Hydration and Hydrolysis of α-Oxo Carboxylic Acid Derivatives and Conjugate Addition to α,*β*-Unsaturated Carbonyl Compounds: A Density Functional Study

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Hydration of the keto group as well as hydrolysis (ester and amide) of α-oxo carboxylic acid derivatives has been studied by density functional theory (B3LYP/6-31G* and B3LYP/6-311G**). Both uncatalyzed as well as water-assisted processes have been considered. Solvent effects were approximated by the self-consistent isodensity surface polarized continuum (SCIPCM) model. For hydrolysis reactions a concerted as well as a stepwise mechanism was calculated. In the latter one, addition of the nucleophile to a tetrahedral intermediate was found to be rate determining. In uncatalyzed processes both concerted and stepwise mechanisms are calculated to have comparable activation energies and free enthalpies. In catalyzed reactions the stepwise mechanism is predicted to be considerably more favorable. Hydration of the α-oxo group should be much more feasible than either ester or amide hydrolysis.

Introduction

Heterocyclic 2,3-diones **1** (e.g., furan (X = O) or pyrrole-2,3-diones (X = N-R^3) besides being versatile synthons for a great variety of polycyclic heteroaromatic compounds[1] or a source of α-oxo ketenes[2] also show typical carbonyl reactions, e.g., addition of nucleophiles. Due to the rather unique feature of these compounds in combining different types of carbonyl groups as well as conjugated C=C double bonds, at least three modes of reaction are conceivable (Scheme 1). Addition to C2 leads to lactone (lactam) ring opening (or, more generally, ester (amide) hydrolysis); reaction at C3 corresponds to ketalization of α-keto carboxylic acid derivatives; and finally, conjugate (1,4-) addition at C5 also might be possible. In fact, depending on the nature of the substituents R^1−R^3 and the nucleophile used in these reactions, examples for all three addition modes have been described.[3]

Since reactions of carbonyl compounds with nucleophiles are among the most important transformations in organic chemistry and biochemistry,[4] a great number of both experimental[4−8] as well as computational[7−18] studies have been (and still are) devoted to these reactions. Of special interest are reactions of α-keto carboxylic acid derivatives as exemplified by structures **2**, **4**, and **5**,

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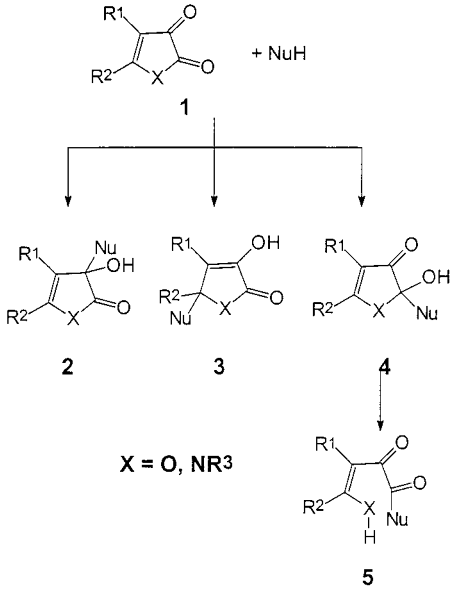
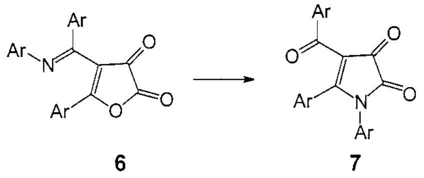
10.1021/jo990105o CCC: $18.00

Scheme 1



Scheme 2



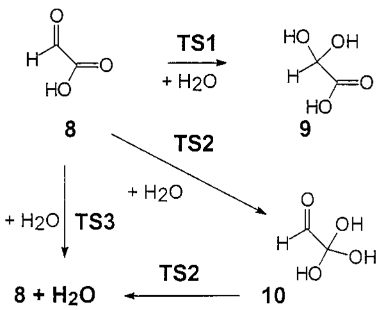
respectively. Compounds of this type play a crucial role in biochemistry, e.g., as substrates of oxidoreductases or as energy providing systems for the unfavorable conversion of ADP to ATP.[5] Ester or amide hydrolysis as well as hydration of the keto functionality in α-oxo carboxylic acid derivatives is susceptible to enzymatic catalysis.[5] Given this general importance of carbonyl–nucleophile reactions in chemistry and biochemistry, we found it worthwhile to study theoretically the peculiar reactions (see Scheme 1) of **1** by means of suitable model systems in somewhat more detail. Further incentive for this work stems from the still elusive mechanistic details of the rather facile rearrangement reactions shown by these compounds (Scheme 2).[19,20]

In the following, results of hybrid HF/density functional calculations for a variety of representative reactions of model systems will be presented. The model reactions (Schemes 3–5) were chosen to grasp not only the essential features of the reactions of **1** depicted in Scheme 1 but also those for a nucleophile-catalyzed rearrangement **6** → **7** (Scheme 2, addition of the nucleophile either at C2 or C5) and the general reactivity toward nucleophiles shown by α-oxo carboxylic acid derivatives. The only problem in choosing model compounds **8**, **11**, and **14** might arise from the possible ring strain relief in ring-opening reactions of compound **1**.

