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Computational Calculation of Equilibrium Constants: Addition to Carbonyl Compounds

Rafael Gómez-Bombarelli, Marina González-Pérez, María Teresa Pérez-Prior, Emilio Calle, and Julio Casado*

Departamento de Química Física, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos, s/n E-37008 Salamanca, Spain

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Hydration reactions are relevant for understanding many organic mechanisms. Since the experimental determination of hydration and hemiacetalization equilibrium constants is fairly complex, computational calculations now offer a useful alternative to experimental measurements. In this work, carbonyl hydration and hemiacetalization constants were calculated from the free energy differences between compounds in solution, using absolute and relative approaches. The following conclusions can be drawn: (i) The use of a relative approach in the calculation of hydration and hemiacetalization constants allows compensation of systematic errors in the solvation energies. (ii) On average, the methodology proposed here can predict hydration constants within ± 0.5 log K_{hyd} units for aldehydes. (iii) Hydration constants can be calculated for ketones and carboxylic acid derivatives within less than ± 1.0 log K_{hyd}, on average, at the CBS-Q level of theory. (iv) The proposed methodology can predict hemiacetal formation constants accurately at the MP2 6-31++G(d,p) level using a common reference. If group references are used, the results obtained using the much cheaper DFT-B3LYP 6-31++G(d,p) level are almost as accurate. (v) In general, the best results are obtained if a common reference for all compounds is used. The use of group references improves the results at the lower levels of theory, but at higher levels, this becomes unnecessary.

Introduction

For more than a century, aldehydes have been known to undergo hydration, such that for example the equilibrium of formaldehyde hydration is strongly displaced toward the hydrate, to the extent that less than 0.1% of formaldehyde is present as the carbonyl compound in aqueous solution. Ketones and other carbonyl compounds also add a water molecule to form *gem*-diols.[1]

Hydration reactions represent one of the simplest addition reactions to the carbonyl group and are of great importance in understanding many organic reactions. Since the formation of a tetrahedral intermediate is a step in some possible hydrolysis mechanisms, the hydration of carboxylic acid derivatives, esters, thioesters, and amides, is also important. Hemiacetalization may also form part of certain alcoholysis mechanisms.[2−9]

Much attention has been devoted to the measurement and calculation of hydration rates.[10−13] Hydration free energies can be used to calculate hydration rate constants in neutral, acidic, and basic media, using multidimensional Marcus theory and the no-barrier theory.[14,15]

Since aldehydes in their hydrate form cannot react with nucleophilic sites in DNA, the hydration of aldehydes is also significant in their role as alkylating and potentially mutagenic and carcinogenic agents. For instance, 99.997% of chloral is in its hydrate form, which significantly reduces its potential reactivity as an electrophile, and this in turn influences its genotoxic potential.[16−22]

Because carbohydrates show intramolecular hemiacetal equilibria, and since the reactivity of aldehydes as alkylating agents may be strongly influenced by the formation of cyclic and linear hemiacetals, hemiacetal formation is also of biological importance.

Hydration and hemiacetalization equilibrium constants have been measured with a variety of methods, most commonly UV and NMR spectroscopy. ^{1}H, ^{13}C, ^{17}O, and ^{19}F have been used.[23−25]

The experimental determination of hydration and hemiacetalization equilibrium constants is complex. The sensitivity of NMR spectroscopy makes it difficult to measure very displaced equilibria directly, and the use of UV spectroscopy forces the assumption that the molar absorption coefficient is solvent-independent, which is an important source of error.[26] Therefore, indirect methods are often used: linear free energy relationships, equilibrium constant extrapolations, acetalization constants or hemiacetalization constants, calculation of formation and solvation free energies, and so forth.[14,15]

Since computational calculations are now a plausible alternative to the experimental determination of equilibrium constants such as pK_a[27−29] and to our knowledge no first-principle approaches have been proposed for the calculation of hydration and hemiacetalization constants, here, we were prompted to address this issue.

Methods of Calculation

The computational calculation of equilibrium constants in solution is very demanding. It may be seen from the thermodynamic definition of K (eq 1) that an error of 5.7 kJ mol^{-1} in $\Delta G°$ results in a deviation of 1 logarithmic unit in K.

$$\log K = -\frac{\Delta G^{\mathrm{o}}}{\ln 10RT} \qquad (1)$$

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* To whom correspondence should be addressed. Phone: +34 923 294486. Fax: +34 923 294574. E-mail: jucali@usal.es.

