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Ab initio and density functional theory studies on the mechanism of nucleophilic vinylic substitution of 4*H*-pyran-4-one and 2-methyl-4*H*-pyran-4-one with ammonia

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Abstract. Nucleophilic vinylic substitutions of 4*H*-pyran-4-one and 2-methyl-4*H*-pyran-4-one with ammonia were calculated by the B3LYP method using the 6-31G(d,p) basis set. Bulk solvent effects of aqueous solution were estimated by the polarized continuum and Poisson–Boltzmann self-consistent reaction field models using the 6-311 + G(d,p) basis set. In the gas phase different mechanisms were found for the two reaction systems calculated. The reaction of 4*H*-pyran-4-one proceeds through enol, whereas a feasible path for the less reactive 2-methyl-4*H*-pyran-4-one is the mechanism through a keto intermediate. Addition of ammonia in concert with proton transfer is the rate-determining step ofthe reaction. The mechanism proceeding either by a bimolecular nucleophilic substitution (S_N2) or by one involving a tetrahedral zwitterionic intermediate is shown to be unlikely in the gas phase or nonpolar solution. The effects of bulk solvent not only consist in a reduction of the various activation barriers by about 25–40 kJ mol^{-1} but also in a change in the reaction mechanism.

Keywords: 4*H*-Pyran-4-one – Ammonia – Nucleophilic vinylic substitution – Addition–elimination mechanism – Ab initio

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Introduction

Our previous studies [1] dealing with ab initio and density functional theory calculations on the mechanism of nucleophilic vinylic substitution of 4*H*-1-benzopyran-4-one (chromone) and 4*H*-pyran-4-one with a hydroxide ion indicated different mechanisms of the reaction in the gas phase and aqueous solution, i.e., addition of hydroxide ion to the C2 carbon of the pyranone is the rate-determining step in aqueous solution, whereas the elimination step can be expected as rate-determining in the gas phase. These calculations confirmed the mechanism proposed by Zsuga and coworkers [2], who studied the kinetics of the reactions of flavone, isoflavones and chromones with a hydroxide ion in aqueous solution. But a more recent kinetics study by Davidson and Kaye [3] demonstrated a different mechanism for this type of the reaction. They established elimination of the leaving group (i.e., ring fission) as the rate-determining step of the reactions of 4-oxo-4*H*-1-benzopyran-2-carboxamides with ethanolic dimethylamine. In the previously mentioned kinetics studies, two different nucleophiles (anionic oxygen versus neutral nitrogen nucleophile) were used, and thus one might expect different mechanisms for ring-opening reactions of the pyranones depending on the nucleophile as well as the substrate, solvent effects and pH conditions [4]. The kinetics studies with the amine nucleophile [3] were carried out in polar solution, and therefore among other things, the question arises whether the same mechanism can be expected in nonpolar solution. Moreover, owing to the partial aromatic character of the pyranone ring a different mechanism might be expected for the ring-opening reactions of pyranones with amines compared with similar nucleophilic vinylic substitutions, for example, of α,β-unsaturated carbonyl compounds and their analogues with amines [5]. In this paper we investigate the mechanism of nucleophilic vinylic substitution between a pyranone derivative and amine nucleophile, namely, the reactions of 4*H*-pyran-4-one (2-H) and 2-methyl-4*H*-pyran-4-one (2-CH_3) with ammonia assisted

by a second ammonia molecule using quantum-chemical methods.