Computational Methods

All computations were done by the Gaussian 94 program suite.[21] The 6-31G* and 6-311G** basis sets were used throughout. Geometries were completely optimized with the aid of Becke's three-parameter[22] hybrid density functional–HF method with the Lee–Yang–Parr correlation functional[23] (B3LYP/6-31G* and B3LYP/6-311G**). All stationary points were characterized as minima or transition states by vibrational frequency calculations at the same level of theory as geometry optimization. In addition, for transition states intrinsic reaction coordinate (IRC) calculations at the B3LYP/6-31G* level of theory were performed. Zero-point energies (ZPE) are unscaled. Bulk solvent effects (aqueous solution, $\epsilon = 79.5$) were estimated by single-point self-consistent isodensity polarized continuum model (SCIPCM) calculations[24] with an isodensity surface cutoff of 0.0004 au. Thermodynamic quantities were calculated at 298 K and 1 atm using standard rigid-rotor harmonic oscillator partition function expressions.

Scheme 3



Results

The model reactions considered here are depicted in Schemes 3–5. In each case both uncatalyzed reactions as well as H_2O-assisted processes including one ancillary water molecule are considered. Total energies, zero-point energy contribution, and ΔG corrections (B3LYP/6-31G* and B3LYP/6-311G**) for all minima and transition states shown in Schemes 3–5 (gas phase and aqueous solution (SCIPCM[24])) are collected in Table S1 of the Supporting Information. In the following, transition states of uncatalyzed reactions will be denoted by **A** and those for H_2O-assisted reactions by the letter **B**. Apart from hydration at C2 in **8**, reaction at the carboxylic carbon atom as a model for ester hydrolysis or lactone ring opening—either via a stepwise mechanism involving intermediate **10** or a direct hydrolysis—is conceivable (**TS3A** for the uncatalyzed and **TS3B** for the H_2O-assisted reaction; Scheme 3). Analogous reactions are considered for the corresponding glyoxylic amide **11** (Scheme 4). Although ring-opening reactions of α,β-unsaturated five-membered lactones in alkaline solution have been proposed to occur via stepwise 1,2-addition at the carbonyl carbon atom,[6b,7] addition of the nucleophile at C5 might be a possibility.[20] The corresponding model reactions are shown in Scheme 5. Again, a direct hydrolysis, modeled by the identity reaction **(E)-14** → **(E)-14** via transition state **TS12A** (uncatalyzed) and **TS12B** (H_2O-assisted), can be envisaged.

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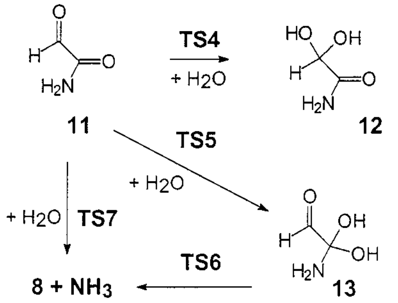
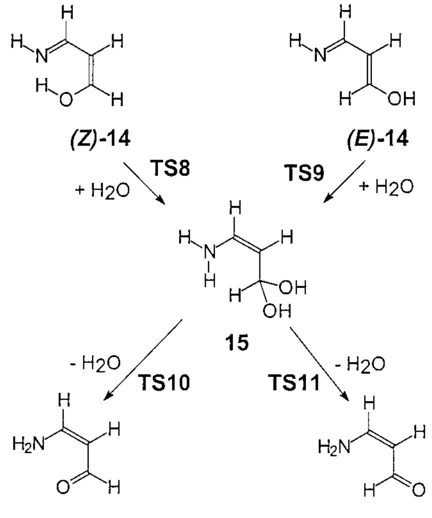
Scheme 4



