Ab initio and DFT studies on the mechanism of ring-opening reactions of 4*H*-1-benzopyran-4-one with hydroxide ion †

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The mechanism of the first steps of the degradation of 4*H*-1-benzopyran-4-one in alkaline media, *i.e.*, nucleophilic addition of hydroxide ion at the C2 carbon of 4*H*-1-benzopyran-4-one followed by ring-opening, is investigated by *ab initio* [HF/6-31+G(d) and MP2/6-31+G(d)] and density functional theory [B3LYP/6-31+G(d)] methods. In addition, bulk solvent effects are estimated by the polarised continuum (overlapping spheres) model (PCM) and the polarizable conductor PCM model (CosmoPCM). Depending on the level of theory used three reaction coordinates are found: path **A** (1→TS1→2→TS2A→3A), path **B** (1→TS1→2→TS2B→3B) and path **C** (1→TS1→2→TS2A→3C). The ring-opening step passing through **TS2B** has a lower activation energy than the step proceeding through **TS2A**. These second barriers are higher compared with the barrier of the first step. Therefore fission of the γ-pyrone ring (2→TS2B→3B) seems to be the rate-determining step in the gas phase. Contrary to these gas phase results, addition of hydroxide ion to C2 (reactants→TS1→2) is the rate-determining step for the reaction in aqueous solution, in agreement with experimental results.

Introduction

Some 4*H*-1-benzopyran-4-one (4*H*-chromen-4-one) derivatives (chromones), mainly those with an acidic group at C2 or C3, are known to exhibit anti-allergic activity.[1] The synthetic drug disodium chromoglycate (DSCG) is used in asthma therapy. In order to understand its action *in vivo* investigations have been carried out.[2] However, a detailed mechanism of the activity of DSCG is not known yet. It has been shown that DSCG can interact with biogenetic nucleophiles such as mast-cell proteins. Davidson *et al.*[3] proposed a model of the covalent interaction between DSCG and a nucleophilic side chain of the protein. The essential feature of this simple model is a nucleophilic reaction at the C2 carbon of DSCG, which proceeds by fission of the γ-pyrone ring.

The ring-opening reaction (ROR) of chromone and related vinylogous lactones can be classified as a vinylic nucleophilic substitution, which takes place by the addition–elimination mechanism. Experimental research, mainly kinetic [3,4] and isotopic-labelling studies,[5] has brought new insights into the basic mechanistic principles of such reactions. Because conclusive evidence of a tetrahedral intermediate in the ROR has not been demonstrated so far, enol, enolate or zwitterionic intermediates cannot be excluded. Although Zagorevskii *et al.*[5d] demonstrated the absence of isotope exchange in the reaction of chromone with 1-deuteriopiperidine and of 3-deuteriochromone with piperidine, isotopic-labelling studies of γ-pyrones [5a,c] and chromone [5d] with D₂O do not exclude a mechanism through an enol intermediate. According to the kinetics measured by Davidson *et al.*,[3] a mechanism with ring-fission as the rate-determining step (RDS) for the ROR of 4-oxo-4*H*-1-benzopyran-2-carboxamides with ethanolic dimethylamine is indicated. In striking contrast, kinetic studies of Szabó *et al.*[4a,b] have established the addition of hydroxide ion to C2 as the RDS for the ROR of flavone, isoflavones and chromones in aqueous alkali. Given the present knowledge concerning nucleophilic additions and substitutions on activated double bonds,[6] one could suspect a different mechanism with nitrogen and oxygen nucleophiles, respectively.

Several authors have dealt with quantum-chemical calculations [7] on pyrans and related six-membered oxygen heterocycles, but, to the best of our knowledge, calculations on the mechanism of the ROR have not been published yet. Opening of the γ-pyrone ring was only calculated in a semiempirical study of the Mannich type reactions of 3-formylchromones with amides.[8] To obtain some new insights into this problem we have performed quantum-chemical calculations on the first steps of the degradation of 4*H*-1-benzopyran-4-one in alkaline media, *i.e.*, the nucleophilic addition of hydroxide ion at the C2 carbon of 4*H*-1-benzopyran-4-one followed by ring-opening. For this purpose *ab initio* and DFT methods were used to investigate the proposed mechanism of Szabó *et al.*[4a,b] It is important to note that in the degradation of the 4*H*-1-benzopyran-4-one derivatives in alkaline media, two kinetically separable reactions can be distinguished: the first is a ring fission that begins with addition of hydroxide ion at C2, and the other is a hydrolysis that proceeds at a rate lower by several orders of magnitude.[4] Therefore ring fission by hydroxide ion can be considered as a separable process where products of the ring-opening step are not final products but just intermediates (in contrast, the reaction with amines only leads to the ring-opened products).