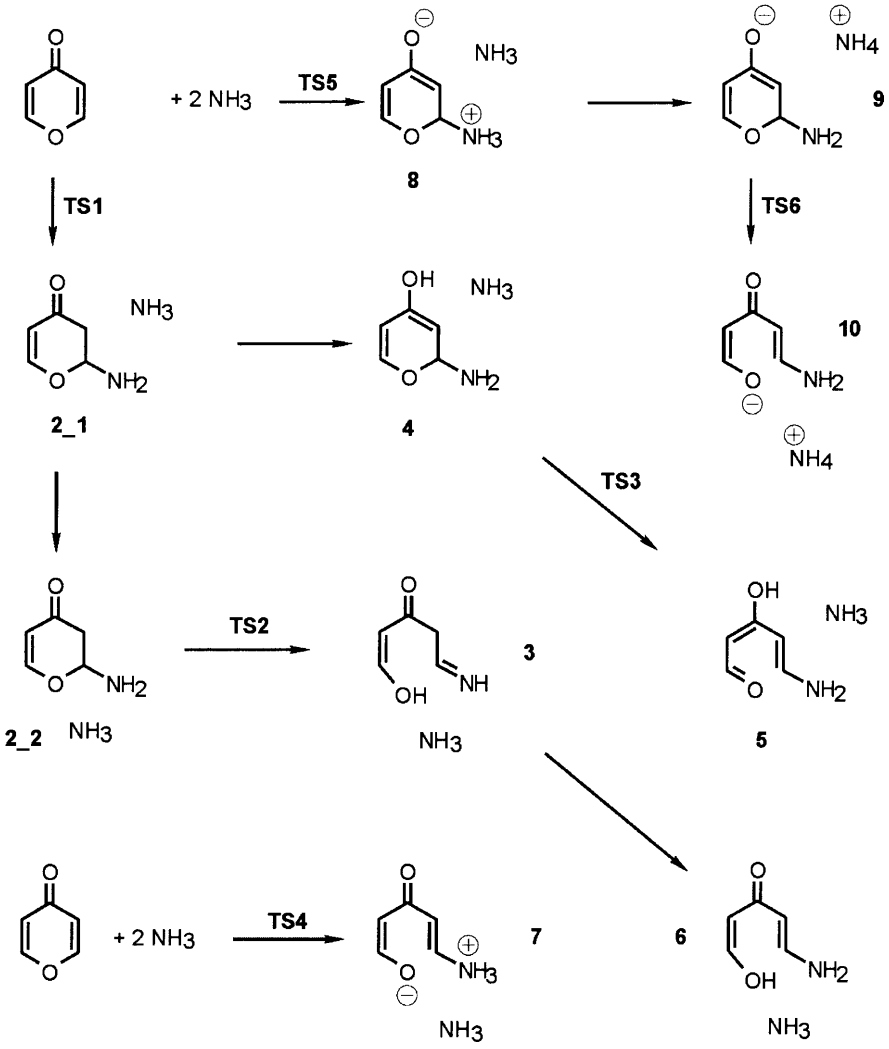
Computational details

Calculations were performed using the Gaussian 98 [6] and Jaguar 4.1 [7] program packages. The geometries were completely optimized with the aid of Becke's three-parameter hybrid density functional–Hartree–Fock (HF) method with the Lee–Yang–Parr correlation functional (B3LYP//B3LYP) [8] using the 6-31G(d,p) basis set. Bulk solvent effects (aqueous solution, $\varepsilon = 78.39$) were estimated by single-point calculations using the Poisson–Boltzmann (SCRF) model [9] [PB–SCRF–B3LYP/6-311 + G(d,p)// B3LYP/6-31G(d,p)]. In order to elucidate the existence of a zwitterionic intermediate **8** in the mechanism, the addition reaction step (reactants→**TS5**→**8**) was also fully optimized at the HF [10] level of theory by employing the polarized continuum model (PCM) [11] [PCM–HF/6-31G(d,p)//PCM–HF/6-31G(d,p), aqueous solution, $\varepsilon = 78.39$]. All stationary points were characterized as minima or transition states by vibrational frequency calculations. In addition, for transition states intrinsic reaction coordinate calculations at the B3LYP//B3LYP and PCM–HF// PCM–HF levels of theory were performed. Thermodynamic quantities were calculated at 298 K and 101.325 kPa using standard rigid-rotor harmonic oscillator partition function expressions. Zero-point energies are unscaled.

