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Thermochemistry of Carbonyl Reactions. 6. A Study of Hydration Equilibria

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Abstract: The hydration of carbonyl compounds, along with hemiketal and ketal or hemiacetal and acetal formation, has been studied both experimentally and theoretically. The heats of hydrolysis of some acetals and ketals were determined calorimetrically. Equilibrium constants for hydrate, hemiacetal, and acetal formation were determined via NMR spectroscopy, and heats of reaction were obtained from the change in equilibrium constants with temperature. Calculations of the hydration energies were made using a set of theoretical models through MP2/6-311++G**//HF/6-31G* for formaldehyde, acetaldehyde, acetone, cyclopropanone, and cyclobutanone and through MP2/6-31G**//HF/6-31G* for crotonaldehyde, bicyclo[1.1.1]pentan-2-one, cyclohexanone, 7-norbornanone, methyl acetate, chloral, and fluoral. Additional calculations were carried out using the CBS-4 theoretical model. The energies of hemiacetalization and acetalization also were calculated for formaldehyde, acetaldehyde, and acetone. The origin of the changes in hydration energies was analyzed using group transfer reactions of formaldehyde with an alkane to give the substituted carbonyl compound and of formaldehyde hydrate with an alkane to give the substituted carbonyl hydrate.

1. Introduction

The addition of a nucleophile to a carbonyl group is one of the most important reactions in chemistry and biochemistry. Despite its importance, there are not many data concerning the effect of substituents on the thermochemistry of these additions.[1] In many cases, addition leads to a reactive intermediate that rapidly forms the products of the reaction, and therefore the intermediate is not easily studied. One of the few types of reactions that leads to a stable addition product is hydration, and the related processes of hemiacetal and acetal formation. Some information concerning these reactions is available.

Acetaldehyde is 60% hydrated in aqueous solution, whereas acetone is only about 0.1% hydrated.[2] Cyclopropanone[3] and chloral[4] form quite stable hydrates, but methyl acetate does not give any evidence for hydrate formation.[5] What is the origin of this difference in behavior? It is possible that the difference between formaldehyde (essentially completely hydrated),[1] acetaldehyde, and acetone results from stabilization of the carbonyl group by alkyl substitution[6] in much the same fashion as is found with C=C double bonds.[7] The hydration of cyclopropanone may be a result of the strain incorporated into the three-membered ring by a trigonal center, which would be relieved by hydrate formation. Methyl acetate may be stabilized by "ester resonance" leading to its low degree of hydration, and with fluoral and chloral, the F_3C and Cl_3C groups having positively charged carbons may destabilize the carbonyl group[8] more than the hydrate. These are all reasonable explanations, but there is little direct evidence for any of them.

We have initiated a study of carbonyl hydration by carrying out some additional measurement and by using theoretical calculations. The compounds studied experimentally were acetone, cyclobutanone, cyclopentanone, cyclohexanone, 7-norbornanone, acetaldehyde, butyraldehyde, crotonaldehyde, and chloral. The compounds studied theoretically were formaldehyde (**1**), acetaldehyde (**2**), crotonaldehyde (**3**), acetone (**4**), cyclopropanone (**5**), cyclobutanone (**6**), cyclohexanone (**7**), bicyclo[1.1.1]pentan-2-one (**8**), 7-norbornanone (**9**), fluoral (**10**), chloral (**11**), and methyl acetate (**12**) as well as the corresponding hydrates (**1a−12a**), hemiacetals (**1b, 2b, 4b**), and acetals (**1c, 2c, 4c**). The experimental data will be presented first, followed by the results of the theoretical calculations and an analysis of the origin of the substituent effects.

2. Experimental Studies of Equilibrium Constants for Hydrate, Hemiacetal, and Acetal Formation

The enthalpy change resulting from addition to a carbonyl may be studied either via reaction calorimetry or by measuring equilibrium constants as a function of temperature. The latter method is generally less accurate than the former, but it is not constrained by the need to isolate all of the compounds involved in pure form. Thus, it may be applied to hydration and hemiacetalization equilibria even though the hydrates and hemiacetals are generally not sufficiently stable to be isolated out of solution. The one general case in which reaction calorimetry may effectively be used is the hydrolysis of acetals and ketals. The measurement of ΔH_r in this fashion would provide a check on the results obtained via equilibrium constant measurements. The results of the equilibrium constant study will be presented first, followed by the calorimetric data.

The earliest reliable thermochemical data for these equilibria were reported by Bell and his co-workers.[9] Many other studies of hydrate and hemiacetal formation have been reported using UV spectroscopy[10] and NMR spectroscopy.[11] Both of these methods have presented experimental problems. The UV

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Table 1. Equilibrium Constants As Determined by NMR

reactant	K(10 °C)[a]	K(25 °C)	K(40 °C)
acetaldehyde			
$+D_2O$	2.24	1.25	0.816
$+CD_3OD$	34.9	18.0	9.18
$+CD_3OD + D^+$	acetal formed completely		
n-butyraldehyde			
$+D_2O$	1.27	0.80	0.478
$+CD_3OD$	24.7	13.7	7.45
$+CD_3OD + D^+$	acetal formed completely		
crotonaldehyde			
$+D_2O$	no observable reaction		
$+CD_3OD$	2.07×10^{-2}	1.51×10^{-2}	1.30×10^{-2}
$+CD_3OD + D^+$	7.54×10^{-2}	4.39×10^{-2}	2.87×10^{-2}
acetone			
$+D_2O$	2.43×10^{-3}	1.75×10^{-3}	1.36×10^{-3}
$+CD_3OD$	9.69×10^{-3}	7.32×10^{-3}	5.09×10^{-3}
$+CD_3OD + D^+$	1.33×10^{-2}	7.68×10^{-3}	4.42×10^{-3}
cyclobutanone			
$+D_2O$	2.59×10^{-3}	2.18×10^{-3}	
$+CD_3OD$	6.29×10^{-2}	4.47×10^{-2}	2.96×10^{-2}
$+CD_3OD + D^+$	0.493	0.248	0.138
cyclopentanone			
$+D_2O$	no reaction observed		
$+CD_3OD$	no reaction observed		
$+CD_3OD + D^+$	1.09×10^{-2}	7.45×10^{-3}	4.91×10^{-3}
cyclohexanone			
$+D_2O$	4.59×10^{-2}	3.06×10^{-2}	1.85×10^{-2}
$+CD_3OD$	0.208	0.108	0.064
$+CD_3OD + D^+$	0.363	0.148	0.075
7-norbornanone			
$+D_2O$	4.13	2.07	1.08
$+CD_3OD$	84.6	28.5	13.2
$+CD_3OD + D^+$	complete reaction observed		

[a] Nominal temperature; the exact temperatures are available in the Ph.D. thesis of K.M.M.

method makes the assumption that solvents will not affect the extinction coefficient of the carbonyl compound, and the resolution of the earlier NMR spectrometers often made it difficult to obtain accurate integrals for individual bands. The limited dynamic range of the NMR spectrometers also presented a problem.

Hine and Redding have reported that the hydrate of acetone may be observed via NMR spectroscopy in aqueous solution by comparing the hydrate signal with the ^{13}C satellite from the ketone.[12] We have confirmed his observation and have obtained essentially the same equilibrium constant. This technique made it possible to examine acetone, cyclobutanone, cyclopentanone, cyclohexanone, and 7-norbornanone, and the use of a high-field NMR spectrometer considerably simplified the analysis. Butyraldehyde and crotonaldehyde were also compared. The equilibrium constants were obtained as a function of temperature, giving the data summarized in Table 1. The enthalpies and free energies of reaction derived from these data are summarized in Table 2. In the cases where only one species could be observed at equilibrium, an estimate was made of the minimum or maximum value of the equilibrium constant, and an estimated limit of the reaction enthalpy is given assuming ΔS by analogy with the other compounds. The estimated uncertainty in the equilibrium constants is ±10%, and the estimated uncertainty in the temperature is ±0.3°. This leads to an uncertainty in ΔG of ±0.1 kcal/mol and in ΔH of ±0.5 kcal/mol.