In addition, the influence of solvent effects on the mechanism of the ROR is elucidated and, finally, reliability and limitations of the different computational procedures are addressed.

Computational details

All calculations were performed by the Gaussian 98 program package.[9] The geometries were completely optimised at the Hartree–Fock (HF//HF) level [10] and with the aid of Becke's

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three-parameter hybrid density functional–HF method with the Lee–Yang–Parr correlation functional[11] (B3LYP//B3LYP) using the 6-31+G(d) basis set. In addition, correlation energy was also evaluated using second-order Møller–Plesset theory[12] by single point calculations at the HF and B3LYP geometries [MP2/6-31+G(d)//HF/6-31+G(d) and MP2/6-31+G(d)// B3LYP/6-31+G(d), respectively]. All stationary points were characterised as minima or transition states by vibrational frequency calculations at the same level of theory as the geometry optimisations were done. In addition, for transition states intrinsic reaction coordinate (IRC) calculations at the HF//HF and B3LYP//B3LYP levels of theory were performed. Bulk solvent effects (aqueous solution, $\varepsilon = 78.39$) were estimated by single-point calculations using the polarised continuum (overlapping spheres) model[13] (PCM-B3LYP//B3LYP) and polarizable conductor PCM model[14] (CosmoPCM-B3LYP//B3LYP). In order to check the relative accuracies of this methodological approach we added calculations with the fully optimised geometries of the transition states **TS1**, **TS2A** and their corresponding IRC calculations at the PCM-B3LYP//PCM-B3LYP level of theory using the 6-31+G(d) basis set. Thermodynamic quantities were calculated at 298 K and 101.325 kPa using standard rigid-rotor harmonic oscillator partition function expressions. Zero-point energies (ZPE) are unscaled. Zero-point corrections and thermal corrections to Gibbs free energies were calculated at the same level of theory as the geometry optimisation was done.

Results and discussion

The model reaction considered here (see Scheme 1) is based on
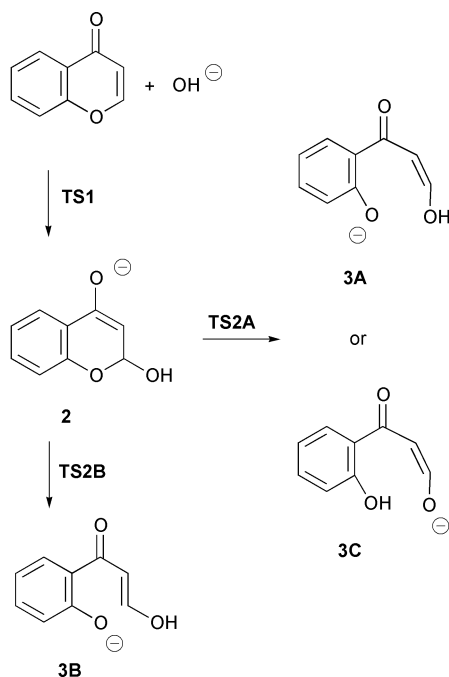
Scheme 1

the proposed mechanism of Szabó *et al.*[4a,b] In the first step, a hydroxide ion attacks the C2 carbon of chromone forming the enolate **2**. Then the enolate **2** undergoes fission of the γ-pyrone ring in three possible ways: paths **A** and **C** present the ring-fission where the bonded hydroxide ion moves toward the O1 ring-oxygen by a rotation of the C2–C3 bond. In path **A** the resulting species **3A** is formed without any proton-transfer reaction. In contrast, path **C** describes a concerted ring-fission and proton-transfer from the O8 oxygen of the bonded hydroxide ion to the O1 ring-oxygen providing the intermediate **3C**. In path **B** the ring-fission takes place with an outward rotation of the hydroxy group at C2 forming species **3B**.