Results and discussion

On the basis of theoretical [12] and experimental knowledge [3, 4, 5, 13] several possible mechanisms for nucleophilic vinylic substitutions of the pyranones were considered for the calculations (Scheme 1).

The path reactants→**TS1**→**2_1**→**2_2**→**TS2**→**3** includes nucleophilic vinylic substitution proceeding by an addition–elimination mechanism [13]. Formation of the initial dipole–dipole complex **1_1** from substrate + 2 NH_3 is exothermic but endergonic (Table 1), and therefore it is not considered further. The attack of ammonia to the C2 carbon (see Scheme 2 for the atom numbering) in the presence of another ammonia molecule proceeds through transition state **TS1** forming a tetrahedral keto intermediate **2_1** (figures for all B3LYP and PCM–HF optimized geometries as well as the corresponding Gaussian input files are provided in the electronic supplementary material). This step presents addition of ammonia in concert with the proton transfer from the ammonia nitrogen onto the C3 carbon assisted by the second ammonia molecule (N8-H9→N10-H11→C3). Although the addition of ammonia to C2 in **TS1** is in advance [d(C2–N8) = 0.158 nm in **TS1**(2-H)

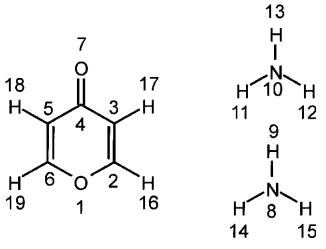


Scheme 1

Table 1. Calculated relative energies (relative to the separated reactants) including zero-point-energy (*ZPE*) corrections, ΔE_{rel}, and Gibbs free energies, ΔG_{rel}, of the various minima and transition states for the reactions of 4*H*-pyran-4-one and 2-methyl-4*H*-pyran-4-one with ammonia in the gas phase and aqueous solution ($\varepsilon = 78.39$) (kJ mol^{-1})

	2-H			2-CH_3		
	ΔE_{rel}[a]	ΔG_{rel}[a]	ΔG_{rel}[b]	ΔE_{rel}[a]	ΔG_{rel}[a]	ΔG_{rel}[b]
1_1	−49.4	23.3	75.0	−53.3	20.1	78.6
TS1	134.2	219.3	184.1	145.6	234.1	203.2
2_1	−38.7	39.7	60.3	−22.1	58.4	84.4
2_2	−56.4	22.2	48.4	−39.7	42.7	73.4
TS2	25.7	111.4	98.5	31.3	116.5	99.5
3	−16.6	63.0	89.3	−12.1	67.5	97.3
6	−25.0	51.8	60.0	2.5	81.7	96.1
4	−2.5	71.0	109.9	8.4	86.6	124.4
TS3	25.2	102.2	122.8	41.0	117.8	140.8
5	−34.3	39.2	43.9	−6.0	71.8	86.5
1_2	−34.3	30.9	69.2	−26.8	41.4	72.1
TS4	157.7	243.1	218.1	166.7	253.0	230.3
7	63.0	145.8	118.7	71.3	154.7	131.8
TS5				159.3[c]	244.6[c]	214.6[d]
8				154.2[c]	237.7[c]	195.7[d]

[a] B3LYP/6-31G(d,p)//B3LYP/6-31G(d,p)
[b] PB–SCRF–B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d,p)
[c] PCM–HF/6-31G(d,p)//PCM–HF/6-31G(d,p)
[d] PB–SCRF–B3LYP/6-311 + G(d,p)//PCM–HF/6-31G(d,p)



