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Site of Nucleophilic Attack and Ring Opening of Five-Membered Heterocyclic 2,3-Diones: A Density Functional Theory Study

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Received July 4, 2002

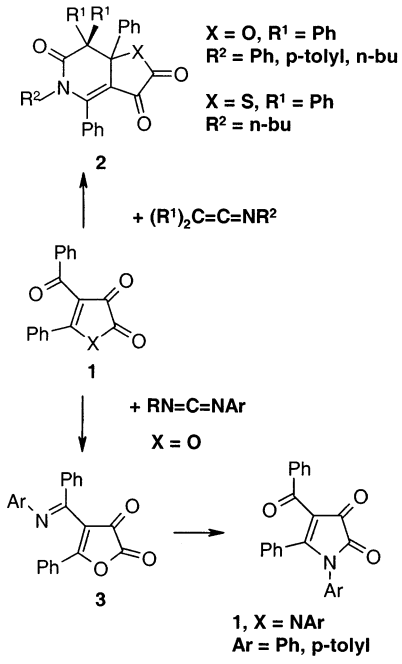
The site of nucleophilic addition to five-membered heterocyclic 2,3-diones (4-iminomethylfuran-2,3-dione **A1** and 4-formyl-pyrrole-2,3-dione **B1**) is studied by density functional theory calculations (B3LYP/6-31G*) with water as the nucleophile. Both uncatalyzed and water-assisted 1,2-addition to the lactone (lactam) and the keto carbonyl group, and conjugate addition to C_5 of the heterocycle and the heteroatom of the 4-iminomethyl (formyl) moiety are considered. In addition, concerted and stepwise ring fission of the lactone (lactam) ring is also treated. The effect of solvation (aqueous solution) is taken into account by the polarizable continuum model (PCM) and the Poisson−Boltzmann SCRF method (PB-SCRF), as well as explicit water molecules. Only this latter approach yields meaningful activation free energies. Barriers for addition of H_2O increase in the order 1,4-addition to C_5 < addition to the lactone (lactam) carbonyl < hydration of the 3-keto group. No reaction path for concerted water-assisted ring opening could be found.

Introduction

Five-membered heterocyclic 2,3-diones **1** (X = O, N−R, S) are versatile synthons in heterocyclic chemistry.[1] First, thermal decarbonylation yields α-oxoketenes offering a great variety in subsequent synthetic possibilities.[2] Second, 4-acyl-substituted derivatives of **1** contain an oxa-1,3-diene moiety that can undergo a wealth of [4+2] cycloaddition reactions. Of particular importance are reactions with heterocumulenes, e.g., ketenimines[3a] or carbodiimides[3b] leading to a number of novel polycyclic heteroaromatic systems (Scheme 1). The outcome of these cycloadditions depends strongly on the nature of the respective heterocumulene and its substituents, as well as on the type of heteroatom X. Generally, the primary [4+2] cycloadducts are not isolable but rather undergo subsequent unusual and novel rearrangement (furandione−furandione rearrangement) and/or fragmentation reactions.[1]

The proposed mechanism for these reactions was corroborated by isotopic labeling studies[4] and theoretical calculations.[5] 4-*N*-Aryliminobenzylfuran-2,3-diones **3**, obtainable from **1** (X = O) by reaction with aryl carbodiimides[3b] (Scheme 1), easily rearrange via a so-called long-range Dimroth rearrangement at elevated temperatures to 4-acylpyrrole-2,3-diones **1** (X = N−Ar).[3b,4]

SCHEME 1. Heterocumulene Cycloaddition Reactions and Rearrangements of Five-Membered Heterocyclic 2,3-Diones 1



Although also purely thermally possible, the Dimroth rearrangement generally is base catalyzed following a

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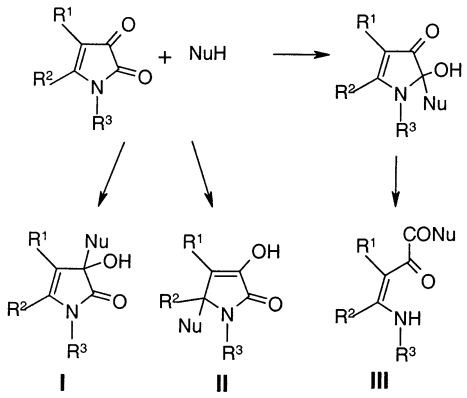
10.1021/jo026142o CCC: $22.00
Published on Web 09/27/2002