It is known that hemiacetals and acetals have larger formation constants than hydrates, but few quantitative data are available. Therefore we also have determined the equilibrium constants for the formation of hemiacetals and acetals derived from the above compounds. They were studied in methanol-d_4 solution. In neutral solution, the hemiacetals were rapidly formed, and in the presence of an acid catalyst, they were converted to acetals.

The present results are compared with the data available from the literature in Table 3. There is very good agreement between the present and previous results for acetaldehyde, acetone, and cyclopentanone. Our previous calorimetric work indicates that the heats of reaction of acetaldehyde and butyraldehyde going to acetals are essentially the same,[13] and the same is probably true for hydrate formation. Thus, the literature value for the reaction of butyraldehyde with water is probably incorrect.

It might be noted that our entropy of ketal formation for cyclohexanone appears to be unusually negative as compared with the other cyclic ketones and leads to an enthalpy of reaction that will be seen to be too negative in comparison with a direct calorimetric measurement. If the entropy of reaction were −25 eu as found with the other compounds, the enthalpy of reaction would be −7.2 kcal/mol, which would then be in agreement with the literature value. It will be seen that this value is also in good agreement with a direct calorimetric measurement. Therefore, we shall use the literature value in the following discussion.

3. Calorimetric Studies

We have previously measured the heats of hydrolysis of a number of acetals and ketals,[13] including acetaldehyde, acetone,

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Table 2. Thermochemical Parameters Derived from the NMR Study[a]

reactant	ΔH_r	ΔG_r	ΔS_r
acetaldehyde			
+ D_2O	−5.30	−0.18	−17.2
+ CD_3OD	−7.14	−1.67	−18.3
+ CD_3OD + D^+	[≤9.1]	[≤−2.2]	[−23]
n-butyraldehyde			
+ D_2O	−5.36	0.16	−18.5
+ CD_3OD	−6.44	−1.51	−16.5
+ CD_3OD + D^+	[≤9.1]	[≤−2.2]	[−23]
crotonaldehyde			
+ D_2O	[>−2.5]	[>4.4]	[−23]
+ CD_3OD	−2.33	2.46	−16.1
+ CD_3OD + D^+	−4.79	1.84	−22.2
acetone			
+ D_2O	−3.09	3.74	−22.9
+ CD_3OD	−3.36	2.95	−21.2
+ CD_3OD + D^+	−5.85	2.88	−29.3
cyclobutanone			
+ D_2O	−2.08	3.65	−19.2
+ CD_3OD	−3.94	1.87	−19.5
+ CD_3OD + D^+	−6.71	0.83	−25.3
cyclopentanone			
+ D_2O	[>−2.5]	[>4.4]	[−23]
+ CD_3OD	[>−2.5]	[>4.4]	[−23]
+ CD_3OD + D^+	−3.93	2.92	−23.0
cyclohexanone			
+ D_2O	−4.97	2.10	−23.7
+ CD_3OD	−6.41	1.31	−25.9
+ CD_3OD + D^+	−8.66	1.12	−32.8
7-norbornanone			
+ D_2O	−7.34	−0.42	−23.2
+ CD_3OD	−9.19	−2.03	−24.0
+ CD_3OD + D^+	[≤8.7]	[≤−1.9]	[−23]

[a] ΔH and ΔG are given in kcal/mol, ΔS is given in cal/(mol deg^{-1}).

Table 3. Comparisons with Previous Results (kcal/mol at 25 °C)

reactants	ΔH_r (this work)	ΔH_r (lit.)[b]
acetaldehyde + D_2O	−5.30	−5.7, −5.1
n-butyraldehyde + D_2O	−5.36	−7.1
acetone + CD_3OD + H^+	−5.85	−5.4
cyclohexanone + CD_3OD + D^+	−8.66 (−7.2)[a]	−7.3
cyclopentanone + CD_3OD + D^+	−3.92	−4.0

[a] See text. [b] Hydrates, ref 2; ketals, ref 10.

and butyraldehyde, and in the present study, we also have carried out such measurements for the hydrolysis of the ketals from cyclobutanone, cyclopentanone, and cyclohexanone, as well as 7-norbornanone and crotonaldehyde. The heat of hydration of chloral was also measured.

In each case, the enthalpy of reaction of the pure ketal or acetal with water in the presence of an acid catalyst was measured in either dioxane−water or methanol−water. The enthalpies of solution of the products and of water in the reaction solvent also were measured, allowing the calculation of the overall heat change for all compounds in the pure liquid form. The data are summarized in Tables 4 and 5.

In order to compare the results of these measurements with the theoretical calculations which refer to the gas phase, it is necessary to correct for the difference between the heats of vaporization of the reactants and products. In some cases the heats of vaporization are known,[14] and in other cases they were obtained by measuring the vapor pressure as a function of temperature and correcting the resulting ΔH_v to 298 °C. The details of the measurements are given in the Experimental Section, and the heats of vaporization are given in Table 6. The heats of hydrolysis calculated for the gas phase are given in Table 5. The heats of formation of the acetals and ketals could be derived from these data and the known heats of formation of the carbonyl reactants, water and methanol. We were interested in seeing how well the molecular mechanics program MM3[15] would reproduce these heats of formation, and the predicted values are given in the last column of Table 5. It can be seen that the agreement is quite good.

One interesting comparison may be made at this point. The difference in enthalpy of forming the acetals of butyraldehyde and crotonaldehyde is 5.0 kcal/mol. The less favorable acetal formation with crotonaldehyde is presumably due to resonance stabilization of the carbonyl group via its interaction with the double bond, and the reactions provide a measure of this stabilization.

In order to allow a comparison of the liquid phase calorimetric data with the results of the NMR experiments, a correction is required for the heats of solution of all of the components in methanol. The needed heats of solution were measured, and the corrected values are given in Table 7. It can be seen that the two sets of data are in good accord.

The heat of hydration of chloral was measured in the same fashion, but here it was not possible to correct the result to the gas phase because the heat of vaporization of chloral hydrate cannot be measured experimentally since it thermally reverts to chloral and water. The heat of reaction of chloral with water was −11345 ± 19 cal/mol, and the heat of solution of chloral hydrate was 1026 ± 12 cal/mol. Thus, the heat of the reaction

$$Cl_3CCHO(l) + H_2O(l) \rightarrow Cl_3CCH(OH)_2(c)$$

is −12.37 ± 0.02 kcal/mol. The heat of fusion of chloral hydrate was found to be 6.98 ± 0.03 kcal/mol. The heat of reaction with all compounds in the pure liquid state is then −5.39 ± 0.04 kcal/mol.

4. Theoretical Calculations

We were interested in comparing the experimental data with the results of theoretical calculations which might allow an insight into the factors that control the degree of hydration. The compounds were studied using RHF/6-31G* optimized geometries. In some cases the 6-31G* optimized geometries were available,[16] and in the others optimization was carried out giving the energies summarized in Table 8. There were no conformational problems associated with the carbonyl compounds. It is known that the lower energy conformers for acetaldehyde and acetone have a methyl hydrogen eclipsed with the carbonyl group.[17] Cyclobutanone was found to be planar. Methyl acetate prefers the Z conformation and has an acetate methyl hydrogen eclipsed with the carbonyl.[18] Two conformers for fluoral were examined, with a fluorine either eclipsed or staggered with respect to the carbonyl group. The former was found to have the lower energy.