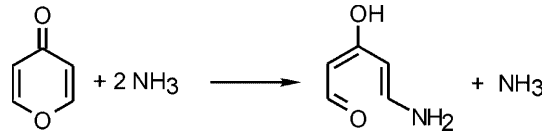
Scheme 2

and 0.142 nm in **2_1**(2-H)] of proton transfer taking place from N8 onto N10 {*d*(N8–H9) = 0.140 nm [**TS1** (2_H)] and 0.286 nm [**2_1**(2-H)]; *d*(H9-N10) = 0.121 nm in **TS1**(2-H) and 0.102 nm in **2_1**(2-H)}, proton transfer from N10 to C3 significantly lags behind [*d*(H11-C3) = 0.193 nm and 0.110 nm in **2_1**(2-H)]. The geometrical constraints by incorporating the enone moiety into a cyclic system prevents it from adopting the s-cis conformation necessary for the energetically preferred 1,4 addition [12]. Thus, only the energetically disfavored 1,2 addition via transition state **TS1** with an activation free energy of 219.3 kJ mol^{-1} (2-H) and 234.1 kJ mol^{-1} (2-CH_3), respectively, (see $\Delta G^{\ddagger}$ in Table 2) is found. The high activation barrier for this step could also be caused by the partial aromatic nature of the pyranone ring. The aromatic driving forces tend to delocalize electron density over the ring and maintain the pyranone ring in a planar conformation. In contrast to simple acyclic α,β-unsaturated carbonyl compounds, where attack of the nucleophile occurs almost perpendicular to the π bond of the alkene moiety [12], here surprisingly high values of the torsion angle φ (N8–C2–C3–C4) = 117.2° (2-H) and 148.0° (2-CH_3) are found in **TS1**. These geometrical constraints could be responsible for the high activation barrier observed for the addition step. It is interesting to note that the free energy of activation for 4*H*-pyran-4-one with the smaller value of 117.2° of the previously mentioned torsion angle in **TS1** is lower ($\Delta G^{\ddagger}$ = 219.3 kJ mol^{-1}) compared with that of 2-methyl-4*H*-

Table 2. Calculated activation energies including ZPE corrections, $\Delta E^{\ddagger}$, and Gibbs free energies, $\Delta G^{\ddagger}$, for the reactions of 4*H*-pyran-4-one and 2-methyl-4*H*-pyran-4-one with ammonia in the gas phase and aqueous solution (ε = 78.39) (kJ mol^{-1})

	2-H			2-CH_3		
	$\Delta E^{\ddagger a}$	$\Delta G^{\ddagger a}$	$\Delta G^{\ddagger b}$	$\Delta E^{\ddagger a}$	$\Delta G^{\ddagger a}$	$\Delta G^{\ddagger b}$
$\Delta E_1^{\ddagger}$ (**1_1**→TS1)[c]	183.6	219.3	184.1	198.9	234.1	203.2
$\Delta E_2^{\ddagger}$ (**2_2**→TS2)	82.1	89.2	50.1	71.0	73.8	26.1
$\Delta E_3^{\ddagger}$ (**4**→TS3)	27.7	31.2	12.9	32.6	31.2	16.4
$\Delta E_4^{\ddagger}$ (**1_2**→TS4)[d]	192.0	243.1	218.1	193.5	253.0	230.3
$\Delta E_5^{\ddagger}$ (reactants→TS5)				159.3[e]	244.6[e]	214.6[f]

[a] B3LYP/6-31G(d,p)//B3LYP/6-31G(d,p)
[b] PB–SCRF–B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d,p)
[c] $\Delta G_1^{\ddagger}$ (reactants→TS1)
[d] $\Delta G_4^{\ddagger}$ (reactants→TS4)
[e] PCM–HF/6-31G(d,p)//PCM–HF/6-31G(d,p)
[f] PB–SCRF–B3LYP/6-311 + G(d,p)//PCM–HF/6-31G(d,p)



Scheme 3

pyran-4- one (($\Delta G^{\ddagger} = 234.1$ kJ mol^{-1}) where $\tau = 148.0°$. Owing to the specific geometry of **TS1** this transition structure leads to a tetrahedral intermediate **2_1** in which the amino group attached to C2 is in an equatorial position [φ (N8–C2–C3–C4) = 174.4° (2-H) and 166.4° (2-CH_3), respectively]. Despite several attempts, no transition state for formation of a tetrahedral intermediate with the amino group attached to C2 axially could be located.