SCHEME 2. Possible Sites of Nucleophilic Attack at Pyrrole-2,3-diones



mechanism involving addition of a nucleophile, opening of the heterocyclic ring, and reclosure to the rearranged product.[6] Similarly, although for the iminobenzylfurandione−pyrroledione rearrangement **3** → **1** several mechanisms are conceivable,[4b] a nucleophile-catalyzed reaction is also feasible, especially since addition of nucleophiles to **1** constitutes the third important group of transformations (Scheme 2).[1,7] Compounds of type **1** contain at least three electrophilic positions (the lactone/lactam carbonyl C_2, the activated keto carbonyl C_3, and the vinylic carbon C_5 of the α,β-unsaturated oxa-1,3-diene moiety) amenable to attack by nucleophiles (Scheme 2). In fact, although the structures of some of the originally proposed products of type **I** had to be revised, examples for all three addition modes have been found.[7] With suitable nucleophiles formation of such adducts is the first step in the synthesis of a variety of heterocyclic systems, e.g. pyrazoles, pyridazinones, or pyrimidine derivatives,[1] stressing the broad range of synthetic possibilities offered thereby. Apart from these specific examples, reactions of carbonyl compounds with nucleophiles belong to the most important transformations in organic chemistry and biochemistry.[8] Consequently, numerous experimental studies, e.g., hydration of heterocumulenes[9] and carbonyl groups,[10] hydrolysis of esters (lactones) and amides,[11] combined experimental/computational,[12−16] as well as purely computational studies, e.g., hydrolysis or formation of simple amides (peptides),[17,18] esters,[18,19] anhydrides,[20] addition to aldehydes and ketones,[21] 1,2- vs 1,4-addition to α,β-unsaturated carbonyl compounds,[22] and models of enzymatic reactions[23] have been published. Ring opening of lactams with special emphasis on models of β-lactam antibiotics also has attracted a wealth of theoretical studies.[24−26] The unique feature of the heterocyclic 2,3-diones investigated in this paper is to allow comparison

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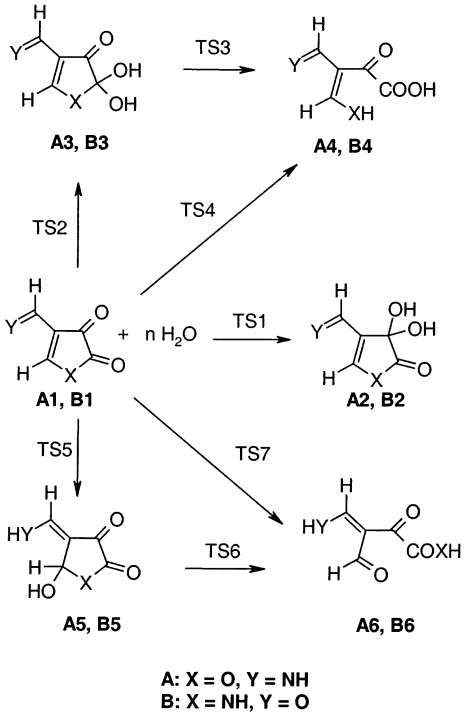
SCHEME 3. Reaction Pathways of 4-Iminomethylfuran-2,3-dione A1 and 4-Formylpyrrole-2,3-dione B1 with H_2O as a Nucleophile ($n = 1-5$)

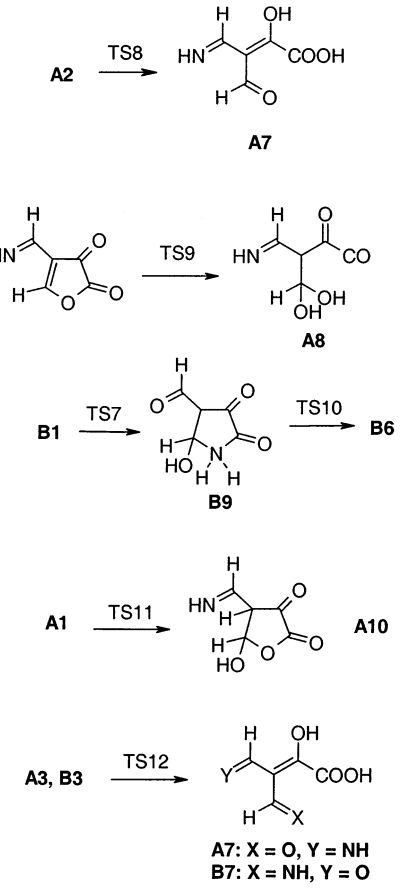


of different types of carbonyl reactions (hydration of a keto group, concerted and/or stepwise ester (amide) hydrolysis, and conjugate addition of the nucleophile to an α,β-unsaturated carbonyl moiety) within one single molecule.

