chemical shift difference between these two hydroxyl protons. We also note a small but significant overlap population (0.045 e) consistent with a hydrogen bond between the carbonyl oxygen and one of the *o*-hydroxyl hydrogens.

The chemical shifts reported here for 2,4,6-trihydroxyacetophenone (IV) can be compared with chemical shifts of 12.85 and 9.64 ppm which have been reported[35] for the hydroxyls of 2,4-dihydroxyacetophenone. The latter values refer to an acetone solvent at ambient temperature and are about 1.3 ppm upfield from our values for the corresponding hydroxyl groups of IV measured at $\sim$−90 °C. The discrepancy may be due in part to the rather sizable temperature coefficients of these chemical shifts. Large chemical shift differences for phenolic hydroxyls have also been reported[36] for 1-(2,5-dihydroxyphenyl)butanone in CCl_4. The 2-hydroxy proton which is involved in hydrogen bonding absorbs at 12.02 ppm while the hydrogen at the 5-position absorbs at 5.63 ppm. The chemical shift and line shape of this latter hydroxy proton are very sensitive to environmental factors while those of the hydroxy proton involved in the intramolecular hydrogen bond are less so. This behavior is consistent with our observations concerning the relative temperature and solvent dependence of the hydroxy resonances of compounds III and IV.

Summary

Detailed analysis of the exchange-broadened ^{1}H NMR spectra of 2,4,6-trihydroxy derivatives of benzaldehyde and acetophenone yield activation enthalpies of 8.0 and 6.9 kcal/mol, respectively, for the exchange of the *o*-hydroxyl environments. Slightly lower barriers are surmised for the corresponding 2,6-dihydroxy compounds. Theoretical calculations using approximate molecular orbital theory indicate that the exchange process may be more complex than a simple rotation of an acyl group. The exchange may be a three-step process involving a rate-limiting initial rotation of the hydrogen-bonded hydroxyl group. The theoretical barriers are substantially higher than the experimental values. This is likely to be due to the tendency of a minimum basis set to overestimate hydrogen bond strengths as well as to the neglect of solvent interactions in the theoretical calculations.

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Registry No. I, 387-46-2; II, 699-83-2; III, 487-70-7; IV, 480-66-0; benzaldehyde, 100-52-7; acetophenone, 98-86-2; phenol, 108-95-2; *p*-hydroxybenzaldehyde, 123-08-0; *p*-hydroxyacetophenone, 99-93-4; *p*-(dimethylamino)benzaldehyde, 100-10-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-methylbenzaldehyde, 104-87-0; *p*-isopropylbenzaldehyde, 122-03-2; *p*-fluorobenzaldehyde, 459-57-4; *p*-chlorobenzaldehyde, 104-88-1; *p*-(trifluoromethyl)benzaldehyde, 455-19-6; *p*-(dimethylamino)acetophenone, 2124-31-4; *p*-methoxyacetophenone, 100-06-1; *p*-methylacetophenone, 122-00-9; *p*-fluoroacetophenone, 403-42-9; *p*-chloroacetophenone, 99-91-2; *p*-bromoacetophenone, 99-90-1; *p*-(trifluoromethyl)acetophenone, 709-63-7; *p*-nitroacetophenone, 100-19-6; 2-nitrobenzaldehyde, 552-89-6; 2-hydroxy-3-methoxybenzaldehyde, 148-53-8; *p*-aminoacetophenone, 99-92-3.

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(34) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.
(35) De Keukeleiere, D.; Verzele, M. *Tetrahedron* **1970**, *26*, 385.
(36) Pala, G. *Nature (London)* **1964**, *204*, 1190.

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gem-Dimethyl Effect in a Grignard Reagent Cyclization–Cleavage Rearrangement

E. Alexander Hill,* Daniel C. Link, and Peter Donndelinger

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

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(2,2-Dimethyl-4-penten-1-yl)magnesium bromide (1) is in equilibrium with its cyclic isomer, [(3,3-dimethylcyclobutyl)methyl]magnesium bromide (2). The equilibrium constant for this cyclization has a value of 2×10^{-3}. The *gem*-dimethyl substitution leads to an increase of a factor of about 22 in the equilibrium constant and also retards the rate of cleavage of 2. The sources of the *gem*-dimethyl effect in this system are discussed.

Because of the strain inherent in the small ring, ring-cleavage rearrangements of the cyclobutylmethyl[1] (k'_0 in eq 1) and cyclopropylmethyl[2] Grignard reagents proceed essentially to completion.[3] Although the equilibrium

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