The elimination step started from a keto intermediate **2_2** (the structures **2_1** and **2_2** are the same intermediates differing only in the position of the second ammonia molecule. **2_2** is more stable than **2_1** by about 16–18 kJ mol^{-1}, ΔG_{rel}) and proceeded through transition state **TS2** [111.4 kJ mol^{-1} (2-H) and 116.5 kJ mol^{-1} (2-CH_3), ΔG_{rel}]. As evidenced by the geometric features of **TS2**, ring opening, i.e., elimination occurs in concert with NH_3-assisted proton transfer from the N8 nitrogen onto the O1 oxygen (N8–H15→N10–H12→O1). Elimination of the O1 leaving group from C2 is more advanced [*d*(O1–C2) = 0.151 nm in **2_2**(2-H) and 0.231 nm in **TS2**(2-H)] than proton transfer [*d*(N8–H15) = 0.102 nm in **2_2**(2-H) and 0.140 nm in **TS2**(2-H); *d*(H15–N10) = 0.212 nm in **2_2**(2-H) and 0.120 nm in **TS2** (2-H)]. The corresponding free energies of activation are substantially lower [89.2 kJ mol^{-1} (2-H) and 73.8 kJ mol^{-1} (2-CH_3) ($\Delta G^{\ddagger}$)] than those for the primary addition step. The resulting imine intermediate **3** can undergo a sequence of processes as imine–enamine tautomerism (**3→6**) or conformational interconversions to form a more stable intermediate. The ring-opened products of the pyranones are not stable and undergo recyclization to give the nitrogen analogue of the starting oxygen heterocycle (in contrast, in the reaction of chromones with amines no such recyclizations can be observed because of the resistance of the benzene ring to nucleophilic attack [14]).

In the mechanism described so far, **TS1** possesses not only the highest energy overall [219.3 kJ mol^{-1} (2-H) and 234.1 kJ mol^{-1} (2-CH_3), ΔG_{rel}] but also the highest free energy of activation of 219.3 kJ mol^{-1} (2-H) and 234.1 kJ mol^{-1} (2-CH_3), respectively [see $\Delta G^{\ddagger}$ in Table 2, the activation Gibbs free energies are calculated relative to the separated reactants]. Consequently, the addition step in concert with proton transfer (reactants→**TS1→2_1**) is the rate-determining step in the gas phase for the mechanism reactants→**TS1→2_1→2_2→ TS2→3**.

The path reactants→**TS1→2_1→4→TS3→5** includes the same addition step as was considered for the previously mentioned mechanism. After addition, the keto intermediate **2_1** undergoes a keto-enol tautomeric interconversion to give an enol intermediate **4**, which is less stable than **2_1** by 30 kJ mol^{-1} (ΔG_{rel}). The activation barrier of the elimination (**4→TS3→5**) is 31.2 kJ mol^{-1} for both systems calculated. **TS3** was found at a distance *d*(O1–C2) = 0.191 nm (2-H) of the breaking bond and decomposed to form an enamine intermediate **5**.