Results

The reactions of H_2O as a nucleophile with 4-iminimethylfuran-2,3-dione **A1** and 4-formylpyrrole-2,3-dione **B1** considered in the following are depicted in Scheme 3. They include the following: (i) addition of H_2O to C_3, i.e., hydration of an activated carbonyl group (**A1** (**B1**) → TS1 → **A2** (**B2**); (ii) stepwise (**A1** (**B1**) → TS2 → **A3** (**B3**) → TS3 → **A4** (**B4**)) and concerted (**A1** (**B1**) → TS4 → **A4** (**B4**)) opening of the lactone ring (ester hydrolysis) via addition to the lactone carbonyl C_2; (iii) stepwise opening of the lactone ring via conjugate addition to C_5 and the exocyclic iminomethyl (formyl) group (**A1** (**B1**) → TS5 → **A5** (**B5**) → TS6 → **A6** (**B6**)); and (iv) concerted opening of the lactone ring via addition to C_5 (**A1** (**B1**) → TS7 → **A6** (**B6**)). It should be noted that on one hand not all of these reactions were found for all cases; on the other hand, depending on the system treated, some additional possible reaction paths (Scheme 4) were obtained. Furthermore, the ring-opened structures **A4** (**B4**) and **A6** (**B6**) need not necessarily be the final products of the reactions of furan- and pyrrole-2,3-diones with nucleophiles. For instance, with oxygen nucleophiles, a complete degradation to dibenzoylmethane + oxalic acid derivatives has been observed.[1] Tautomerism, e.g., **A4** → **A6**, or conformational and *E*/*Z* equilibria, e.g., **A6** → **B4**, are further possible transformations.

SCHEME 4. Additional Reactions Found by the Calculations



The calculations were done both for the uncatalyzed ($n = 1$, Scheme 3) and the catalyzed (water-assisted, $n = 2$) reaction. One of the main goals of the present work is the comparison of the reactivities of the various functional groups within model compounds **A1** (**B1**), i.e., reactions proceeding via the different TS's indicated in Scheme 3. To avoid complications arising from possibly large rearrangements of the reacting species to accommodate the different spatial arrangements necessary for reaction at the individual electrophilic sites in **A** (**B**), additional water molecules ($n = 4$, 5) placed to act as nucleophile, as catalyst, or as solvating spectator[18] were added. The initial placement of these extra H_2O molecules was guided by possible formation of hydrogen bonds to the various functional groups of the heterocyclic dione or the water molecules already present, followed by full geometry optimization.

Inter- and intramolecular hydrogen bonding and proton-transfer processes play an important role in the reactions considered. Therefore, for a correct description of the energetics, polarization functions at hydrogen atoms might be important. Consequently, besides the 6-31G* basis set, for the uncatalyzed and the water-assisted reactions of **A1**, the geometry optimizations were also done with use of the 6-31G** basis set.

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TABLE 1. Calculated Gas-Phase Relative Energies (E_{rel}) and Gibbs Free Energies (ΔG_{rel} and $\Delta G_{rel} + \Delta G_{solv}$) for the Aqueous Solution[a] of the Reaction of 4-Iminomethylfuran-2,3-dione A (4-Formylpyrrole-2,3-dione B) + H_2O