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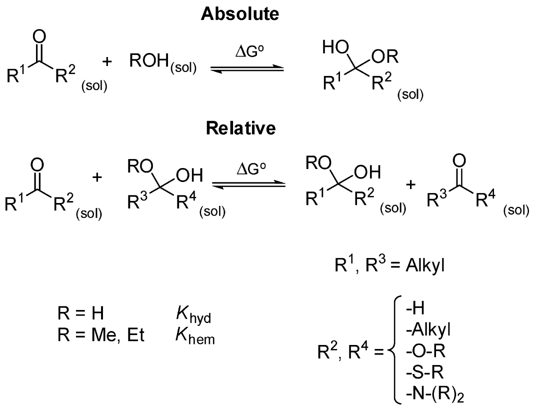
SCHEME 1: Absolute and Relative Calculation of Hydration and Hemiacetalization Energies



Gas-phase free energies are usually calculated using high accuracy ab initio methods, and solution energies are calculated using Self-Consistent Reaction Field (SCRF) methods.

In this work, carbonyl hydration and hemiacetalization constants were calculated from free energy differences between compounds using two different approaches (Scheme 1): an absolute and a relative approach.

In the absolute approach, the reaction free energy is calculated directly as

$$\Delta G^{o} = G_{R^1C(OH)(OR)R^2} - G_{ROH} - G_{R^1COR^2}$$

However, this method has a drawback: short-range solvent−solute interactions (hydrogen bonding, ion-dipole, etc.) are not rigorously modeled by Polarizable Continuum Methods (PCM). Since all three molecules (carbonyl compound, water/alcohol, and diol/hemiacetal) show very different degrees of hydrogen bonding to the solvent, this approach is likely to introduce systematic errors.

In the relative calculation, an exchange reaction is used with a species (R^3COR^4), similar to R^1COR^2, whose K_{hyd} or K_{hem} is well-known experimentally. In this case, the reaction free energy is

$$\Delta G^{o} = G_{R^1C(OH)(OR)R^2} + G_{R^3COR^4} - G_{R^1COR^2} - G_{R^3C(OH)(OR)R^4} \quad (3)$$

and the equilibrium constant can be calculated as

$$\log K = \log K(R^3COR^4) - \frac{\Delta G^{o}}{\ln 10RT} \quad (4)$$

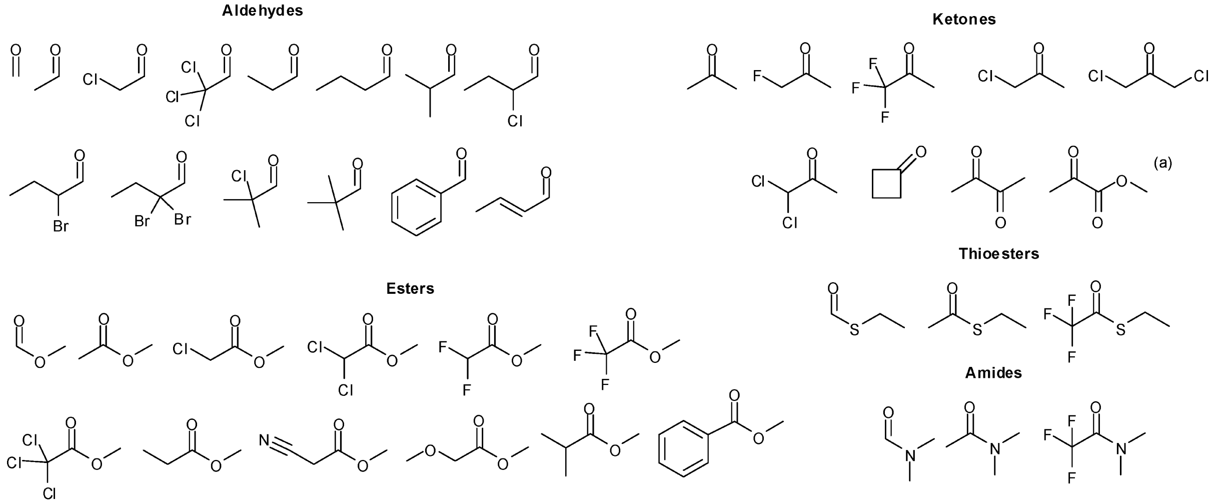
The use of a homodesmic reaction allows (partial) compensation of the effects that could be due to the method systematically evaluating the solvation energies for the carbonyl and the diol/hemiacetal compound differently, because there is one of each on each side of the chemical equation. The effect of solvent hydrogen bonding, which is not taken into account in SCRF models, is also diminished, because the species on both sides of the chemical equation should show very similar degrees of hydrogen bonding with the solvent. Since the charge is present on both sides of the chemical equation and solvent effects are compensated, the method can also be applied to charged molecules.