The energy of **TS1** is higher than that of **TS3** by about 117 kJ mol^{-1} (see ΔG_{rel} in Table 1). The concerted addition-proton transfer of ammonia to C2 (reactants→**TS1→2_1**) is the rate-determining step also for this mechanism (reactants→**TS1→2_1→4→TS3→5**). As shown in Figs. 1 and 2, for both 2-H as well as 2-CH_3, the two alternative mechanisms for decomposition of the primary adduct **2_1**, i.e., **2_1→2_2→TS2→3** and **2_1→4→TS3→5** have quite similar energetic requirements. Notably, however, for 4*H*-pyran-4-one **TS3** has a lower energy than **TS2** by about 9 kJ mol^{-1}, whereas for 2-methyl-4*H*-pyran-4-one **TS2** is lower, albeit just marginally (about 1 kJ mol^{-1}, Fig. 2) than **TS3.** For chromones, however, ring fission via **TS3** seems to be less probable: In order for the step **4→TS3→5** to take place, a shift of the conjugated double bonds must be allowed to form the O1 = C6-C5 = C4(OH)-C3 = C2-NH2 configuration of the structure **5**. The ring-opening of chromones gives an intermediate where the O1 leaving group is a phenolate ion, and thus, the previously mentioned bond reorganization would lead to a highly unfavorable

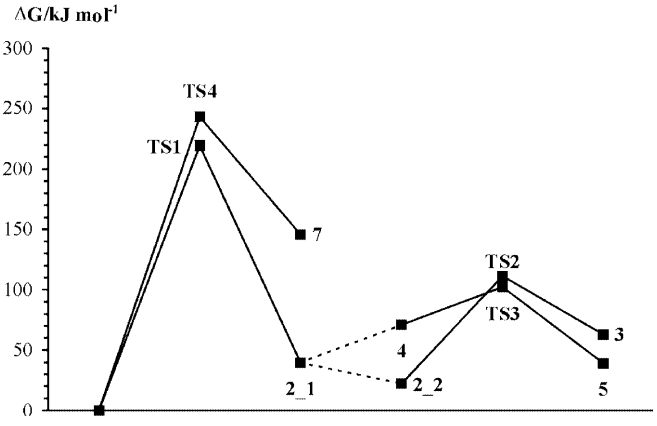


Fig. 1. B3LYP energy profile (ΔG_{rel}) for the reaction of 4*H*-pyran-4-one with ammonia depicted in Scheme 1

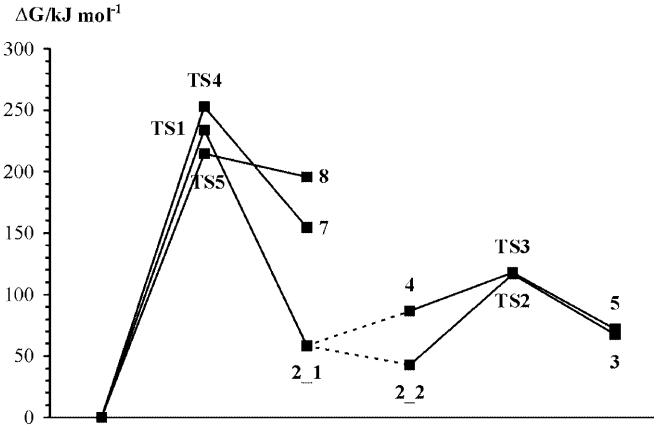


Fig. 2. Energy profile (ΔG_{rel}) for the reaction of 2-methyl-4*H*-pyran-4-one with ammonia in the gas phase (B3LYP//B3LYP) and aqueous solution (reactants→**TS5→8**, PB–SCRF–B3LYP// PCM–HF)

o-quinoid structure. Thus, for chromone derivatives one would reasonably expect a higher activation barrier for ring fission via **TS3** than via **TS2**.