Scheme 5



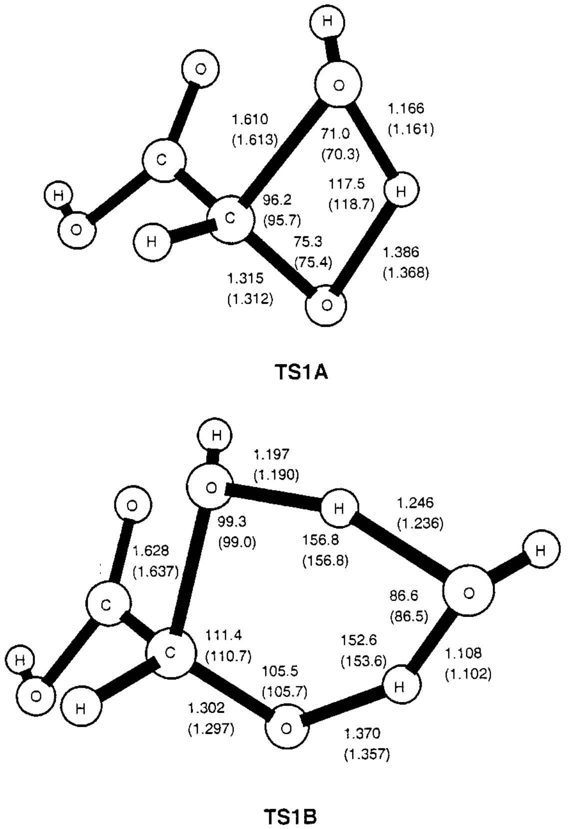


Figure 1. B3LYP/6-31G* and B3LYP/6-311G** (values in parentheses) calculated structures (bond lengths in Å, bond angles in deg) of transition states for the uncatalyzed (**TS1A**) and H_2O-assisted (**TS1B**) hydration at C2 of glyoxylic acid **8**.

Relative energies including zero-point energy corrections and $\Delta\Delta G$ values in gas phase and aqueous solution (measured with respect to the reactants **8**, **11**, and **(E)-14** + $n H_2O$ at infinite separation) for the uncatalyzed reactions ($n = 1$) are summarized in Table 1; those for the H_2O-assisted reactions ($n = 2$) are summarized in Table 2.

As typical examples of transition states for the uncatalyzed and catalyzed, respectively, addition of H_2O the structures of **TS1A** and **TS1B** are depicted in Figure 1. As evidenced by the imaginary frequencies (see Table S2 of the Supporting Information) of the various transition states as well as their structures, the barrier to reaction mainly results from proton transfer. The rather high activation energies obtained for the uncatalyzed reactions can be attributed to unfavorable proton-transfer geometries.[15,25] Any catalyst, e.g., an ancillary water molecule, which leads to more linear H-bonds H−O−H at the transition state, should lower the corresponding activation energy.[15] However, since entropic effects are known to be determining for the reactivity of weakly interacting systems,[26] any such energy lowering might be offset by the $T\Delta S$ contribution. This is obviously the case for reactant and/or product−H_2O complexes, e.g., **[8 + H_2O]**, **[11 + H_2O]**, **[8 + NH_3]** in Table 1 or **[8 +2 H_2O]** and **[11 + 2 H_2O]** in Table 2, which are computed to be stable if energies but unstable if $\Delta\Delta G$ values are considered. Similar results have been observed previously.[11,13,16] However, it should be pointed out that the systems investigated here contain many low-frequency modes. In such cases a statistical thermodynamic analysis based on the harmonic oscillator approximation may result in significant errors.[27,28] Even more problematic appears to use the ideal-gas-phase rigid-rotor harmonic-oscillator partition function expressions to describe molecules in solutions where many intermolecular interactions are likely to be significant. However, it appears to have become common practice to use ΔG corrections not only in gas phase but also in combination with SCRF models of bulk solvent effects.[11,12,16] Therefore, for the sake of completeness and comparability, we have also included $\Delta\Delta G$ values in Tables 1 and 2. As pointed out above, the following discussion using these calculated ΔG values has to be taken cum grano salis. A further caveat arises from the definition of the standard state used in the calculation of thermodynamic quantities (1 atm, 298 K). For solutions, a more natural choice of standard state would be mol L^{-1}. For all but unimolecular reactions such a change in standard states is accompanied by a change in entropies.[29] At 298 K an increase of $T\Delta S^{\ddagger}$ of ~2 and ~4 kcal mol^{-1} for bimolecular (i.e., uncatalyzed additions)

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(28) For $(H_2O)_2$, calculated dimerization enthalpies (kcal mol^{-1}) are −5.9 (B3LYP/6-311G**, −4.1 (B3LYP/6-311++G**, −5.3 (MP2/6-311G**), and −4.3 (MP2/6-311++G**); dimerization free enthalpies are −0.6, 2.3, 0.7, and 2.1, respectively. The experimental gas-phase enthalpy and entropy of association for the water dimer are −3.59 kcal mol^{-1} and −18.59 cal K^{-1} mol^{-1}, respectively.[30] Thus, at room temperature, $\Delta G \approx 2$ kcal mol^{-1}.