It was necessary to take the anomeric effect into account with the diols, hemiacetals and acetals.[19] With the symmetrically substituted hydrates of formaldehyde, acetone, cyclopropanone, bicyclo[1.1.1]pentan-2-one, and 7-norbornanone, the hydrate

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Table 4. Results of Calorimetric Studies: Enthalpies of Hydrolysis of Methyl Acetals and Ketals[a,b]

compound	reaction medium	carbonyl cmpd ΔH(soln), cal/mol	ketal or acetal ΔH(hydrol), cal/mol
acetone	0.001 M H^+, 65% dioxane	67 ± 2 (3)	5013 ± 23 (5)
	0.1 M H^+, 65% dioxane	4 ± 3 (4)	4930 ± 50 (3)
crotonaldehyde	0.25 M H^+, 50% methanol	687 ± 32 (6)	4016 ± 27 (4)
cyclobutanone	0.1 M H^+, 65% dioxane	560 ± 59 (6)	6664 ± 33 (5)
cyclopentanone	0.001 M H^+, 65% dioxane	543 ± 5 (5)	4407 ± 36 (6)
cyclohexanone	0.001 M H^+, 65% dioxane	812 ± 9 (5)	7730 ± 30 (5)
7-norbornanone	0.1 M H^+, dry methanol	−11500 ± 500 (7)	923 ± 14 (3)

[a] The enthalpy of solution of methanol was −104 ± 2 (6) in 0.001 m H^+ in 65% dioxane, −88 ± 6 (3) in 0.1 M H^+ in 65% dioxane, and −267 ± 3 (2) in 0.25 M H^+ in 50% methanol. The enthalpy of solution of water was −225 ± 2 (7) in 0.001 M H^+ in 65% dioxane, −212 ± 4 (2) in 0.1 M H^+ in 65% dioxane, −199 ± 6 (2) in 0.25 M H^+ in 50% methanol, and −1636 ± 7 (4) in 0.1 M H^+ in dry methanol. [b] The number of runs is given in parentheses. The error is given as two times the standard deviation of the mean ($2\bar{s}$).

Table 5. Enthalpies of Methyl Acetal and Ketal Formation (kcal/mol at 25 °C)

	ΔH_r		ΔH_f(acetal or ketal)		
compound	liquid phase	gas phase	liquid phase	gas phase	MM3[a]
acetaldehyde	−8.57 ± 0.02	−14.8 ± 0.3	−100.4 ± 0.4	−93.1 ± 0.5	−92.2
n-butyraldehyde	−8.65 ± 0.03	−14.1 ± 0.3	−111.7 ± 0.2	−101.8 ± 0.4	*b*
crotonaldehyde	−3.66 ± 0.04	−10.0 ± 0.4	−82.7 ± 0.5	−72.4 ± 0.5	*c*
acetone	−4.86 ± 0.01	−11.1 ± 0.3	−110.1 ± 0.2	−101.5 ± 0.3	−102.3
cyclobutanone	−6.07 ± 0.07	−12.6 ± 0.4	−83.9 ± 0.3	−73.9 ± 0.4	−71.8
cyclopentanone	−3.85 ± 0.04	−10.4 ± 0.3	−106.0 ± 0.3	−95.0 ± 0.4	−96.0
cyclohexanone	−6.90 ± 0.03	−12.9 ± 0.3	−117.6 ± 0.2	−105.5 ± 0.4	−106.0
7-norbornanone	−10.8 ± 0.5	−16.5 ± 0.8	−100.0 ± 0.9	−87.2 ± 1.0	−89.4

[a] The appropriate POP and TORS corrections were made in each case. [b] Butyraldehyde acetal was not studied because of the number of low-energy conformers. [c] Crotonaldehyde ketal was not studied because MM3 does not account for the conjugation energy in unsaturated carbonyl compounds.

Table 6. Heats of Vaporization[a,b]

compound	T_{range}	T_{mid}	P_{range}	ΔH(Ant)	ΔH(CC)	ΔC_p	ΔH(corr)
2,2-dimethoxypropane	299−348	323.9	98.2−657	8.44	8.06	18.6	8.54
1,1-dimethoxybutane	304−329	317.0	29.6−99.8	9.84	9.53	23.6	9.97
crotonaldehyde	300−350	325.2	40.7−348.9	9.28	8.89	14.7	9.29[d]
1,1-dimethoxy-3-butene	305−334	319.6	23.2−97.5	10.03	9.80	25.0	10.34
cyclobutanone	301−344	322.4	48.4−303.4	9.02	8.86	11.9	9.15[e]
1,1-dimethoxycyclobutane	301−348	324.5	24.2−213.0	10.17	9.44	19.2	9.95
1,1-dimethoxycyclopentane	307−343	324.7	10.9−65.0	11.02	10.43	22.0	11.01
1,1-dimethoxycyclohexane	315−347	331.4	6.3−33.3	12.52	11.33	24.2	12.13
7-norbornanone	322−348		10.6−37.9	11.45	11.00	*c*	11.15
7,7-dimethoxynorbornane	321−357	338.9	5.0−32.8	11.72	11.82	24.9	12.83
chloral	300−348	324.3	48.7−369.5	9.18	8.80	14.5	9.18[f]

[a] T_{range} is the range of temperatures (K) used for the vapor pressure measurements, T_{mid} is the midpoint of the range, P_{range} is the observed range of pressures (Torr), ΔH(Ant) is the heat of vaporization calculated using the Antoine equation (kcal/mol), ΔH(CC) is the heat of vaporization calculated from a van't Hoff plot, ΔC_p is the difference in heat capacity between the vapor and liquid (cal/(mol deg)$^{-1}$), and ΔH(corr) is ΔH(CC) corrected to 25 °C for the effect of the heat capacity difference. The latter value is believed to be the more reliable (see text). The estimated uncertainty in ΔH(corr) is 0.3 kcal/mol (see text). [b] The literature values of ΔH_v are the following: water, 10.52 ± 0.01; methanol, 8.94 ± 0.01; acetaldehyde, 6.15 ± 0.03; acetone, 7.37 ± 0.01; *n*-butyraldehyde, 8.05 ± 0.10; cyclohexanone, 10.77 ± 0.05; cyclopentanone, 10.21 ± 0.05 (ref 14). [c] Heat of sublimation, corrected by $2R\Delta T$ (cf. ref 46). ΔH_s has been reported to be 11.3 kcal/mol: Steele, W. V. *J. Chem. Thermodyn.* **1978**, *10*, 585. [d] The ΔH_v based on reported Antoine constants (Stephenson, R. M.; Malanowski, S. *Handbook of Thermodynamics of Organic Compounds*; Elsevier: New York, 1987) is 9.09 kcal/mol. [e] The ΔH_v based on reported Antoine constants is 9.16 kcal/mol. [f] The ΔH_v based on reported Antoine constants is 8.58 kcal/mol. The pressures calculated from the equation do not agree with those we have measured.

was assigned the normal +sc,−sc conformation, and C_2 symmetry was enforced. With acetaldehyde, cyclohexanone, and fluoral hydrates, the same conformation was used as a starting point, but it was slightly distorted allowing the geometry optimization to go to the lower energy unsymmetrical conformation. In the case of cyclobutanone hydrate, both a planar and a nonplanar rings were used as starting points, and the latter gave the lower energy. A considerable effort was taken in locating the lower energy conformation for the hydrate of methyl acetate. Here, there are many conformations that are possible. It is still possible that a lower energy form could be found.

It is known that satisfactory relative energies for reactions such as those in this study frequently require more flexible basis sets and correction for electron correlation. Single-point calculations were carried out using the 6-31G* geometries at the MP2/6-311++G** theoretical level[20] where practical. The basis set size had a significant effect on the calculated energy changes, and correction for electron correlation also had a significant effect. In other studies, we have found that the 6-311++G** basis set generally gives results in good accord with experimental measurement when corrected for electron correlation.[21] The MP3 energies[22] also were obtained, but they were found to give less satisfactory relative energies than MP2. This has also been observed by Pople et al.[23]

With the larger molecules, it was not possible to use such a large basis set. Here, the MP2/6-31G**//HF/6-31G* energies were obtained. It was found that there was a constant difference

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(22) The MP3 energies are available in the Ph.D. thesis of K.M.M., Yale University, 1994.