The path reactants→**TS4**→**7** presents a bimolecular nucleophilic substitution (S_N2). Again, the dipole–dipole complex **1_2** is unstable compared with the separated reactants (see ΔG_{rel} in Table 1), and thus it is not considered further. The main difference to the first mechanism considered in this paper is the concerted although asynchronous [d(C2–N8) = 0.154 nm and d(O1–C2) = 0.180 nm in **TS4** (2-H) compared to d(C2–N8) = 0.147 nm and d(O1–C2) = 0.308 nm in **7** (2_H)] addition of ammonia and ring-opening, i.e., elimination of the O1 ring oxygen (**TS4**). The calculated activation barrier of the process is very high [243.1 kJ mol^{-1} (2-H) and 253.0 kJ mol^{-1} (2-CH_3) ($\Delta G^{\ddagger}$)], and is, in fact, the highest among all the barriers (Table 2, Figs. 1, 2). Consequently, the S_N2-type mechanism is excluded from the feasible paths. Despite the presence of a second ammonia molecule the computational procedures used did not result in a structure for **TS4** indicative for concerted proton transfer from the N8 nitrogen onto the O1 oxygen. The catalytic ammonia molecule only forms two hydrogen bonds with the pyranone moiety [d(O1–H11) = 0.217 nm and d(N10–H9) = 0.178 nm in **TS4** (2-H)]. **TS4** decomposes to the acyclic zwitterionic intermediate **7**. It is rather unstable, lying 118.7 kJ mol^{-1} (2-H) and 131.8 kJ mol^{-1} (2-CH_3) above the reactants.

Finally, the path reactants→**TS5**→**8**→**9**→**TS6**→**10** corresponds to the mechanism proposed by Davidson and Kaye [3] for the reaction of some chromone derivatives with dimethylamine in ethanolic solution. Here, addition of ammonia via **TS5** gives a zwitterionic intermediate **8**. This species **8** is stabilized by an acid–base reaction (intermolecular proton transfer) where the second ammonia acts as a base rather than a catalyst. The resulting enolate species **9** undergoes elimination through **TS6** to form an intermediate **10** which can convert to a more stable conformation. Unfortunately, in the gas phase none of the transition states and intermediates postulated for this mechanism could be localized. As was demonstrated by quantum-chemical calculations [15], charge-localized species such as the zwitterionic intermediate **8** and the corresponding transition state are unstable in the gas phase and can only be found by inclusion of several discrete molecules of a polar solvent into the reaction system. Nevertheless, to obtain some idea of the influence of bulk solvent (aqueous solution, $\varepsilon = 78.39$) single-point calculations at the PB–SCRF–B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d,p) level of theory were first performed for all stationary structures localized in the gas phase. The effects exerted by solvent (aqueous solution, $\varepsilon = 78.39$) consist in a reduction of the various activation barriers by about 25–40 kJ mol^{-1} (Table 2). The general energetic features are, however, unaffected thereby, i.e., the addition step remains rate-determining. Second, in order to elucidate the possibility for the existence of such a tetrahedral zwitterionic intermediate optimizations (only for the 2-CH_3 system) at the PCM–HF/6-31G(d,p)//PCM–HF/6-31G(d,p) level of theory was done. Thereby, the structure **TS5** [d(C2–N8) = 0.181 nm] could be established as a true transition state of the addition step. Furthermore, intrinsic reaction coordinate calculations starting from **TS5** indeed led to the anticipated tetrahedral zwitterionic intermediate **8** [d(C2–N8) = 0.156 nm]. The torsion angle φ (N8–C2–C3–C4) = 86.9° in **8** indicates an axial orientation of the ammonium group. Both in **TS5** and **8** the second ammonia is placed close to the O1 oxygen and stabilizes the zwitterionic structure by hydrogen bonding [d(H14–N10) = 0.206 nm in **TS5** and 0.193 nm in **8**]. An analogous transition state with the second ammonia molecule placed above the pyranone ring close to the C4 = O7 carbonyl group is almost isoenergetic. Attempts to locate **TS1** also in aqueous solution by PCM calculations invariably resulted in structures resembling **TS5.** This clearly indicates that in contrast to the gas phase, where addition via **TS1** is the preferred pathway, in polar solution the addition step via **TS5** is the more preferred process, in agreement with the mechanism proposed by Davidson and Kaye [3]. Obviously then, formation of the zwitterionic intermediate **8** via **TS5** requires stabilization by a sufficiently polar solvent. Consequently, neither in the gas phase nor in apolar solution will this mechanism be operative at all. The change of the reaction mechanism by transition from nonpolar to polar solution is also corroborated by additional PCM calculations on the reaction step reactants→**TS5**→**8**. For the weakly polar dimethylamine solution ($\varepsilon = 5.26$) both **TS5** and **8** were localized as true stationary points. In striking contrast, however, neither could be found with benzene ($\varepsilon = 2.25$) as a solvent. Consequently, our calculations indicate that solvent polarity differences indeed can induce a change of the reaction mechanism for addition of nucleophiles to chromones and/or pyranones: whereas in the gas phase as well as in nonpolar solution the nucleophilic vinylic substitutions between pyranones and ammonia starts with the concerted 1,2 addition (reactants→**TS1**→**2_1**), in polar solution the stepwise addition via the zwitterion is preferred (reactants→**TS5**→**8**). Essentially, it was not possible at all to locate a transition structure corresponding to **TS1** when bulk solvent effects via the PCM were included in the geometry-optimization procedure.