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Table 1. Calculated (B3LYP/6-31G* and B3LYP/6-311G) Relative Energies E_{rel} (including ZPE corrections) and Free Enthalpies ΔG_{rel} of the Various Minima and Transition States for the Uncatalyzed Reactions (gas phase and aqueous solution) Depicted in Schemes 3–5 (in kcal mol^{-1})**

	gas phase				aqueous solution[a]			
	B3LYP/6-31G*		B3LYP/6-311G**		B3LYP/6-31G*		B3LYP/6-311G**	
compd	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}
8 + H_2O	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
[8 + H_2O]	−4.7	3.3	−4.7	3.2	−1.0	7.0	−1.2	6.7
TS1A	27.7	37.9	30.5	40.6	31.7	41.8	34.2	44.3
9	−13.5	−3.6	−11.5	−1.7	−9.0	0.9	−7.2	2.7
TS2A	32.8	43.2	35.2	45.5	39.0	49.4	41.0	51.3
10	−1.9	8.1	−0.2	9.8	4.1	14.1	5.6	15.6
TS3A	36.4	46.1	37.0	46.6	40.9	50.6	41.8	51.3
11 + H_2O	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
[11 + H_2O]	−5.4	2.6	−5.3	2.6	−0.9	7.1	*b*	*b*
TS4A	24.2	34.6	27.0	37.1	31.4	41.8	34.8	44.9
12	−16.2	−6.0	−14.3	−4.2	−8.6	1.6	−6.9	3.1
TS5A	33.7	44.2	35.7	45.9	41.8	52.4	43.4	53.7
13	0.4	10.8	2.2	12.4	9.0	19.4	10.6	20.9
TS6A	34.9	45.3	37.9	48.1	38.8	49.2	41.6	51.8
[8 + NH_3]	−7.1	0.7	−5.0	2.4	−0.2	7.7	*b*	*b*
8 + NH_3	−2.3	−2.9	−0.2	−0.9	2.5	1.9	4.8	4.1
TS7A	35.7	45.8	37.4	47.3	37.9	48.0	39.0	49.0
(E)-14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
(Z)-14	−11.5	−10.9	−11.2	−10.6	−8.4	−7.8	−8.4	−7.8
[(E)-14 + H_2O]	−8.8	−0.2	−8.9	−0.3	−6.2	2.4	−6.5	2.1
[(Z)-14 + H_2O]	−14.5	−7.0	−14.3	−6.5	−9.8	−2.3	−9.9	−2.1
TS8A	17.8	28.3	19.3	29.8	24.7	35.2	25.6	36.1
TS9A	15.5	25.9	16.4	26.7	20.1	30.4	20.7	31.0
15	−14.9	−5.1	−12.2	−2.6	−9.0	0.8	−6.4	3.2
TS10A	16.6	26.5	19.3	29.1	20.7	30.5	22.6	32.4
[(Z)-16 + H_2O]	−28.7	−20.0	−27.3	−18.7	−24.0	−15.3	−22.9	−14.3
(Z)-16	−20.7	−20.4	−19.2	−18.8	−20.2	−20.0	−18.9	−18.6
TS11A	22.0	31.9	24.0	33.7	25.5	35.4	26.9	36.6
[(E)-16 + H_2O]	−20.5	−13.1	*b*	*b*	−20.9	−13.5	*b*	*b*
(E)-16	−13.0	−13.0	−11.9	−12.0	−15.7	−15.7	−14.8	−15.0
TS12A	57.4	67.1	58.3	67.9	59.4	69.1	60.4	70.1

[a] SCIPCM ($\epsilon = 79.5$). [b] Not converged.

and termolecular (i.e., catalyzed hydrations) reactions, respectively, is expected.[29] With respect to basis size effects on calculated relative energies and enthalpies, the data of Tables 1 and 2 clearly indicate that there is little difference between results obtained at the B3LYP/6-31G* and B3LYP/6-311G** levels of theory. Similarly, there is also little effect on calculated structures. Relevant geometric parameters of the various transition states are collected in Table S3 (uncatalyzed reaction) and Table S4 (water-assisted reaction) of the Supporting Information. Mean deviations between these data obtained from B3LYP/6-31G* and B3LYP/6-311G** calculations are 0.02 Å (bond lengths) and 0.9° (bond angles).