	A				B	
	B3LYP/6-31G*		B3LYP/6-31G**		B3LYP/6-31G*	
	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$
TS1	35.0 (44.9)	48.6 (37.7)	34.1 (44.0)	47.6 (36.4)	34.6 (44.5)	48.7 (49.2)
2	−2.7 (7.2)	9.9 (7.6)	−2.9 (6.9)	9.6 (7.3)	−3.7 (6.2)	10.8 (8.3)
TS2	34.7 (44.7)	43.5 (35.3)	33.8 (43.7)	42.4 (34.2)	34.3 (44.2)	48.8 (48.4)
3	−6.7 (3.3)	4.9 (3.6)	−7.0 (3.0)	4.2 (3.2)	−4.2 (5.0)	9.7 (6.0)
TS3	9.6 (19.7)	18.1 (17.9)	9.3 (19.4)	17.7 (18.4)	23.7 (33.8)	39.3 (34.1)
4	−25.2 (−15.4)	−8.9 (−9.0)	−26.0 (−16.2)	−9.7 (−9.9)	−13.0 (−4.0)	0.6 (−2.6)
TS4	19.0 (28.3)	28.9 (32.7)	18.8 (28.1)	28.9 (33.3)	29.7 (39.0)	49.4 (46.5)
4′	−4.6 (4.4)	4.2 (5.6)	−4.8 (4.2)	3.8 (5.4)		
TS5	5.5 (16.1)	17.7 (7.4)	5.5 (16.1)	17.6 (7.0)	8.2 (18.8)	21.3 (9.2)
5	−27.3 (−17.2)	−22.4 (−24.0)	−26.1 (−16.0)	−21.4 (−22.9)	−10.0 (0.3)	5.1 (−1.5)
TS6	13.7 (23.4)	5.8 (6.3)	14.7 (24.4)	6.6 (7.2)	51.8 (61.5)	62.9 (56.5)
6	−24.8 (−15.9)	−24.6 (−22.0)	−24.0 (−15.1)	−24.5 (−21.7)	−24.7 (−15.5)	−1.2 (−5.8)
TS7					45.2 (55.2)	51.6 (46.8)
9					15.6 (25.6)	25.0 (16.1)
TS10					17.0 (27.5)	29.7 (20.7)
TS8	35.0 (45.4)	39.2 (38.3)	34.9 (45.4)	38.9 (38.2)		
7	−6.6 (2.3)	−0.9 (−0.9)	−6.7 (2.0)	−1.3 (−1.2)		
TS9	45.6 (55.6)	49.6 (31.6)	44.8 (54.8)	48.6 (31.7)		
8	22.1 (31.7)	34.2 (33.5)	22.1 (31.7)	34.1 (33.2)		

[a] ΔG_{solv} obtained by single-point Poisson−Boltzmann SCRF calculations; results from the polarizable continuum model of solvation are given in parentheses.

Computed gas-phase relative energies (including zero-point energy contributions and relative free enthalpies in aqueous solution) are collected in Table 1 (uncatalyzed reaction), Table 2 (water-assisted process), Table 3 (+4H_2O), and Table 4 (+5H_2O). Total energies are provided in the Supporting Information. For the uncatalyzed reactions, relative energies are given with respect to the separated reactants. For reactions with $n = 2-5$ the hydrated species of **A1** (**B1**) are taken as energy zero. Formally, then, all subsequent reaction steps are intramolecular. Thus, especially for reactions in solution, problems with the definition of the standard state in the calculation of entropic contributions can be avoided: calculated thermodynamic quantities refer to 1 atm and 298 K whereas for solutions mol L^{-1} would be a more natural choice of standard state with a concomitant change in entropies for all but unimolecular reactions.[27] By using the hydrated complexes as reference, no such correction term is required. In addition, for reactions involving two or more species, the conversion of translational and rotational degrees of freedoms into vibrations can alternatively be described by a single effective frequency,[15] rather than by using the corresponding low frequency and, thus, quite inaccurate modes obtained from the frequency calculation within the rigid-rotor harmonic-oscillator approximation.