Limitations of the current approach

One source of uncertainties in the calculated reaction paths and energetics consists in using a continuum model for solvation in combination with single-point energy evaluations. As already pointed out, especially for zwitterionic systems, gas-phase calculations do not result in the desired structures. However, geometry optimizations with the inclusion of solvent effects (PCM) are very time-consuming and, more often than not, do not converge to a true minimum or transition state as evidenced by the incorrect number of negative eigenvalues of the respective force constant matrix. Free energies, by default, are computed for 1 atm and 298 K. In solution, a more natural choice of the standard state would be 1 mol l^{-1}. In that case, free energies of activation for bimolecular processes will be higher by

about 10 kJ mol^{-1}, whereas monomolecular reactions will be unaffected by using different standard states. The main difficulty, however, stems from the possibility of several acid–base equilibria associated with the oxyanions–hydroxy compounds depicted in Scheme 1. Ab initio determination of such protonation/deprotonation equilibria in solution is still an unsolved problem [16]. Finally, these protonation/deprotonation reactions, for example, transformation **8**→**9** could equally well act as a proton-transfer network. In that case, no additional ammonia molecule acting as a catalyst with a concomitant increase in free energies would be required. On the basis of the kinetic results [3], however, involvement of an additional amine is likely.

Conclusion

On the basis of our quantum-chemical calculations of nucleophilic vinylic substitutions of 4*H*-pyran-4-one and 2-methyl-4*H*-pyran-4-one with ammonia in the presence of an ancillary ammonia molecule we have made the following conclusions:

1. The reactions studied may take place by several possible paths depending on even quite subtle differences in substrate structure (e.g., hydrogen at C2 replaced by methyl) and/or solvent polarity. So, for instance, 2-methyl-4*H*-pyran-4-one reacts with ammonia via the mechanism in which the ring fission starts from the keto intermediate **2_2** (reactants→**TS1**→**2_1**→**2_2**→**TS2**→**3**). On the other hand, for 4*H*-pyrane-4-one tautomerization of the primary adduct to the enol **4** prior to ring opening, i.e., the path reactants→**TS1**→**2_1**→**4**→**TS3**→**5**, appears to be more favorable.
2. For both systems, 2-H and 2-CH_3, the addition of ammonia to C2 in concert with proton transfer (reactants→**TS1**→**2_1**) is the rate-determining step of the reactions in the gas phase.
3. The presence of the methyl group at C2 increases the activation barrier for the rate-determining addition step and decreases the barrier for the elimination step. Consequently, 2-methyl-4*H*-pyran-4-one is less reactive compared with 4*H*-pyran-4-one.
4. Apart from substrate structure and type of the nucleophile [anionic, e.g., OH^-, neutral, e.g., $NH(CH_3)_2$] solvent polarity and pH conditions [5] also substantially affect the precise mechanism of addition/ring opening by nucleophiles of pyranones and chromones.

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