Because the quality of the results in the relative approach depends strongly on the similarity between R^3COR^4 and R^1COR^2, we checked how choice of the reference affects the calculation of K_{hyd}. Two types of references were used: (i) a common reference for all the compounds: acetaldehyde, whose hydration and hemiacetalization constants are well-known and easy to calculate; (ii) group references: acetaldehyde for aldehydes, acetone for ketones, and methyl acetate for esters, thioesters, and amides in the calculation of the hydration constants.

Although the experimental K_{hyd} values for acetone and methyl acetate are not as accurate as those of acetaldehyde, the greater similarity between the sample and the reference molecules should increase the accuracy of the results.

In the case of hemiacetalization constants, since the equilibrium constant for acetone was not available, acetaldehyde and chloroacetone were used as group references. However, the lack of sufficient experimental data hinders the study of how this choice affects the results.

Computational Details. All calculations were performed using Gaussian 03.[30]



(a) acting as a ketone

Figure 1. Chemical structures of the molecules studied.

TABLE 1: Experimental and Calculated Relative log K_{hyd} Values Using Group References

	log (K_{hyd})				
	DFT-B3LYP[a]	MP2[b]	CBS-Q	mean[c]	exp
aldehydes					
CH_2O	5.00	2.94	3.13	3.69 ± 1.14	3.36[38,39]
CH_3CHO	ref	ref	ref	ref	0.03[39,40]
CH_2ClCHO	2.14	1.52	2.48	2.05 ± 0.49	1.6[39]
CCl_3CHO	3.62	4.59	4.85	4.35 ± 0.65	4.45[39,41]
CH_3CH_2CHO	−0.12	0.11	0.40	0.13 ± 0.26	−0.20[38,39]
$CH_3CH_2CH_2CHO$	−0.19	0.09	0.53	0.14 ± 0.36	−0.30[39,42]
$(CH_3)_2CHCHO$	−0.48	−0.09	0.33	−0.08 ± 0.40	−0.21[38,39]
$CH_3CH_2CHClCHO$	1.02	2.13	2.37	1.84 ± 0.72	1.2[43]
$CH_3CH_2CHBrCHO$	0.98	1.16	0.34	0.83 ± 0.43	0.6[43]
$CH_3CH_2CBr_2CHO$	1.47	0.74	0.65	0.95 ± 0.45	1.0[43]
$(CH_3)_2CClCHO$	1.24	2.22	1.27	1.58 ± 0.56	0.7[43]
$(CH_3)_3CCHO$	−1.74	−0.55	0.79	−0.50 ± 1.27	−0.63[38,39]
PhCHO	−3.28	−2.66	−2.05	−2.66 ± 0.61	−2.1[44]
ketones					
CH_3COCH_3	ref	ref	ref	ref	−2.85[14,39]
CH_2FCOCH_3	−0.13	0.22	−0.64	−0.18 ± 0.43	−0.78[42]
CF_3COCH_3	3.40	3.40	3.80	3.53 ± 0.23	1.54[45]
$CH_2ClCOCH_3$	−0.43	0.48	0.71	0.26 ± 0.60	−1.05[42]
$CH_2ClCOCH_2Cl$	2.14	2.85	1.41	2.13 ± 0.72	1.0[23]
$CHCl_2COCH_3$	0.90	1.86	0.33	1.03 ± 0.77	0.46[23]
cyclobutanone	−2.21	−2.03	−0.69	−1.64 ± 0.83	−2.66[46]
$CH_3COCOCH_3$	−0.47	−0.74	−0.27	−0.49 ± 0.23	0.3[43]
$CH_3COCOOCH_3$	−0.79	−1.35	0.23	−0.64 ± 0.80	0.41[42]
esters					
$HCOOCH_3$	−8.20	−5.76	−5.21	−6.39 ± 1.59	−6.6[47]
CH_3COOCH_3	ref	ref	ref	ref	−8.2[47]
$CH_2ClCOOCH_3$	−6.08	−5.39	−5.20	−5.56 ± 0.46	−6.66[47]
$CHCl_2COOCH_3$	−4.06	−2.59	−2.98	−3.21 ± 0.76	−4.34[47]
CHF_2COOCH_3	−2.36	−2.14	−2.19	−2.23 ± 0.12	−2.92[47]
CF_3COOCH_3	−1.41	−0.99	−1.11	−1.17 ± 0.22	−0.9[47]
CCl_3COOCH_3	−2.70	−4.70	−3.58	−3.66 ± 1.00	−4.24[47]
$CH_3CH_2COOCH_3$	−7.73	−7.17	−7.82	−7.57 ± 0.35	−9.43[47]
$NCCH_2COOCH_3$	−5.40	−5.22	−4.75	−5.12 ± 0.34	−5.87[47]
$CH_3OCH_2COOCH_3$	−6.18	−5.87	−6.56	−6.20 ± 0.35	−9.21[47]
$(CH_3)_2CHCOOCH_3$	−8.89	−7.92	−7.11	−7.97 ± 0.89	−10.42[47]
$PhCOOCH_3$	−10.63	−10.09	−10.03	−9.43 ± 0.64	−10.07[47]
thioesters					
$HCOSC_2H_5$	−0.98	−1.79	−2.07	−1.61 ± 0.57	−3.5[48]
$CH_3COSC_2H_5$	−6.52	−6.42	−6.40	−6.45 ± 0.06	−8.2[48]
$CF_3COSC_2H_5$	−1.11	−2.04	−1.59	−1.58 ± 0.46	−2.8[48]
amides					
$HCON(CH_3)_2$	−11.57	−11.18	−11.70	−11.48 ± 0.27	−13.8[48]
$CH_3CON(CH_3)_2$	−14.73	−11.76	−13.04	−13.18 ± 1.49	−14.2[48]
$CF_3CON(CH_3)_2$	−9.66	−7.63	−8.36	−8.55 ± 1.03	−9.2[48]