Relative energies (ΔE_{rel}) including zero-point energy contributions and relative Gibbs free energies (ΔG_{rel}) for the gas phase (B3LYP//B3LYP, MP2//B3LYP) and aqueous solution (PCM-B3LYP//B3LYP and CosmoPCM-B3LYP//B3LYP) are summarised in Table 1. Activation energies ($\Delta E^{\ddagger}$), Gibbs free energies ($\Delta G^{\ddagger}$) and solvent contributions to free energy (ΔG_{solv}) are presented in Tables 2 and 3. Important structural features for all transition states are shown in Figs. 1, 2 and 3. Structures for all minima, Gaussian input files with Cartesian coordinates of all geometries optimised by the HF//HF, B3LYP//B3LYP and PCM-B3LYP//PCM-B3LYP methods, total electronic energies (including zero-point energy contributions) and Gibbs free energies, as well as relative and activation energies obtained at the HF//HF and MP2//HF levels of theory, are provided in the Supplementary Information.

Mechanism of the ring-opening reaction

The addition of hydroxide ion to C2 proceeds first by the exothermic formation of the ion–dipole complex **1** (Fig. S2). This complex, which is formed without a reaction barrier, leads *via* transition state **TS1** to the enolate **2**. As found in the addition of hydroxide ion to acrolein,[6c] stereoelectronic effects, *i.e.*, the electron–electron repulsion between the nucleophile's lone pairs and the negative charge on the C3 carbon of chromone, are important for the geometry of **TS1**. The normal mode associated with the imaginary frequency [ν(HF//HF) *ca.* 162 i cm^{-1}, ν(B3LYP//B3LYP) *ca.* 163 i cm^{-1}] describes mainly the C2–O8 bond stretching, thus confirming the nature of **TS1** as that for the addition of hydroxide ion at C2. Despite the surprising geometry of **TS1** [φ(O8–C2–C3–C4) = 121.8°, see also Fig. 1] calculated by the B3LYP method, this structure has been confirmed by the IRC calculations as a correct transition state of addition of hydroxide ion to the C2 carbon. The enolate **2** formed on passing **TS1** can be characterised as a tetrahedral intermediate that can react *via* either transition state **TS2A** or **TS2B**, respectively. The fission of the γ-pyrone ring taking place through **TS2A** [r(O1–C2) = 0.195 nm (HF//HF) and 0.201 nm (B3LYP//B3LYP)] forms intermediate **3A**. However, this structure could only be localised by the HF method. In contrast, by the B3LYP method the proton of the hydroxide moiety is transferred to the O1 ring-oxygen in the process of ring-fission forming the intermediate **3C** (see Scheme 1 and Fig. S4 in the Supplementary Information). This structure was confirmed by the IRC calculations as a correct product of the **TS2A**. Transfer of the H9 hydrogen onto the O1 ring-oxygen is rather delayed compared to the fission of the O1–C2 bond [r(O1–H9) = 0.282 nm, see Fig. 2] in the geometry of **TS2A** (B3LYP//B3LYP). The imaginary frequencies of **TS2A** [ν(HF//HF) *ca.* 576 i cm^{-1} and ν(B3LYP//B3LYP) *ca.* 385 i cm^{-1}] belong to the O1–C2 stretching modes. In addition, the PCM-B3LYP//PCM-B3LYP calculations on **TS2A** were performed. The corresponding IRC calculations indicate the same mechanism of ring-opening as the B3LYP//B3LYP level of theory provides, *i.e.*, in aqueous solution the proton of the hydroxide moiety is transferred to the O1 ring-oxygen resulting in **3C**.

If the hydroxy group at C2 is rotated outward from the O1 ring-oxygen, the transition state **TS2B** will be obtained (Fig. 3). The resulting species **3B** has the *E* configuration of the C2–C3 bond (Fig. S5 in the Supplementary Information). Under the experimental conditions used by Szabó *et al.*[4a,b] these intermediates (**3A**, **3B** or **3C**) are stabilised by excess alkali as β-dicarbonyl enolates.