Discussion

Uncatalyzed Reactions. As a general feature, formation of initial reactant–water encounter complexes is in all cases except that of **[(Z)-14 + H_2O]** exothermic but endergonic, stressing the importance of entropic contributions. Inclusion of bulk solvent effects enforces this trend (see Table 1). Product complexes **[8 + NH_3]**, **[(Z)-16 + H_2O]**, and **[(E)-16 + H_2O]** are also unstable with respect to the corresponding separated products. As anticipated, the entropic term increases activation barriers of addition steps (**TS1A**–**TS5A**, **TS7A**–**TS9A**), even if activation energies are measured relative to the primary encounter complexes rather than separated reactants. For 1,2-addition transition states this increase amounts to ≈ 5 kcal mol^{-1} for the gas-phase reaction and nearly 10 kcal mol^{-1} in aqueous solution. As a consequence—although $\Delta E^{\ddagger}$ in solution is only slightly higher than in the gas phase—a significant increase of $\Delta G^{\ddagger}$ is calculated in aqueous solution. For the 1,4-addition (**TS8A** and **TS9A**) a substantially smaller entropic effect is calculated (gas phase, 2–3 kcal mol^{-1}; aqueous solution, 3–4 kcal mol^{-1}). Clearly, in stepwise reactions, the contribution of the $T\Delta S$–term to the barrier of the second step is expected to be smaller than for the bimolecular first step (**10** → **8**, i.e., **TS2A** relative to **10**, **TS6A**, **TS10A**, **TS11A**). The data of Table 1 are in line with this expectation, e.g., $\Delta E^{\ddagger}$(**10** → **8** + **H_2O**) ≈ $\Delta G^{\ddagger}$(**10** → **8** + **H_2O**), $\Delta E^{\ddagger}$(**13** → **8** + **NH_3**) ≈ $\Delta G^{\ddagger}$(**13** → **8** + **NH_3**), $\Delta E^{\ddagger}$(**15** → **(Z)-16** + **H_2O**) ≈ $\Delta G^{\ddagger}$(**15** → **(Z)-16** + **H_2O**), and $\Delta E^{\ddagger}$(**15** → **(E)-16** + **H_2O**) ≈ $\Delta G^{\ddagger}$(**15** → **(E)-16** + **H_2O**). Inclusion of bulk solvent effects either has little effect (**10** → **8** + **H_2O**) or—in all other reactions—leads to a lowering of this second barrier. This lowering is, however, to a large extent counterbalanced by the effect arising from the definition of the standard state: using the definition of mol L^{-1} instead of atm lowers $\Delta G^{\ddagger}$ of the first bimolecular step by ~2 kcal mol^{-1}. Consequently, in the gas phase formation of the tetrahedral intermediates **10** and **13** are rate determining in the stepwise uncatalyzed hydrolysis reactions **8** → **10** → **8** and **11** → **13** → **8** + **NH_3**. In contrast, in solution both steps are of comparable free enthalpies of activation. Hydration of the α-oxo carbonyl group (**TS1A**, **TS4A**) is predicted to be considerably more feasible than that of either ester and even more so than that of amide hydrolysis, especially in aqueous solution. With respect to a direct or stepwise hydrolysis mechanism, for the uncatalyzed reaction in

Table 2. Calculated (B3LYP/6-31G* and B3LYP/6-311G) Relative Energies E_{rel} (including ZPE corrections) and Free Enthalpies ΔG_{rel} of the Various Minima and Transition States for the H_2O-Assisted Reactions (gas phase and aqueous solution) Depicted in Schemes 3–5 (in kcal mol^{-1})**