[a] DFT-B3LYP 6-31++G(d,p). [b] MP2 6-31++G(d,p). [c] Values are given with standard deviations.

Hydration free energies were obtained at the DFT-B3LYP 6-31++G(d,p),[31,32] MP2 6-31++G(d,p), and CBS-Q levels, and all structures were checked to be true minima (zero imaginary frequencies).

The Complete Basis Set methods (CBS) are a model chemistry that use a complete basis set extrapolation of the correlation energy, performed at the MP2 level of theory and then corrected to the CCSD(T) level via additivity corrections.[33]

Owing to the large size of the hemiacetals, K_{hem} values were only calculated at the DFT-B3LYP 6-31++G(d,p) and MP2 6-31++G(d,p) levels.

The effect of solvation on structure and energy was computed via the SCRF keyword, using the Gaussian 03 default Integral Equation Formalism IEF-PCM.[34−36]

Results and Discussion

Hydration. The molecules studied are shown in Figure 1. They were chosen to cover a wide range of K_{hyd} values, almost 20 logarithm units, and different types of carbonyl compounds: aldehydes, ketones, and carboxylic acid derivatives (esters, thioesters, and amides). It should be noted that hydration free energies are only available for few compounds, which narrows the range of choice.

The K_{hyd} values (Table 1) of aldehydes are higher than those of ketones, and carboxylic acid derivatives have the lowest hydration constants, in the order thioesters ≈ esters > amides.

Electron-withdrawing groups on the α carbons increase the hydration constant, since they increase the electrophilicity of the carbonyl group, whereas electron-donating groups, such as alkyl substituents, decrease the hydration K_{hyd}.

Figure 2 shows the absolute calculated values plotted against the experimental ones for each of the three methods. The following can be seen: (i) The DFT-B3LYP 6-31++G(d,p) values are well correlated; however, the slope shows a significant deviation from unity ($\alpha = 1.23 \pm 0.04$). (ii) MP2 6-31++G(d,p) shows a slightly lower correlation, although the slope is much