Thermodynamics of the ring-opening reaction

As indicated in Tables 1, 2 and S1, S2 of the Supplementary Information, calculations at several levels of theory were performed in order to check the relative accuracies of the

Table 1 Calculated relative energies (ΔE_{rel}), including ZPE corrections and Gibbs free energies (ΔG_{rel}), of the various minima and transition states for the ring-opening reaction of chromone with hydroxide ion in the gas phase and aqueous solution depicted in Scheme 1 (in kJ mol^{-1})[a]

| | Gas phase | | | | Aqueous solution | | | |
| | B3LYP//B3LYP | | MP2//B3LYP | | PCM-B3LYP//B3LYP[b] | | CosmoPCM-B3LYP//B3LYP | |
	ΔE_{rel}	ΔG_{rel}	ΔE_{rel}	ΔG_{rel}	ΔE_{rel}	ΔG_{rel}	ΔE_{rel}	ΔG_{rel}
1	−118.5	−88.6	−113.1	−83.1	76.7	106.6	94.0	124.0
TS1	−93.3	−59.2	−84.5	−50.4	100.0	134.1	117.2	151.3
					(142.0)	(176.8)		
2	−185.8	−148.6	−197.2	−160.0	−6.2	31.1	13.8	51.0
TS2A	−122.0	−84.4	−124.4	−86.9	98.2	135.8	113.5	151.0
					(111.7)	(149.5)		
3C	−254.4	−219.2	−253.2	−218.0	−24.6	10.6	−1.8	33.4
TB2B	−134.8	−97.4	−133.6	−96.1	75.0	112.4	89.2	126.7
3B	−181.9	−153.2	−165.5	−136.9	43.6	72.2	61.9	90.5

[a] HF//HF and MP2//HF results are provided in Table S1 of the Supplementary Information. [b] Calculated PCM-B3LYP//PCM-B3LYP results are in parentheses.

Table 2 Calculated activation energies ($\Delta E^{\ddagger}$) and Gibbs free energies ($\Delta G^{\ddagger}$) for the ring-opening reaction of chromone with hydroxide ion in the gas phase and aqueous solution depicted in Scheme 1 (in kJ mol^{-1})[a]

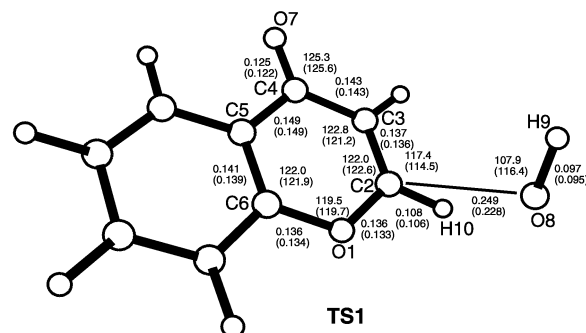| | Gas phase | | | | Aqueous solution | | | |
| | B3LYP//B3LYP | | MP2//B3LYP | | PCM-B3LYP//B3LYP | | CosmoPCM-B3LYP//B3LYP | |
	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta E^{\ddagger}$	$\Delta G^{\ddagger}$
$\Delta E_1^{\ddagger}$ (**1→TS1**)[b]	25.3	29.3	28.6	32.7	100.0	134.1	117.2	151.3
$\Delta E_{2A}^{\ddagger}$ (**2→TS2A**)	63.8	64.2	72.8	73.1	104.4	104.7	99.7	100.0
$\Delta E_{2B}^{\ddagger}$ (**2→TS2B**)	51.0	51.2	63.6	63.8	81.1	81.3	75.5	75.7

[a] HF//HF and MP2//HF results are provided in Table S2 of the Supplementary Information. [b] $\Delta E_1^{\ddagger}$ (reactants→**TS1**) for the PCM-B3LYP//B3LYP and CosmoPCM-B3LYP//B3LYP methods.

Table 3 Calculated free energies of solvation (ΔG_{solv}) of the various minima and transition states for the ring-opening reaction of chromone with hydroxide ion in aqueous solution depicted in Scheme 1 (in kJ mol^{-1})

|	ΔG_{solv}[a]	ΔG_{solv}[b]	ΔG_{solv}[c]
Substrate	−29.1	−28.9	−28.7
OH$^-$	−458.3	−437.1	−455.4
	(−435.1 ± 8)[d]		
1		−270.8	−271.6
TS1	−257.2	−272.7	−273.6
2		−286.4	−284.5
TS2A	−252.4	−245.8	−248.7
3C		−236.2	−231.5
TS2B		−256.2	−260.0
3B		−240.6	−240.4

[a] PCM-B3LYP//PCM-B3LYP. [b] PCM-B3LYP//B3LYP. [c] CosmoPCM-B3LYP//B3LYP. [d] Experimental value (see ref. 16).