Table 7. Heats of Solution and Reaction in Methanol and Comparison with NMR Results[a]

compound	ΔH_{soln} carbonyl[b]	ΔH_{soln} ketal	ΔH_r	ΔH_r(NMR)
acetaldehyde	512 ± 100 (est)	512 ± 16 (5)	−9.29 ± 0.10	≤−9.1
n-butyraldehyde	692 ± 100 (est)	692 ± 9 (4)	−9.37 ± 0.10	≤−9.1
crotonaldehyde	735 ± 30 (4)	643 ± 35 (3)	−4.48 ± 0.06	−4.8 ± 0.5
acetone	541 ± 15 (4)	450 ± 22 (4)	−5.67 ± 0.03	−5.85
cyclobutanone	710 ± 10 (4)	744 ± 13 (3)	−6.76 ± 0.07	−6.7 ± 0.5
cyclopentanone	724 ± 15 (5)	752 ± 15 (5)	−4.54 ± 0.04	−3.9 ± 0.5
cyclohexanone	705 ± 100 (est)	878 ± 15 (5)	−7.45 ± 0.11	−7.3 ± 0.5
7-norbornanone	926 ± 100 (est)	926 ± 15 (5)	−11.50 ± 0.50	≤−8.7

[a] The heat of solution of water in methanol was −724 ± 4 cal/mol. The number of runs is given in parentheses. ΔH_{soln} are given in cal/mol; ΔH_r are given in kcal/mol. [b] In the case of the aldehydes, the heats of solution could not be measured since they react to form hemiacetals. It was estimated to be the same as for the corresponding acetal based on the other compounds. The same was true with norbornanone. Most of the other ketones did not react appreciably with methanol. However, cyclohexanone gives about 10% hemiketal, and the observed heat of solution was corrected accordingly.

Table 8. Calculated Energies of Carbonyl Compounds and Their Hydrates[a]

compound	ZPE	MP2 6-31G*	MP2 6-311++G**	CBS-4
formaldehyde (**1**)	16.4	−114.181 21	−114.240 20	−114.358 36
1,1-dihydroxymethane (**1a**)	34.9	−190.423 62	−190.533 45	−190.719 28
acetaldehyde (**2**)	33.6	−153.376 34	−153.448 13	−153.609 59
1,1-dihydroxyethane (**2a**)	51.4	−229.616 38	−229.738 68	−229.966 97
crotonaldehyde (**3**)	54.2	−230.529 10		−230.875 33
1,1-dihydroxybut-2-ene (**3a**)	71.6	−306.760 63		−307.226 41
acetone (**4**)	50.4	−192.569 43	−192.654 10	−192.859 36
2,2-dihydroxypropane (**4a**)	67.9	−268.806 23	−268.941 40	−269.213 51
cyclopropanone (**5**)	37.1	−191.312 13	−191.395 44	−191.601 93
1,1-dihydroxycyclopropane (**5a**)	54.8	−267.567 43	−267.701 15	−267.977 56
cyclobutanone (**6**)	54.9	−230.528 51	−230.625 08	−230.873 35
1,1-dihydroxycyclobutane (**6a**)	72.4	−306.764 40	−306.912 35	−307.228 00
cyclohexanone (**7**)	91.0	−308.932 63		−309.387 14
1,1-dihydroxycyclohexane (**7a**)	108.0	−385.173 50		−385.746 22
bicyclo[1.1.1]pentan-2-one (**8**)	59.7	−268.468 16		−268.869 18
2,2-dihydroxybicyclo[1.1.1]pentane (**8a**)	76.4	−344.700 28		−345.221 44
7-norbornanone (**9**)	95.3	−346.909 07		−347.422 05
7,7-dihydroxynorbornane (**9a**)	112.2	−423.151 79		−423.784 18
fluoral (**10**)	20.7	−450.419 87		−451.124 13
fluoral hydrate (**10a**)	38.2	−526.670 63		−527.492 50
chloral (**11**)	17.5	−1530.416 54		−1531.043 69
chloral hydrate (**11a**)	34.9	−1606.661 64		−1607.408 43
methyl acetate (**12**)	54.4	−267.617 43		−268.017 20
1,1-dihydroxy-1-methoxyethane (**12a**)	70.9	−343.834 07		−344.352 61
water	12.9	−76.219 36	−76.274 57	−76.348 69
formaldehyde hemiacetal (**1b**)	52.0	−229.592 58	−229.710 69	−229.939 45
acetaldehyde hemiacetal (**2b**)	68.5	−268.784 14	−268.914 87	−269.187 19
acetone hemiacetal (**4b**)	85.0	−307.972 96	−308.116 57	−308.433 04
methanol	31.0	−115.381 28	−115.444 53	−115.561 26
formaldehyde−H_2O_2 (**1d**)	37.1	−265.360 60		−265.769 36
hydrogen peroxide	16.4	−151.148 71	−151.240 92	−151.388 53
formaldehyde−HOF				−289.760 32
HOF				−175.379 55
dimethoxymethane (**1c**)	69.0	−268.760 59	−268.887 55	−269.160 93
dimethoxyethane (**2c**)	85.6	−307.949 58	−308.089 47	−308.406 20
2,2-dimethoxypropane (**4c**)	102.1	−347.136 19	−347.289 16	−347.651 40
methane				−40.428 21
ethane				−79.661 19
propane				−118.898 77
cyclopropane				−117.673 69
cyclobutane				−156.909 84
cyclohexane				−235.428 15
bicyclo[1.1.1]pentane				−194.909 14
norbornane				−273.469 28
1,1,1-trifluoroethane				−377.200 52
methyl ethyl ether				−194.025 78

[a] The zero-point energies (kcal/mol) are based on HF/6-31G* calculations and scaled by 0.893. The total energies are given in hartrees.

in energy of hydration (2.8 ± 0.2 kcal/mol) between the MP2/6-311++G** and MP2/6-31G** calculations for the smaller molecules, and this difference was extended to the other compounds.

Before comparing the energy changes with the experimental values, they must be corrected for the changes in zero-point energies on going from reactants to products. This can be relatively large for bimolecular reactions since six translational and rotational degrees of freedom will be converted into vibrations in the product. The zero-point energies calculated at the HF/6-31G* level and scaled by 0.893 are included in Table 8.

Table 9. Effect of MP2/6-31G* Optimization on Relative Energies[a]

	MP2/6-31G* opt		RHF/6-31G* opt	
compound	*E*(MP2)	Δ*E*	*E*(MP2)	Δ*E*
formaldehyde	−114.174 96	−14.7	−114.172 61	−15.3
1,1-dihydroxymethane	−190.397 61		−190.395 33	
acetaldehyde	−153.358 97	−12.4	−153.356 73	−12.8
1,1-dihydroxyethane	−229.577 91		−229.575 50	
acetone	−192.540 87	−10.3	−192.538 70	−10.7
2,2-dihydroxypropane	−268.756 56		−268.754 11	
water	−76.199 24		−76.198 37	

[a] The total energies are given in hartrees; the relative energies are given in kcal/mol.

It is known that RHF geometry optimizations significantly underestimate the lengths of C−O bonds, and therefore we wished to have an estimate of the errors that might be introduced using these geometries. It was not practical to carry out higher level optimizations for the larger compounds. The MP2/6-31G* theoretical level usually gives quite satisfactory structures, and therefore we have compared the MP2/6-31G* energy changes obtained using MP2/6-31G* geometries with those found using RHF/6-31G* structures (Table 9). The hydration of formaldehyde, acetaldehyde, and acetone was examined, and there was only a small systematic difference in energy of about 0.5 kcal/mol. It can be seen that the error introduced using the RHF/6-31G* structures is quite small.

The estimated ΔH_r derived from the MP2/6-311++G** energy changes and the scaled zero-point energy changes are summarized in Table 10. The energy changes are for 0 K, and it is assumed that they will not change much on going to 298 K. Since comparisons will be made, any error introduced in this way would approximately cancel.

A recently developed theoretical model, CBS-4,[24] also was used in studying these compounds. It is based on the complete basis set extrapolation method developed by Petersson[25] and makes use of a large basis set RHF calculation, a complete basis set extrapolation, MP2 and higher order corrections, and the zero-point energy. The CBS-4 energies of the compounds included in this study are given in Table 8. The energy changes for the reactions are summarized in Table 10. In a comparison with a large number of organic compounds,[26] CBS-4 predicted heats of formation with an error only slightly larger than the computationally much more demanding G2 procedure developed by Pople et al.[27] The G2 energy changes for the hydration of formaldehyde and acetaldehyde were −7.3 and −5.6 kcal/mol, respectively, in very good agreement with the CBS-4 energy changes.