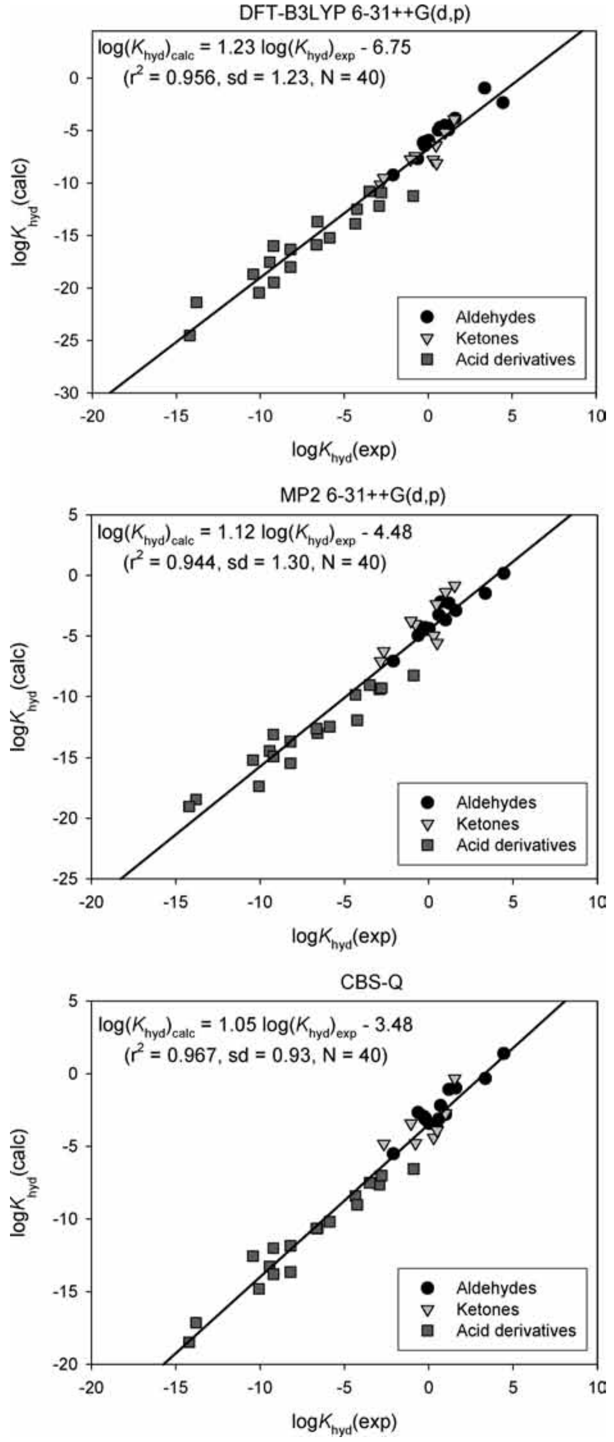


Figure 2. Correlation between the experimental and absolute calculated log K_{hyd} values.

closer to unity than in the case of DFT-B3LYP 6-31++G(d,p) ($\alpha = 1.12 \pm 0.04$). (iii) CBS-Q shows the best correlation, and the slope is significantly equal to unity ($\alpha = 1.05 \pm 0.03$).

In all cases, there is a significant y-intercept, which corresponds to the systematic error in all calculations. This is mostly attributable to errors in the solvation energy, and it can be largely corrected by the use of a relative approach (see below). When choosing the reference molecules (acetaldehyde, acetone, and methyl acetate), their capacity to account for the whole of the y-intercept was considered.

Table 1 shows the calculated relative K_{hyd} values for the molecules studied as compared to the experimental ones. Only relative values calculated with group references are shown; absolute and relative values using a common reference are shown in the Supporting Information.

The results suggest that the use of a relative approach allows the compensation of systematic errors in the solvation energies. A minor tendency for calculated values to be larger than experimental ones can be observed (Table 1). The use of the calibration lines (Figure 2) instead of just one single reference molecule would further correct this remaining systematic error, at the cost of reducing the applicability of this method to other groups of compounds or to hemiacetalization reactions (see below), where experimental values are scarce.

It is also important to keep in mind that, in certain cases, the literature values are estimations, sometimes obtained by making excessively optimistic assumptions; this can lead to error in the experimental values. For instance, the high deviations observed for CF_3COCH_3, $CH_3OCH_2COOCH_3$, and $(CH_3)_2CHCOOCH_3$ suggest that the experimental values may be affected by significant error. Although the amount of data is limited, the difference between calculated and experimental data seems to increase with increasing Taft σ^* for the R groups in $RCOCH_3$. This could be indicative of the known difficulties of PCM methods with halogenated compounds.[37]

Table 2 shows the mean unsigned errors (mues) computed for each of the methods and the mean of all three, using either a common reference or group references.