	gas phase				aqueous solution[a]			
	B3LYP/6-31G*		B3LYP/6-311G**		B3LYP/6-31G*		B3LYP/6-311G**	
compd	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}	E_{rel}	ΔG_{rel}
[8 + $2H_2O$]	−14.3	3.0	−14.0	2.8	−6.8	10.4	−6.8	10.0
TS1B	0.2	19.8	3.1	22.7	7.9	27.5	10.6	30.2
[9 + H_2O]	−23.2	−4.6	−20.9	−2.5	−14.6	4.1	−12.5	6.0
9 + H_2O	−14.8	−3.6	−12.9	−1.7	−9.0	0.9	−7.2	2.7
[8 + $2H_2O$]′	−17.7	0.4	−17.2	0.5	−8.5	9.6	−8.5	9.3
TS2B	6.8	26.9	9.4	29.1	15.9	35.7	18.1	37.8
[10 + H_2O]	−9.8	8.8	−8.1	10.4	−1.4	17.2	0.2	18.7
10 + H_2O	−1.9	8.1	−0.2	9.8	4.1	14.1	5.6	15.6
TS3B	18.1	37.8	19.9	39.5	24.7	44.3	26.5	46.0
[11 + $2H_2O$]	−17.1	0.1	−17.6	−0.7	−7.4	9.8	−8.0	8.9
TS4B	−4.8	15.2	−1.7	18.0	6.1	26.1	8.8	28.6
[12 + H_2O]	−26.7	−7.8	−24.5	−5.9	−14.1	4.9	−12.3	6.3
12 + H_2O	−16.2	−6.0	−14.3	−4.2	−8.6	1.6	−6.9	3.1
[11 + $2H_2O$]′	−18.8	−0.7	−18.4	−0.8	−8.1	10.0	−8.5	9.1
TS5B	9.2	29.0	11.6	31.3	21.6	41.5	23.7	43.4
[13 + H_2O]	−9.1	9.7	−7.4	11.3	4.1	22.9	5.6	24.2
13 + H_2O	0.4	10.8	2.2	12.4	9.0	19.4	10.6	20.9
TS6B	1.0	21.0	4.5	24.3	13.0	33.0	15.9	35.8
[8 + NH_3 + H_2O]	−18.0	0.3	−15.4	2.4	−5.3	12.9	−3.2	14.6
8 + NH_3 + H_2O	−2.3	−2.9	−0.2	−0.9	2.5	1.9	4.8	4.1
TS7B	20.2	40.0	23.1	42.6	*b*	*b*	30.3	49.9
[(E)-14 + $2H_2O$]	−17.5	−0.9	−17.5	−0.8	−11.5	5.1	−11.9	4.7
[(Z)-14 + $2H_2O$]	−21.7	−5.0	−21.6	−5.2	−13.7	3.0	−14.6	1.9
TS8B	−0.2	20.1	2.7	22.8	10.6	30.8	12.8	32.9
TS9B	2.0	21.4	3.7	23.1	9.3	28.7	10.3	29.7
[15 + H_2O]	−25.2	−6.6	−22.1	−3.7	−15.4	3.3	−12.6	5.8
15 + H_2O	−14.9	−5.1	−12.2	−2.6	−9.0	0.8	−6.4	3.2
TS10B	−7.7	11.9	−4.6	14.9	1.5	21.1	3.9	23.4
[(Z)-16 + $2H_2O$]	−36.2	−19.5	−34.8	−18.1	−30.1	−13.5	−29.3	−12.6
(Z)-16 + $2H_2O$	−20.7	−20.4	−19.2	−18.8	−20.2	−20.0	−18.9	−18.6
[(E)-16 + $2H_2O$]	−35.6	−17.8	−33.8	−16.3	−28.0	−10.3	−26.8	−9.3
(E)-16 + $2H_2O$	−13.0	−13.0	−11.9	−12.0	−15.7	−15.7	−14.8	−15.0
TS12B	41.1	60.1	41.6	60.3	42.7	61.6	43.4	62.0

[a] SCIPCM (ϵ = 79.5). [b] Not converged.

the gas phase the stepwise path is favored. In solution either this difference is blurred out (**8**) or the direct hydrolysis becomes more favorable (**11**). These results are in line with previous findings indicating a dependence of the preferred mechanism on both solvent or subtle changes in molecular structure.[11a] The barrier for conjugate addition to **(Z)-14** (**TS8A**) is comparable to that for 1,2-addition to the α-oxo carbonyl in **8** or **11**. At first glance, the energy of **TS9A** seems to be unusually low. However, this low barrier—as compared to **TS8A**—can be attributed to the fact that for formation of **TS8A** an intramolecular hydrogen bond between the imino nitrogen atom and the OH group, not present in **(E)-14**, has to be broken. The low barrier compared to **TS1A** and **TS4A** is explainable in terms of the respective structures (see Figures 1 and 2). In **TS9A** (and also **TS8A**) a considerable more favorable proton-transfer geometry with a concomitant lowering of the respective barrier is achieved than in transition states for uncatalyzed 1,2-additions. Dehydration of the intermediate **15** to β-amino acrolein (**(Z)-16**, **(E)-16**) + **H_2O**, considered as model reaction for the second step in the stepwise lactone ring opening of e.g. **6** via C5-addition of the nucleophile, is calculated to be rate determining in case of formation of **(E)-16**. In contrast, dehydration of **15** to yield **(Z)-16** has a lower barrier, especially in solution, than formation of **15**. For the reverse reaction, i.e., 1,2-addition of the nucleophile to the α,β-unsaturated carbonyl compound β-amino acrolein **(Z)-16** and **(E)-16** rather high barriers (≈45–50 kcal mol^{-1}) are found. Compared to 1,2-addition at C2 of **8** (**TS1A**, see Figure 1) or even more so to **11** (**TS4A**, Table S3), the structures of transition states **TS10A** and, especially, **TS11A** are somewhat unusual: the forming (or breaking) C–O bond is considerably more elongated (1.9–2.2 Å as compared to ≈1.6 Å in **TS1A** and **TS4A**, see Table S3 and Figure 2). The uncatalyzed direct hydrolysis of **(E)-14** appears to be completely unfavorable (**TS12A**).