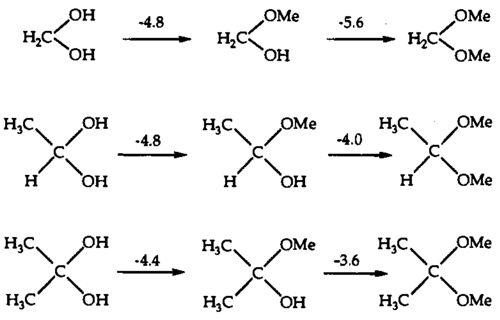
It can be seen that the MP2/6-311++G** and CBS-4 relative energies are generally in very good agreement. It is likely that the latter will prove to be the more accurate, and they will be used in the following discussion.

The experimental NMR studies were carried out in solution, whereas the present calculations are for the compounds in the gas phase. Therefore, the estimated ΔH_r will correspond to the observed values only if the solvation energies for reactants and products are approximately equal. This does appear to be the case for hydration since the ΔH_r for the formation of acetaldehyde hydrate has been found to be −5.7 kcal/mol as compared to the estimated value of −5.5 kcal/mol. However, it is not true for acetal or ketal formation where the gas phase and solution heats of reaction differ by about 5 kcal/mol.

Experimental gas phase enthalpies of reaction are available for acetal and ketal formation (Table 5). A comparison between the experimental and theoretical enthalpy changes shows a very good agreement. This gives one confidence in the use of the theoretical energies for the cases where experimental data are not available.

5. Origin of Structural Effects on Equilibria in Additions to Carbonyl Groups

Several questions can be asked concerning the energy changes caused by changes in structure of the carbonyl compound and of the reagent that adds to the carbonyl group. The first is concerned with the difference between hemiacetal and acetal formation. A direct comparison of the energy changes for these reactions is not useful since hemiacetal formation is an addition reaction and acetal formation is a replacement reaction. However, if one considered the formation of the hemiacetal from the hydrate rather than the carbonyl precursor, it could be directly compared with acetal formation. The data (using the CBS-4 energies) are as follows: It can be seen that the first step is essentially independent of the structure of the carbonyl compound. This is also approximately true for the second step, and the small differences may easily result from steric interactions. The question then becomes why is methoxy substitution preferred to hydroxy substitution?



One might think that it results from the methyl groups acting to donate charge density through the oxygens to the electron deficient central carbons. If that were the case, an electron withdrawing group attached to the oxygens should reduce the interaction. This suggests the following comparison:

$$H_2C{=}O + H_2O \rightarrow H_2C(OH)_2 \qquad \Delta H = -7.7 \text{ kcal/mol}$$

$$H_2C{=}O + MeOH \rightarrow H_2C(OH)(OMe) \qquad \Delta H = -12.4 \text{ kcal/mol}$$

$$H_2C{=}O + H_2O_2 \rightarrow H_2C(OH)(OOH) \qquad \Delta H = -14.1 \text{ kcal/mol}$$

It can be seen that hydrogen peroxide gives a slightly more exothermic reaction than methanol, and that water gives the least exothermic reaction.

The hydroxy group is inductively electron withdrawing, but it also has lone pairs that may be involved in stabilizing the tetrahedral species. The importance of the lone pairs could be tested by examining the reaction of FOH. Here, the fluorine is even more inductively electron withdrawing, and it has negligible π interactions with its non-basic lone pairs. Therefore

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(26) Ochterski, J.; Petersson, G. A.; Wiberg, K. B. To be submitted for publication.

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Table 10. Energy Changes on Hydration, Hemiketalization, and Ketalization (kcal/mol) with ZPE Correction

				obs (phase)		
compound	MP2[a] 6-31G**	MP2[a] 6-311++G**	CBS-4	gas	liq	soln[b]
a. Hydrate Formation						
formaldehyde (**1**)	−8.8	−6.1	−7.7			
acetaldehyde (**2**)	−7.9	−5.0	−5.5			−5.3 ± 0.5
crotonaldehyde (**3**)	−2.5	[+0.3]	−1.5			>−2.5
acetone (**4**)	−6.4	−3.4	−3.4			−4.2 ± 0.5
cyclopropanone (**5**)	−17.7	−14.7	−16.9			
cyclobutanone (**6**)	−5.7	−3.3	−3.7			−3.9 ± 1.0
cyclohexanone (**7**)	−9.3	[−6.5]	−6.5			−5.0 ± 0.5
bicyclo[1.1.1]pentanone (**8**)	−4.0	[−1.2]	−2.2			
7-norbornanone (**9**)	−10.6	[−7.8]	−8.3			−7.3 ± 0.5
fluoral (**10**)	−15.1	[−12.3]	−12.3			
chloral (**11**)	−11.6	[−8.8]	−10.1		−5.4 ± 0.1	−12.2 ± 0.1[c]
methyl acetate (**12**)	5.3	[+8.1]	+8.3			
b. Hemiacetal Formation						
formaldehyde (**1**)	−14.3	−11.7	−12.4			
acetaldehyde (**2**)	−12.7	−10.1	−10.3			
acetone (**4**)	−10.4	−7.7	−7.8			
c. Acetal Formation						
formaldehyde (**1**)	−19.2	−17.1	−18.0	−18.9 ± 0.2[d]		
acetaldehyde (**2**)	−16.0	−14.0	−14.3	−14.8 ± 0.3	−8.6 ± 0.1	−9.3 ± 0.1
n-butyraldehyde				−14.1 ± 0.3	−8.7 ± 0.1	−9.4 ± 0.1
crotonaldehyde (**3**)				−10.0 ± 0.4	−3.7 ± 0.1	−4.5 ± 0.1
acetone (**4**)	−12.3	−10.4	−11.4	−11.1 ± 0.3	−4.9 ± 0.1	−5.7 ± 0.1
cyclobutanone (**5**)				−12.6 ± 0.4	−6.0 ± 0.1	−6.8 ± 0.1
cyclopentanone				−10.4 ± 0.3	−3.9 ± 0.1	−4.5 ± 0.1
cyclohexanone (**6**)				−12.9 ± 0.3	−6.9 ± 0.1	−7.5 ± 0.1
7-norbornanone (**8**)				−16.5 ± 0.8	<−10.8 ± 0.5	−11.5 ± 0.5
d. Reaction with Hydrogen Peroxide						
formaldehyde (**1**)	−14.9		−14.1			
e. Reaction with HOF						
formaldehyde (**1**)			−14.1			

[a] Values in brackets are estimated from the MP2/6-31G** energies. [b] Unless otherwise specified, hydrate formation refers to aqueous solutions and acetal formation refers to methanol solutions. [c] In acetone solution: Henke, S. L.; Hadad, C. M.; Morgan, K. M.; Wiberg, K. B.; Wasserman, H. H. *J. Org. Chem.* **1993**, *58*, 2830. [d] Reference 14.

the energy change for the following reaction was estimated at the CBS-4 level:

$$H_2C{=}O + FOH \rightarrow H_2C(OF)(OH) \qquad \Delta H = -14.1 \text{ kcal/mol}$$

This is essentially the same as for the addition of hydrogen peroxide and of methanol. The electronegativity of the atom attached to oxygen does not appear to be a major determining factor in the disproportionation energies. Thus, the first-row substituents at oxygen give energy changes that are fairly similar, and considerably more negative than that for H as the substituent.

The energy changes are probably related to the disproportionation energies of simple compounds such as:[14]

$$2CH_3OH \rightarrow CH_3OCH_3 + H_2O \qquad \Delta H = -5.5 \text{ kcal/mol}$$

This is analogous to the reaction of formaldehyde hydrate with methanol to give the hemiacetal plus water, as well as the reaction of the hemiacetal to give the acetal. The exothermic disproportionation reactions are not unique to oxygen containing compounds, and some other simple examples are:

$$3CH_3NH_2 \rightarrow (CH_3)_3N + 2NH_3 \qquad \Delta H = -11.1 \text{ kcal/mol}$$

$$2CH_3SH \rightarrow CH_3SCH_3 + H_2S \qquad \Delta H = -2.9 \text{ kcal/mol}$$

$$2CH_3CH3 \rightarrow CH_3CH_2CH_3 + CH_4 \qquad \Delta H = -2.7 \text{ kcal/mol}$$

The origins of these energy changes are not clear at this time and continue to be investigated.