Regarding use of the common reference, global mues are in the order CBS-Q < MP2 < DFT-B3LYP, being under 1.0 log K_{hyd} units only in the case of CBS-Q. The results of all three methods give mues of about 0.5 log K_{hyd} units for aldehydes. In the case of ketones, the DFT-B3LYP results are close to MP2, with the mue higher than 1.0 log K_{hyd} units. CBS-Q gives mue under 1.0 log K_{hyd} units. On considering carboxylic acid derivatives, it can be seen that the DFT-B3LYP results are very inaccurate, with mues over 2.5 log K_{hyd} units. The MP2 mue is also over 1.5 log K_{hyd} units, whereas the CBS-Q remains under 1.0 log K_{hyd} units.

The use of the mean of the three methods gives very good results for aldehydes and ketones, but the high mue of carboxylic acid derivatives using DFT-B3LYP is reflected in the mean values, making the global results inaccurate.

Switching to group references increases the accuracy of the method at the lower levels of theory because, as expected, the higher-level methods need less empirical correction. Thus, this effect is most important for the DFT-B3LYP results, especially with acid derivatives, which is now reflected in the global mue being under 1.0 logarithm units. The MP2 results are almost insensitive to the use of group references and generally the least accurate. The CBS-Q results for carboxylic acid derivatives are in fact worse than those obtained using the common reference, and this translates into an increased global mue.

Since the DFT-B3LYP values are largely corrected with the use of group references, the values obtained with the mean of the three methods also improve. Only the results obtained at the CBS-Q level using the common reference show lower mue values than these means.

In sum, the CBS-Q results with the common reference are the most accurate for all types of compounds, outdoing DFT-B3LYP, MP2, and the mean results, with or without group references. Almost as accurate, but much cheaper in terms of CPU time and resources, is DFT-B3LYP 6-31++G(d,p) using group references. The mean values of the three methods are in general highly accurate due to error cancellation but very expensive computationally.

TABLE 2: Mean Unsigned Errors of Relative K_{hyd} Values

	mean unsigned error						
	aldehydes	ketones		esters, thioesters, and amides		global	
	group ref	common ref	group ref	common ref	group ref	common ref	group ref
DFT-B3LYP 6-31++G(d,p)	0.57	1.11	0.79	2.84	1.19	1.70	0.90
MP2 6-31++G(d,p)	0.41	1.32	1.23	1.58	1.38	1.15	1.08
CBS-Q	0.56	0.93	0.83	0.92	1.32	0.80	1.00
mean	0.33	0.75	0.94	2.40	1.23	1.25	0.86

TABLE 3: Calculated and Experimental K_{hem} Values

	log K_{hem}					
	absolute		relative			
	DFT B3LYP[a]	MP2[b]	DFT B3LYP[a]	MP2[b]	mean	experimental
in methanol						
aldehydes						
CH_2O	−7.11	−4.00	6.32	3.96	5.14	4.51[45]
CH_3CHO	−11.61	−7.29	ref.	ref.	ref.	1.26[45,46]
CH_3CH_2CHO	−7.01	−3.72	0.85	1.22	1.04	1.20[45]
$CH_3CH_2CH_2CHO$	−2.04	−1.30	1.36	1.54	1.45	1.14[45,46]
$(CH_3)_2CHCHO$	−7.74	−3.76	0.62	1.50	1.06	0.95[45]
$(CH_3)_3CCHO$	−8.79	−4.17	−0.43	1.09	0.33	0.50[45]
$CH_3CH{=}CHCHO$	−7.51	−4.04	−3.24	−2.03	−2.64	−1.82[46]
ketones						
CH_3COCH_3	−11.50	−5.56	−1.93	−3.50	−2.72	−2.14[45,46]
$CH_2ClCOCH_3$	−10.34	−4.49	ref.	ref.	ref.	−0.18[45]
$CH_2ClCOCH_2Cl$	−10.77	−5.36	0.98	0.90	0.94	1.16[45]
$CHCl_2COCH_3$	−13.25	−8.88	0.55	0.03	0.29	0.30[45]
cyclobutanone	−12.19	−6.73	−0.87	−1.34	−1.10	−1.35[46]
in ethanol						
aldehydes						
CH_2O	−7.16	−4.26	5.92	3.87	4.90	4.17[45]
CH_3CHO	−7.53	−3.84	ref	ref	ref	0.93[45]
CH_3CH_2CHO	−2.17	−1.32	0.70	1.27	0.99	0.85[45]
$CH_3CH_2CH_2CHO$	−7.40	−3.91	0.57	1.35	0.96	0.74[45]
$(CH_3)_2CHCHO$	−8.12	−3.70	−0.03	1.49	0.73	0.58[45]
$(CH_3)_3CCHO$	−9.38	−4.46	−1.28	0.73	−0.28	0.24[45]
ketones						
$CH_2ClCOCH_3$	−11.91	−5.79	ref.	ref.	ref.	−0.39[45]
$CH_2ClCOCH_2Cl$	−10.30	−4.22	1.22	1.18	1.20	0.96[45]
$CHCl_2COCH_3$	−11.54	−5.40	−0.02	−0.01	−0.02	−0.12[45]