Catalyzed Reactions. The energy gain by formation of additional hydrogen bonds to the ancillary water molecule is offset by the entropy term.[11,13,16] Thus, although ΔE for the primary [reactant + $2H_2O$] complexes is significantly more negative than for the [reactant + H_2O] complexes, on the basis of free enthalpies—except **[(Z)-14 + $2H_2O$]** in the gas phase—none of these complexes are stable. In aqueous solution even formation of this latter complex is calculated to be endergonic. As mentioned above, at the level of theory used here (B3LYP/6-31G* and B3LYP/6-311G**) formation of **[(Z)-14 + H_2O]** is calculated not only to be exothermic but also exergonic. Thus this compound nicely demonstrates the offset of energy gain by entropy loss as the number of interacting species increases (compare **[(Z)-14 + H_2O]** with **[(Z)-14 + $2H_2O$]**). The most significant effect of a catalytic water molecule, however, is the quite substantial decrease in activation energies and free enthalpies. In some cases, as found by others,[11,13,16] even negative $\Delta E^{\ddagger}$ values are obtained. If, however, $\Delta E^{\ddagger}$ is measured relative to the respective primary encounter complexes, the effect of the ancillary water molecule on $\Delta E^{\ddagger}$ is

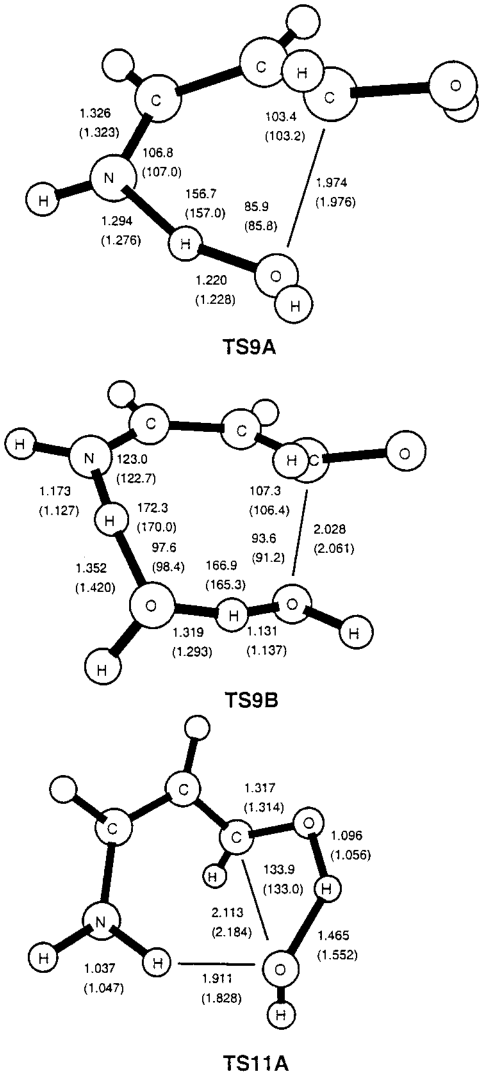

Figure 2. B3LYP/6-31G* and B3LYP/6-311G** (values in parentheses) calculated structures (bond lengths in Å, bond angles in deg) of transition states **TS9A, TS9B**, and **TS11A**.