Another question is concerned with the effect of substituents on the hydration energies. It can be seen from Table 10 that the energies become less exothermic with increasing alkyl substitution. Does this result from the stabilization of the carbonyl component by alkyl groups, or is the effect also seen in the hydrates? This question may be examined via the use of the group transfer reactions shown in Figure 1.

Figure 1a gives the energy changes for transferring a carbonyl group from formaldehyde to different methylene groups. As expected, alkyl groups stabilize the carbonyl groups leading to exothermic transfer energies. The reversal of the sign for forming cyclopropanone is a reflection of the increase in strain when a trigonal center is introduced into a cyclopropane ring.[28] The hybridization of the bonds to the ring may also play a role. With cyclobutane, little strain is introduced with a trigonal center,[28] and some eclipsing strain is lost on going to the ketone, leading to the most exothermic reaction. With cyclohexane, conversion to the ketone will lead to a small increase in strain associated with the bond angles at the carbonyl. It is surprising that bicyclo[1.1.1]pentane gives the same heat of reaction as propane, but the less exothermic reaction of norbornane may be accounted for by an increase in strain. With 1,1,1-trifluoroethane, the reaction becomes endothermic because of the repulsion between the positively charged carbonyl carbon and the positively charged trifluoromethyl carbon.[8] Conversely, methyl ethyl ether gives the most exothermic reaction in part because of the attraction between the positively charged carbonyl carbon and the negatively charged oxygen of the methoxy group.

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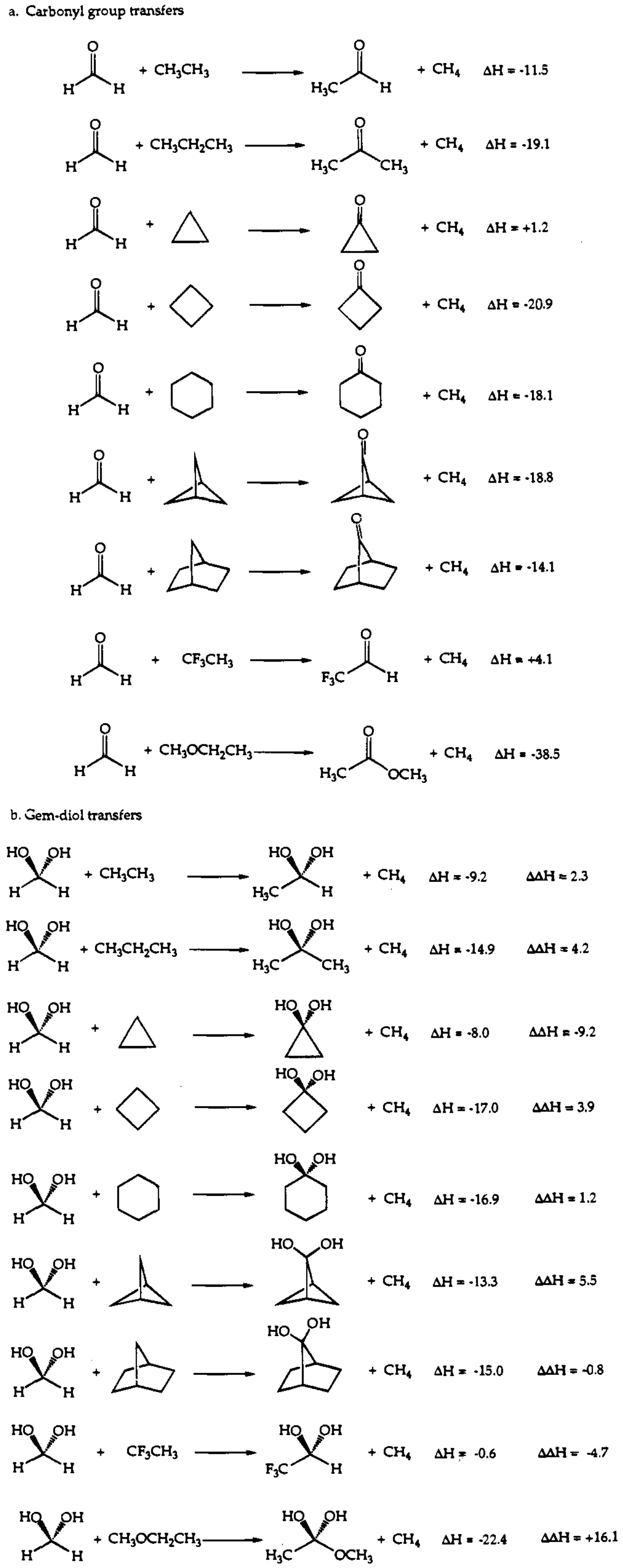

Figure 1. Group transfer energies based on CBS-4 energies: (a) transfer of a carbonyl group; (b) transfer of a gem-diol group. The $\Delta\Delta H$ values are the differences between the ΔH_r in parts a and b.

Here, the π interaction between the ether oxygen and the carbonyl group also plays a role.[8]

Less is known about the effect of substituents at gem-diol groups. Alkyl groups again stabilize the product of the reactions (Figure 1b), but to a smaller extent than the carbonyl compounds. As a result, alkyl substitution disfavors hydrate formation from the carbonyl derivatives. In its diol, the cyclopropane ring gives much less stabilization than two alkyl groups, presumably because of the relatively high s character of the bonds from the carbon. Both cyclobutane and cyclohexane give more exothermic gem-diol transfer reactions than propane. It is possible that there is steric repulsion between the groups in 2,2-propanediol and that ring formation will reduce this interaction leading to a more exothermic reaction. Both bicyclo[1.1.1]pentane and norbornane give transfer energies similar to that for propane. 1,1,1-Trifluoroethane gives an almost thermoneutral gem-diol transfer reaction, but methyl ethyl ether gives a strongly exothermic reaction. Just as polyfluoro substitution is energetically favored by internal Coulombic stabilization,[29] polyoxygen substitution should also be favored, and probably is the reason for the exothermic reaction in the last case.

The last column of Figure 1b gives the difference between the carbonyl and hydrate transfer energies and corresponds to the change in hydration energy as compared to formaldehyde. Positive values indicate a less favorable hydrate formation, and in the few cases in which $\Delta\Delta H$ is negative, hydration is more favored than in the case of formaldehyde. A comparison of the various energy terms indicates that the overall effect is a complex blend of several factors.

6. Conclusions

Experimental measurements of hydration energies and of acetal and ketal formation and calculations at the MP2/6-311++G** and CBS-4 theoretical levels were in good agreement. The factors that control the reaction energies were examined. Hemiacetal formation is favored over hydration by 5 kcal/mol, and conversion of hemiacetals to acetals leads to a further 4−5 kcal/mol stabilization. This appears to be a general effect of replacing OH groups by OR where R could be an alkyl group, OH or F.

The factors that contribute to the stabilization or destabilization of a carbonyl group and of a gem-diol group were examined by the use of group transfer reactions. Alkyl substitution stabilizes a carbonyl group, and the effect on the hydrate is smaller, leading to a net decrease in hydration with alkyl substitution. The reactions of cyclopropanone through cyclohexanone reflect the combined effects of strain and bond eclipsing. The CF_3 and CCl_3 groups act by destabilizing the carbonyl group more than the gem-diol group, leading to increased hydration.

Calculations. The ab initio calculations were carried out with Gaussian-92.[30]

7. Experimental Section

Preparation and Purification of Reagents. (a) Carbonyl Compounds. Acetaldehyde, acetone, cyclobutanone, cyclopentanone, cyclohexanone, butyraldehyde, and crotonaldehyde were commercially available and were purified by fractional distillation from a drying agent, following the suggestion of Perrin.[31] Acetaldehyde and crotonaldehyde were found to decompose relatively quickly when in pure form; these compounds were purified, ampules were filled, and calorimetry runs were performed all on the same day, and filled ampules were stored in a refrigerator prior to use. NMR solutions for these compounds were

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[29] Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1993**, *115*, 614.