Fig. 1 B3LYP and HF (values in parentheses) calculated structure of transition state **TS1**. Distances are given in nm and bond angles in degrees.
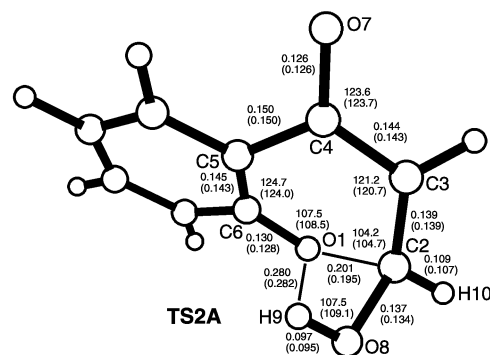
Fig. 2 B3LYP and HF (values in parentheses) calculated structure of transition state **TS2A**. Distances are given in nm and bond angles in degrees.

methods in the gas phase and aqueous solution. Inclusion of correlation energy changes thermodynamic quantities of the chromone reaction system. Activation energies dramatically decrease at the B3LYP//B3LYP, MP2//B3LYP and MP2//HF levels of theory. Calculated HF//HF energies are the highest, MP2//B3LYP and MP2//HF intermediate and B3LYP//B3LYP the lowest in the gas phase, respectively. The B3LYP//B3LYP, MP2//B3LYP and MP2//HF levels of theory provide results comparable to each other and the HF//HF energies are overestimated compared with those mentioned above. Inclusion of bulk solvent effects increases activation parameters for all the reaction steps. Calculated CosmoPCM-B3LYP//B3LYP energies are higher than PCM-B3LYP//B3LYP values. Inclusion of thermal corrections to Gibbs free energies increases activation parameters slightly except the activation energy of addition of hydroxide ion to C2 in aqueous solution (compare $\Delta E_1^{\ddagger}$ with $\Delta G_1^{\ddagger}$ in Table 2).

In the gas phase the formation of the complex **1** is exothermic with ΔG of 72.6 (HF//HF), 83.1 (MP2//B3LYP) and 88.6 (B3LYP//B3LYP) kJ mol^{-1} below the separated reactants. The
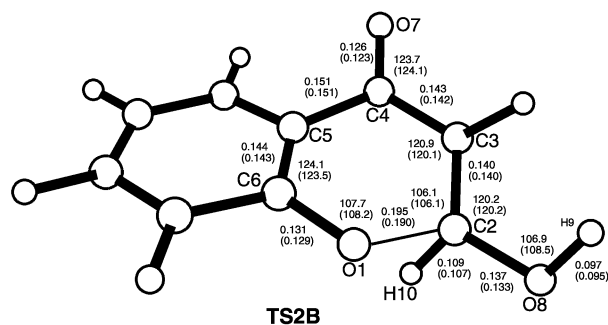
Fig. 3 B3LYP and HF (values in parentheses) calculated structure of transition state **TS2B**. Distances are given in nm and bond angles in degrees.
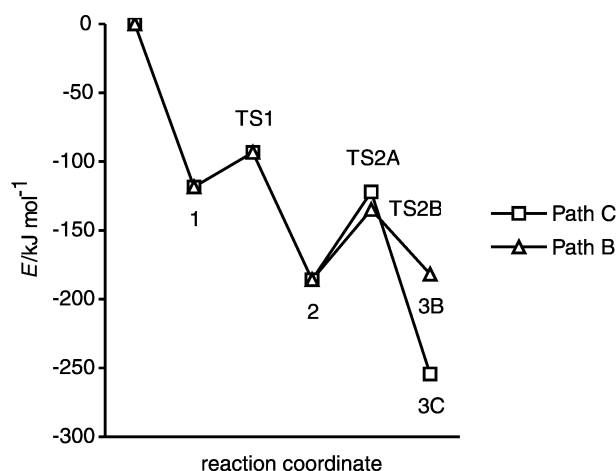

Fig. 4 Energy profile for the ring-opening reaction of chromone with hydroxide ion calculated by the B3LYP method in the gas phase.