[a] DFT-B3LYP 6-31++G(d,p). [b] MP2-B3LYP 6-31++G(d,p).

Thus, with the relative approach, the proposed methodology can predict hydration constants for aldehydes within ± 0.5 log K_{hyd} units on average using any of the three levels of theory. The calculation of the hydration constants of ketones and carboxylic acid derivatives can be carried out on average within ± 1.0 logarithm units using a group reference or the higher levels of theory.

Hemiacetalization. The calculated hemiacetalization constants of the compounds studied in methanol and ethanol as solvents are shown in Table 3; the absolute and relative values calculated using group references are shown. The relative values calculated with the common reference (acetaldehyde) are offered in the Supporting Information.

It can be seen that, as was the case with hydration, the absolute values differ significantly from the experimental ones, and this is more patent in the case of the DFT-B3LYP results. The use of the relative approach corrects this deviation.

Given the scarceness of experimental K_{hem} values, the proposed methodology cannot be tested thoroughly, but the results do suggest that this approach can be a useful tool in the calculation of hemiacetalization constants.

Table 4 shows the mean unsigned errors computed for each of the methods, using both a common reference or group references.

TABLE 4: Mean Unsigned Errors of K_{hem} Values

	mean unsigned error			
	common reference		group references	
	MeOH	EtOH	MeOH	EtOH
DFT-B3LYP 6-31++G(d,p)	1.59	1.57	0.51	0.51
MP2 6-31++G(d,p)	0.40	0.34	0.35	0.34
mean	0.87	0.76	0.27	0.23

Since the lack of appropriate experimental data hampers the study of how the use of group references affects the results, ketones and aldehydes cannot be discussed separately. Nevertheless, it is quite clear that the DFT-B3LYP 6-31++G(d,p) values improve significantly with the use of group references, while those at the MP2 6-31++G(d,p) level of theory are rather insensitive to the change in the reference molecules.

The mues obtained are almost equal for methanol and ethanol, suggesting that the alkyl chain of the alcohol does not affect the accuracy of the method.

The results suggest that the proposed methodology can predict hemiacetal formation constants within ± 0.5 logarithm units on average at the MP2 6-31++G(d,p) level of theory using a common reference. The results obtained using the much cheaper

DFT-B3LYP 6-31++G(d,p) level of theory are almost as accurate if group references are used. The use of mean values further improves the results by favorable error cancellation.

Conclusions

(i) The use of a relative approach in the calculation of hydration and hemiacetalization constants allows compensation of systematic errors in the solvation energies.

(ii) The proposed methodology can predict hydration constants within ± 0.5 log K_{hyd} units on average for aldehydes using any of the three levels of theory studied.

(iii) Hydration constants can be calculated for ketones and carboxylic acid derivatives within less than ± 1.0 log K_{hyd} on average at the CBS-Q level of theory. The DFT-B3LYP results using group references are almost as accurate but much cheaper in terms of CPU time and resources.

(iv) The proposed methodology can predict hemiacetal formation constants accurately at the MP2 6-31++G(d,p) level of theory using a common reference. If group references are used, the results obtained using the much cheaper DFT-B3LYP 6-31++G(d,p) level of theory are almost as accurate.

(v) In general, the best results are obtained at the highest levels of theory (CBS-Q for K_{hyd}, MP2 for K_{hem}) if a common reference is used for all compounds. The use of group references improves the results at the lower levels of theory, but at the higher levels, this becomes unnecessary or even counterproductive.

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Supporting Information Available: Free energies for all optimized structures, calculated equilibrium constants not shown in the text, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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