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made as soon as possible after distillation was complete. 7-Norbornanone was prepared by heating its acetal to reflux overnight in glacial acetic acid;[32] it was purified by repeated sublimation and was freed of water by melting over 4 Å molecular sieves until no carbonyl hydrate resonances were observed by ^{1}H NMR. The most recognizable resonance indicating the presence of hydrate is found at 2.15 ppm. Chloral was prepared by shaking the hydrate with concentrated sulfuric acid, followed by distillation.[33] In this case, too, dryness was ascertained by checking the NMR spectrum for hydrate.

(b) Acetals. Acetals were usually formed by treating the carbonyl compounds with trimethyl orthoformate in acidic dry methanol and were purified by preparative gas chromatography and/or vacuum distillation from sodium metal.[34] 7-Norbornanone acetal was synthesized from 1,2,3,4-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-2-ene following the procedures of Gassman,[32] modified by the sodium dechlorination procedure reported by Lap and Paddon-Row.[35] All acetals studied were at least moderately thermally unstable. To prevent decomposition, acetals were never heated above 100 °C, including during distillations and vapor pressure measurements.

Purity of all compounds was determined by capillary gas chromatography. To assay acetals, a cool (100 °C) injector port prevented thermal decomposition. Acetals also were analyzed by IR to ensure that no detectable carbonyl compound remained, as evidenced by the absence of the characteristic carbonyl stretching frequency. All compounds used for calorimetry and for NMR experiments were found to be ≥99.5% pure.

(c) Other Reagents. Chloral hydrate was available commercially and was used with no further purification. Mesitylene was vacuum distilled from sodium benzophenone ketyl.[31] Methanol was distilled from magnesium and iodine under nitrogen.[31] Water for calorimetry stock solutions was deionized and distilled; that used for calorimetry ampules was distilled once more. 1,4-Dioxane was distilled from benzophenone ketyl under nitrogen.[31] Acetone-d_6 and methanol-d_4 were vacuum transferred from molecular sieves and used without further purification. D_2O was also used without further treatment. Monohydrated *p*-toluenesulfonic acid was dehydrated by heating to 100 °C under vacuum for at least 4 h.[31]

Nuclear Magnetic Resonance Studies. (a) Preparation of Samples. Solutions for the NMR experiments were normally prepared by weighing into a 1 mL volumetric flask approximately 0.001 mol of carbonyl compound, followed by enough perdeuterated solvent to make 1 mL total. A Mettler analytical balance accurate to ±0.00005 g was used for this purpose. Masses used in the equilibrium constant calculations were rounded to the nearest ten-thousandth of a gram. Not all carbonyl compounds were easily soluble in D_2O; care was taken to avoid saturating the solution over the temperature range studied. In general, a 1 mL methanolic solution was divided into two aliquots and was used to measure both hemiacetal and acetal formation. For carbonyl/acetal equilibria, one small crystal of anhydrous *p*-toluenesulfonic acid was added to the solution. NMR tubes charged with solutions were degassed via 3 freeze−pump−thaw cycles and were flame sealed under vacuum to ensure that the solution composition would not change over the course of the experiment. The empty NMR tubes were rinsed with deionized water and acetone. Heating NMR tubes in an oven can cause them to warp. To avoid this, and to ensure that the empty NMR tubes were free of moisture and volatile contaminants, the tubes were placed in a vacuum desiccator which was evacuated for several hours, then refilled with argon.

(b) Acquisition of Spectra. The samples prepared as described above were analyzed soon after filling to minimize potential sample decomposition. One of two instruments was used to record the spectra—a Bruker WM-250 MHz or a Bruker AM-500 MHz NMR spectrometer. In order to ensure that enough time had elapsed between pulses so that the molecules had returned to their equilibrium nuclear populations, the T_1 values of several compounds were measured. The rest of the values were extrapolated from these data. An Omega-300 spectrometer was used for these experiments, and a two-pulse sequence was used. The sample was given a 180° pulse, followed by preset time $t < 5T_1$, followed by a 90° pulse. The integral of the diminished, sometimes inverted, resonance (M) was recorded as a function of time t. The integral of the resonance at equilibrium (M_0), with $t > 5T_1$, was also measured. The data were fit to the equation $[M_0 - M] = [M_0 - M_{t=0}]e^{-t/T_1}$. Integrals were measured for the protons having the slowest relaxation time, in all cases either adjacent to or bonded to the carbonyl carbon. Spectra were acquired with the receiver delay (RD) set to $\geq 5\ T_1$.[36]

Spectra were recorded at three temperatures, nominally 10, 25, and 40 °C. Samples were preequilibrated for at least 30 min at approximately 10 °C before the measurements at this temperature were taken. Temperatures were calibrated by measuring the difference in chemical shifts between the two resonances in methanol. One scan was accumulated then transformed, and $\Delta\delta$ was noted. This measurement was repeated four or five times in order to determine the thermal stability. Temperatures were shown to be stable to ±0.1 °C. The corrected temperature was calculated using this averaged $\Delta\delta$ with the equation proposed by Amman *et al.*,[37] and another ±0.2 °C can be added to the temperature uncertainty due to possible inaccuracies in this empirical equation. Temperatures were calibrated each time spectra were recorded.

(c) Analysis of Spectra. One factor quite critical for the success of the experiment is proper integral measurement. For each resonance, two or three integral curves were drawn. The average of these values, disregarding any obviously strange measurement, provides the integral value used in the equilibrium constant calculation.

When the equilibrium of carbonyl compound and adduct was shifted far to one side, on the order of 1:100, the technique of Hine[12] was used. The relative populations were determined by comparing the integral of the ^{13}C satellite resonance of the major compound to the integral of the less abundant component. The ^{13}C satellite resonance arises from the natural 1.1% abundance of ^{13}C, which splits 1.1% of the proton signal into a doublet, each half of which is equal to 0.55% of the integral of the full resonance. Instead of comparing integrals in a ratio of 100:1 we are now comparing 0.55:1. The equilibria which required this treatment were acetone/hydrate, acetone/hemiacetal, crotonaldehyde/hemiacetal, and cyclobutanone/hydrate.

In some situations, there was only one reactant resonance and one adduct resonance resolved well enough to be measured with confidence. In other situations, two or three pairs of corresponding integrals were of comparable quality, and in these cases, one preferred set was chosen. With integrals in hand, the equilibrium constants for hydrate and hemiacetal formation were easily obtained. The integral measured for the acetal is actually the integral of both acetal and hemiacetal, since the two signals resonate coincidentally. A correction was made for the amount of hemiacetal present in the solution but not involved in the carbonyl/acetal equilibrium making use of the previously determined hemiacetal formation constant. An iterative procedure was used to correct the acetal formation constant. In calculating the equilibrium constants, concentrations were given as mole fractions in order to make the constants unitless. The enthalpies of reaction were found fitting $\ln K_{eq}$ vs $1/T$ to a line whose slope is $-\Delta H/R$. A least-squares fitting program was used for this purpose. All slopes were found by this procedure to have an estimated error less than ±5.4%, with r^2 better than 0.994.

Calorimetry. (a) Description of the Experiment. The automated isoperibol submarine reaction calorimetry system previously described[38] was used to measure reaction enthalpies of acetal formation and enthalpies of solution in methanol. In each calorimetric run, approximately 100 mL of stock solution is placed in a glass cell which possesses two reentrant wells, one which holds a temperature sensor, the other which houses a heater. One ampule is placed in the ampule holder/stirrer, held by the calorimeter head. The head and cell are

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connected by a threaded joint, and together are clamped into a watertight canister. The remaining space in the canister remains filled with air. The apparatus is gently lowered into a constant temperature bath, set at 25.10 °C, held to ±0.0003 °C over the course of the run.