comparable to that on $\Delta G^{\ddagger}$. There is also little influence of the medium (gas phase or aqueous solution) on the change in $\Delta E^{\ddagger}$ or $\Delta G^{\ddagger}$ in going from the uncatalyzed to the catalyzed reaction. The most dramatic decrease in the barrier to addition of the nucleophile is obtained for reaction at C2 (**TS1A** vs **TS1B**, **TS4A** vs **TS4B**) and—to a somewhat lesser extent—for addition at C1 (**TS2A** vs **TS2B**, **TS5A** vs **TS5B**) as well as conjugate addition to **(Z)-14** (**TS8A** vs **TS8B**). In contrast, the computed energy barrier lowering by catalysis of the direct hydrolysis of **8** is only half that obtained for formation of the tetrahedral intermediate **10** (**TS2A** vs **TS2B**, **TS3A** vs **TS3B**). The unfavorable entropy term is expected to be smaller for the decomposition of the tetrahedral intermediates **10** and **13** than for their formation. Therefore, in the catalyzed reaction addition of the nucleophile to the carbonyl group by far is rate determining. The catalytic effect of the additional H_2O on both $\Delta E^{\ddagger}$ as well as $\Delta G^{\ddagger}$ of the direct hydrolysis of **11** (**TS7A** vs **TS7B**) is surprisingly small, especially when bulk solvent effects are taken into account. In this latter case essentially no catalysis at all is found. Consequently, whereas for the uncatalyzed reactions stepwise and concerted hydrolysis have comparable activation energies, for the catalyzed processes a stepwise mechanism should be far more feasible (6−10 kcal mol^{-1} lower barriers). As was the case for the uncatalyzed reactions, hydration of the α-oxo carbonyl is calculated to be considerably more feasible than either ester or amide hydrolysis (**TS1B** vs **TS2B**, **TS4B** vs **TS5B**). Experimentally, for methyl pyruvate[5b] the rate constant for ester hydrolysis is ≈5 orders of magnitude lower than that for hydration. The corresponding ≈7 kcal mol^{-1} difference in activation energies is in good agreement with the difference between e.g. **TS1B** and **TS2B** (Table 2). Formation of the C2 hydrates **9** and **12** is calculated to be exothermic as well as exergonic in the gas phase and exothermic and endergonic in aqueous solution. Experimental hydration constants for pyruvic acid vary from 0.68[31] to 2.31[5a] corresponding to $\Delta G = -0.5$ to 0.2. For pyruvic amide $K_{\mathrm{H}} = 0.8$ corresponding to $\Delta G = 0.1$ kcal mol^{-1} has been found.[5d] Calculated stabilities of the hydrates, thus, appear somewhat underestimated. The comparably low catalytic effect on the 1,4-addition to **(E)-14** may be rationalized by the structures of the respective transition states **TS9A** and **TS9B** (Figure 2): in **TS9A** already a quite favorable proton-transfer geometry can be attained; therefore, apart from an additional hydrogen bond there is little energy gain by involvement of a second water molecule. For dehydration of the intermediate **15**, again a strong catalytic effect (**TS10A** vs **TS10B**) is obtained. Despite several attempts it has not been possible to locate **TS11B.** Instead, only the transition state for proton transfer between the OH group and the imino nitrogen, i.e., tautomerization **[(E)-14 + 2 H_2O] → [(E)-16 + 2H_2O]** catalyzed by two water molecules (**TS13B**), could be found.

Conclusions and Outlook

Hybrid density functional/HF (B3LYP/6-31G* and B3LYP/6-311G**) calculations on the hydration as well as hydrolysis of α-oxo carboxylic acid derivatives (i.e., 1,2-addition of nucleophiles to carbonyl compounds) and conjugate additions to α,*β*-unsaturated carbonyl derivatives have been presented. Both uncatalyzed and water-assisted concerted as well as stepwise reactions were considered. Calculations were performed for gas phase and aqueous solution by treating bulk solvent effects with the self-consistent isodensity surface polarized continuum model (SCIPCM[24]). In the case of uncatalyzed reactions, the concerted and stepwise mechanisms for amide hydrolysis have comparable activation energies; medium or substituent effects, thus, could be decisive for which one of these two alternative pathways will be followed. In water-assisted reactions, however, the stepwise hydrolysis of α-oxo carboxylic acid derivatives should be strongly favored over the concerted one. Addition of the nucleophile to yield a tetrahedral intermediate rather than its decomposition is calculated to be rate determining, especially for the assisted mechanisms. The transition state for 1,4-addition to **(E)-14** is characterized by a six-membered array otherwise adopted in TS's for H_2O-assisted additions, whereas for the catalyzed reaction an eight-membered cyclic TS is obtained. Thus, catalysis of this peculiar addition reaction has only a minor effect on activation energies and, especially, activation free

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enthalpies. Although for catalyzed reactions the $T\Delta S$ contribution is quite unfavorable, generally not only a significant lowering of activation energies but also free enthalpies is calculated. In solution, when the more natural standard state of mol L^{-1} is adopted, for bimolecular and even more so for termolecular (i.e., catalyzed) reactions this effect is enhanced.

Concerning the reactions of compound **1** relief of ring strain in ring-opening reactions might make such reactions more feasible than in the acyclic model compounds **8**, **11**, and **14**. From the results presented in the present paper it is apparent that the B3LYP/6-31G* level of theory should be of sufficient reliability for the treatment of the reactions of carbonyl compounds with neutral nucleophiles. Calculations at this level of theory on the reactions of compound **1** are in progress, and we will report our results in due course.

Supporting Information Available: Tables of total energies, zero point energy corrections, imaginary frequencies, and pertinent geometrical parameters of transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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