transition state **TS1** lies 45.1 (HF//HF), 32.7 (MP2//B3LYP) and 29.3 (B3LYP//B3LYP) kJ mol^{-1} above the complex **1**, while the enolate **2** lies 72.1 (HF//HF), 76.9 (MP2//B3LYP) and 60.0 (B3LYP//B3LYP) kJ mol^{-1} below the complex **1**. Although the intermediate **3B** is less stable than either **3A** or **3C** by 40–80 kJ mol^{-1} (ΔG), its formation through **TS2B** is connected with a significantly lower barrier of 80.5 (HF//HF), 63.8 (MP2//B3LYP) and 51.2 (B3LYP//B3LYP) kJ mol^{-1} (see also Fig. 4). $\Delta G_{2B}^{\ddagger}$(**2**→**TS2B**) is clearly lower than $\Delta G_{2A}^{\ddagger}$ (**2**→**TS2A**), thus path **B** (**1**→**TS1**→**2**→**TS2B**→**3B**) is the most feasible mechanism of the ROR. Although **TS1** is clearly higher than either **TS2A** or **TS2B**, not only $\Delta G_{2A}^{\ddagger}$ but also $\Delta G_{2B}^{\ddagger}$ is higher than $\Delta G_1^{\ddagger}$. Therefore in the gas phase the ring-fission step (**2**→**TS2B**→**3B**) is the RDS of the ROR.

In aqueous solution the formation of the complex **1** is endothermic. Transition state **TS1** lies *ca.* 130–150 kJ mol^{-1} ($\Delta G_1^{\ddagger}$, PCM-B3LYP//B3LYP and CosmoPCM-B3LYP//B3LYP, respectively) above the separated reactants, while transition state **TS2B** lies approximately 80 kJ mol^{-1} above the intermediate **2**. **TS2A** is *ca.* 24 kJ mol^{-1} higher than **TS2B** and a mechanism involving **TS2A** is also excluded in aqueous solution. **TS1** is the highest in energy overall, therefore addition of hydroxide ion to C2 (reactants→**TS1**→**2**) is shown to be the RDS of the ROR (compare the energies of **TS1** and **TS2B** in Table 1). This conclusion is in qualitative agreement with the experimental results.[4a,b] Quantitatively, the calculated activation energies are overestimated at least by a factor of two compared to the experimental values of 54.0 ± 8 kJ mol^{-1} ($\Delta E^{\ddagger}$) and 83 ± 16 kJ mol^{-1} ($\Delta G^{\ddagger}$).[4b] To check the relative accuracies[15] of the single point calculation methodology we also fully optimised the geometry of **TS1** at the PCM-B3LYP//PCM-B3LYP level of theory. The optimised transition state lies 142.0 ($\Delta E_1^{\ddagger}$) and 176.8 kJ mol^{-1} ($\Delta G_1^{\ddagger}$) above the separated reactants. Thus when using PCM-B3LYP//B3LYP calculations we also obtain

rather high values of $\Delta E_1^{\ddagger}$ and $\Delta G_1^{\ddagger}$ at the PCM-B3LYP// PCM-B3LYP level. Another possible origin for this overestimation of the activation energy could be in the overestimation of the free energy of solvation values of hydroxide ion by the continuum solvation models. However, the free energy of solvation of hydroxide ion estimated by the PCM levels of theory (see Table 3) differ by only *ca.* 10 kJ mol^{-1} from the experimental value[16] and should not be a main reason for the calculated discrepancies. We assume that desolvation of hydroxide ion during the addition step and stabilisation of the negatively charged chromone moiety in **TS1** require consideration of specific solvent effects,[15,17] *i.e.*, explicit consideration of the hydrogen-bonding effects, which are clearly beyond the scope of all continuum models.

Conclusion

Ab initio and DFT methods were used for a fairly detailed analysis of the mechanism of the ROR of chromone with hydroxide ion. Correlation energy and solvent effects play a crucial role for the determination of the mechanism. Formation of **3B** through **TS2B** is the most feasible mechanism of the ROR (**1**→**TS1**→**2**→**TS2B**→**3B**) both in the gas phase and aqueous solution. However, different mechanisms of the reaction were found in the gas phase and aqueous solution. Whereas the ring-fission step (**2**→**TS2B**→**3B**) is rate-determining in the gas phase, addition of hydroxide ion to the C2 carbon of chromone (reactants→**TS1**→**2**) is the RDS of the ROR in aqueous solution. Inclusion of specific solvent effects seems to be of great significance for a correct description of the mechanism of ROR in aqueous solution.

Acknowledgements

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