The remainder of the experiment is controlled by a microprocessor given several user-designated variables. The temperature, measured to 0.0001 °C with a quartz probe, is recorded every 10 s starting at a user-designated temperature, roughly 10 min before initiation of the reaction. After the ampule is broken, again at a preset temperature, data collection continues until the reaction is complete—normally 30 min more. An electrical calibration is performed directly following each reaction by passing a known current through a manganin wire resistor of known resistance for a given amount of time. This calibration furnishes the effective heat capacity of the calorimeter for a particular run. The enthalpy of the reaction is calculated from the ΔT determined in the reaction run and the Cp measured in the calibration run. Several calorimetric runs, normally 4−6, were performed for each compound in a given reaction medium to verify reproducibility and to determine the precision of the measurement. The uncertainty interval is given as twice the standard deviation of the mean, following the suggestion of Rossini.[39]

(b) Preparation of Reagents. Carbonyl compounds and methanol were vacuum transferred from activated 4 Å molecular sieves into preweighed spherical ampules that were flame sealed under vacuum and reweighed. Acetals and water were treated similarly, but without the molecular sieves. Norbornanone acetal would not vacuum transfer and was instead introduced to the ampule by pipet. Chloral hydrate was crushed to a fine powder and added to the ampule via a small funnel. A Mettler analytical balance reproducible to 0.000005 g was used for weighings. During a weighing session, each ampule was reweighed until this criterion was met, normally two or three weighings per ampule.

The calorimetry stock solutions for acetal hydrolysis experiments were prepared as follows. Distilled water, 1,4-dioxane, and concentrated perchloric acid were combined to give a solution which was 65% dioxane in water (v/v) and either 0.001 or 0.1 M in perchloric acid. Methanol, distilled water, and perchloric acid were combined to give 50% aqueous methanol (v/v), 0.25 M in acid. The 0.1 M H^+ methanol solution used for 7-norbornanone was prepared by dissolving the appropriate amount of anhydrous *p*-toluenesulfonic acid in dry methanol. Acid concentrations were determined with respect to 0.1 M sodium hydroxide solution, whose precise concentration was determined by titrating against anhydrous potassium acid phthalate. The stock solution used to determine the enthalpies of solution in methanol was prepared by adding clean sodium metal to dry methanol, with resulting pH about 8. All stock solutions were stored under nitrogen in a sealed container which dispensed solution through an outlet when nitrogen gas was passed through an inlet.

Enthalpies of Vaporization, Sublimation, and Melting. The measurement of three different enthalpies will be described in this section. Enthalpies of vaporization were measured by ebulliometry using a new ebulliometer that requires only 1 mL of compound. Vapor pressure manometry provided enthalpies of sublimation. Differential scanning calorimetry was used to determine enthalpies of melting. The general principles behind the methods used in this section are discussed by Cox and Pilcher.[40]

Ebulliometry. Ebulliometry, the process of measuring a compound's boiling point as a function of pressure, has been used successfully to determine enthalpies of vaporization. A new ebulliometer was built, based on the design by Hoover,[41] as reported by Thomson.[42] The apparatus was shown to give reliable data using about 1 mL of pure compound. Mesitylene's heat of vaporization, 11.35 ± 0.01 kcal/mol, has been measured calorimetrically; its heat of vaporization measured in the new ebulliometer was determined to be 11.48 (corrected Clausius−Clapeyron treatment) or 11.42 kcal/mol (Antoine treatment). A description of the ebulliometer may be found in the Ph.D. thesis of K.M.M.

A measurement is taken by adjusting the settings of the manostats to a given pressure and heating the compound to reflux. The temperature of the vapors is measured using a Hewlett-Packard Model 2804A quartz probe. The temperature and pressure values are recorded if they remain constant over a 15 min period. The data have been fit to both the Clausius−Clapeyron equation (eq 1) and the Antoine equation (eq 2). Both analyses require plotting ln *P* (mm Hg) vs 1/*T* (1/K).

$$\ln P = A - B/T \qquad -\mathrm{d}\ln P/\mathrm{d}(1/T) = B \tag{1}$$

$$\ln P = A - B/(T + C) \qquad -\mathrm{d}\ln P/\mathrm{d}(1/T) = BT^2/(T + C)^2 \tag{2}$$

The heat of vaporization calculated using the Clausius−Clapeyron equation is valid at the midpoint of the temperature range, T_m; correcting this value to standard temperature is accomplished through eq 3.

$$\Delta H_{\mathrm{vap},298.16} = \Delta H_{\mathrm{vap},T_m} + (298.16 - T_m)(\mathrm{Cp_g} - \mathrm{Cp_l}) \tag{3}$$

The heat capacity of the vapor is calculated via a standard statistical mechanics method[43] making use of calculated vibrational frequencies analysis derived from an ab initio calculation (with scale factor 0.89) or via MM3.[15] Additionally, there are some experimental gas phase heat capacities tabulated in Reid, Prausnitz, and Sherwood.[44] The heat capacity of the liquid phase is calculated using the bond additivity scheme developed by Chueh and Swanson.[44] Determining the heat of vaporization using the Antoine equation at a specified temperature is more simple in that the temperature is incorporated as part of the derivative expression. However, it generally requires a wider temperature range in order to accurately determine the curvature in the plot.

The estimated uncertainty for ΔH_{vap} determined by ebulliometry is ±0.1 kcal/mol. It is further estimated that the error introduced by correcting a ΔH_{vap} derived from the Clausius−Clapeyron equation is no more than ±0.2 kcal/mol. The uncertainty interval assigned to heats of vaporization measured via the ebulliometric method, evaluated using eqs 1 and 3, is then ±0.3 kcal/mol. In this study, the results obtained using the corrected Clausius−Clapeyron method are preferred to those determined using the Antoine treatment. The Antoine equation describes a curve, not a line, and requires the use of a large temperature range in order to obtain an accurate fit. Here, the temperature ranges are relatively small, and a linear approximation of the data is generally more satisfactory.

Vapor Pressure Manometry. In the current investigation, the manometric method was used solely to measure enthalpies of sublimation. In the experiment, the vapor pressure of a compound is measured as a function of a set temperature. The vapor pressure is determined by measuring the difference between the heights of two columns of mercury contained in a U-tube. A cathetometer is used for this measurement. One column is in contact with vapors from a sample which has been thoroughly degassed; the other column contains nothing. The temperature is adjusted by immersing the U-tube in a transparent constant temperature environment created by the vapors of a solvent at reflux. The apparatus was used as described previously[45] with one adaptation. To prevent the solid from collecting in the unheated zone between the stopcock and the vacuum jacket, Nichrome wire was coiled around the glass and heated electrically. The data obtained using this method were also fit to the Clausius−Clapeyron equation (eq 1). A different correction to the Clausius−Clapeyron enthalpy was used. The correction described by Chickos[46] assumes that the gas is ideal and the

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Dulong–Petit value holds for the solid. Equation 4 provides the correction; T_m is defined as the midpoint of the temperature range, and $\Delta H(T_T)$ is any other phase transition which occurs over the temperature range studied, always equal to zero in the present studies.

$$\Delta H_{\mathrm{sub},298.16} = \Delta H_{\mathrm{sub},T_m} + 2R(T_m - 298.16) + \Delta H(T_T) \qquad (4)$$

Heats of sublimation determined using the manometric technique, Clausius–Clapeyron equation, and the $2R\Delta T$ correction term compare well with heats of sublimation available in the literature. The uncertainty in the vapor pressure manometry measurements, estimated similarly to those for the ebulliometric method, is ±0.3 kcal/mol.

Differential Scanning Calorimetry. Enthalpies of melting were measured by differential scanning calorimetry using a Perkin-Elmer DSC-4. The instrument was calibrated with an indium standard prior to use to ensure accuracy of melting temperature and melting enthalpy. Samples were prepared by weighing about 2 mg of pure compound into an aluminum pan. Three or four samples of each compound were prepared, and the tabulated enthalpies of melting reflect the averages of these runs. The uncertainties in the averaged ΔH_{melt} are calculated as twice the standard deviation from the mean.

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