Uncatalyzed Reactions. The following general conclusions can be drawn from the data presented in Table 1: (i) Irrespective of whether bimolecular, e.g. TS1, TS2, TS5, or monomolecular, e.g. TS3 or TS6, steps are considered, in the gas phase for both systems **A** and **B** ΔG_{rel} values are higher by ca. 10 kcal mol^{-1} than ΔE_{rel} values. (ii) The basis set effect (6-31G* vs 6-31G**), i.e., the effect of p-type polarization functions on hydrogen atoms, is small. (iii) Concerning the individual steps detailed in Scheme 3, in the gas-phase addition of H_2O to either the keto (C_3, TS1) or lactone (C_2, TS2) carbonyl groups have quite substantial and very similar barriers (Table 1). Ring opening (TS3) of intermediate **3** to **4** and direct formation of **4** (TS4) have substantially lower barriers than formation of the tetrahedral intermediate **3**. Both barriers (TS3, TS4) are significantly higher for the reaction of pyrrole-2,3-dione **B** than for furan-2,3-dione **A**. Conjugate addition to C_5 and the exocyclic heteroatom of the 4-iminomethyl (formyl) group not only should have by far the lowest barrier (TS5, Table 1) but also lead to the most stable primary adduct **5**. Consequently, here ring opening (TS6) has a rather high activation energy (ca. 40 kcal mol^{-1} for **A5** and 60 kcal mol^{-1} for **B5**). In the case of furan-2,3-dione **A** no transition state for direct ring opening via addition to C_5 could be found. For pyrrole-2,3-dione a rather high energy two-step mechanism (**B1** → TS7 → **B9** → TS10 → **B6**) was obtained in the gas phase. (iv) Inclusion of solvent effects (aqueous solution) by the Poisson−Boltzmann SCRF approximation (PB-SCRF)[28] yields somewhat contradictory results compared to those obtained by the polarizable continuum model (PCM).[29] For instance, whereas both solvent models predict an increase of ΔG_{rel}(TS1) and ΔG_{rel}(TS2) for the reaction of pyrrole-2,3-dione by ca. 4 kcal mol^{-1} (Table 1), for the corresponding reactions of furan-2,3-dione PCM calculations give a substantial lowering (7−9 kcal mol^{-1}). In contrast, with PB-SCRF here too either an increase (TS1) or only a rather small decrease (TS2) for ΔG_{rel} is obtained. Similarly, contrary to the drastic lowering (ca. 9 kcal mol^{-1}) of the free energy barrier for C_5-addition given by PCM calculations, the PB-SCRF approximation yields a slight increase of ΔG_{rel}(TS5) in aqueous solution. The

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TABLE 2. Calculated Gas-Phase Relative Energies (E_{rel}) and Gibbs Free Energies (ΔG_{rel} and $\Delta G_{rel} + \Delta G_{solv}$) for the Aqueous Solution[a] of the Reaction of 4-Iminomethylfuran-2,3-dione A (4-Formylpyrrole-2,3-dione B) + 2 H_2O

	A				B	
	B3LYP/6-31G*		B3LYP/6-31G**		B3LYP/6-31G*	
	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$
TS1	22.9 (24.9)	24.3 (23.8)	21.9 (23.8)	23.5 (22.5)	24.3 (26.4)	26.4 (25.5)
2	1.7 (2.6)	2.2 (−0.5)	1.5 (2.4)	2.1 (−0.8)	−0.7 (0.7)	2.3 (−0.2)
TS2	18.1 (20.2)	16.7 (2.4)	17.2 (19.1)	14.2 (−0.6)	25.3 (27.0)	24.3 (22.9)
3	−3.8 (−2.6)	−5.2 (−6.3)	−4.0 (−2.9)	−5.3 (−6.6)	−1.6 (−0.3)	1.5 (−2.1)
TS3	9.1 (10.1)	0.4 (2.1)	8.5 (9.7)	0.4 (1.7)	24.5 (26.0)	23.6 (19.3)
4	−8.2 (−8.4)	−11.8 (−11.2)	−8.6 (−8.8)	−12.3 (−11.8)	−5.0 (−5.5)	−4.9 (−9.5)
TS4	23.0 (23.2)	14.9 (18.1)	22.9 (23.2)	14.9 (17.9)		
1′	1.1 (−0.2)	−1.0 (−2.2)	0.9 (−0.3)	−1.2 (−2.5)	−0.4 (−1.5)	−1.2 (−2.1)
TS5	8.6 (10.3)	4.0 (−16.4)	8.1 (9.8)	4.3 (−16.5)	10.5 (12.3)	6.3 (1.5)
5	−20.6 (−19.8)	−29.7 (−31.8)	−19.5 (−18.7)	−28.4 (−30.9)	−5.2 (−3.9)	−4.6 (−12.5)
TS6	3.1 (4.3)	−7.6 (−12.9)	2.8 (4.0)	−7.7 (−13.1)	22.5 (24.9)	24.9 (21.2)
6	−13.7 (−15.3)	−29.7 (−27.3)	−12.6 (−14.1)	−28.6 (−26.4)	−3.9 (−4.5)	−2.4 (−6.1)
TS11	26.8 (28.3)	11.8 (−6.1)	26.3 (27.8)	10.9 (−6.9)		
10	−2.7 (−3.8)	−10.0 (−11.9)	−0.6 (−1.7)	−7.9 (−10.3)		

[a] ΔG_{solv} obtained by single-point Poisson−Boltzmann SCRF calculations; results from the polarizable continuum model of solvation are given in parentheses.

large differences between the two solvent models might be at least partly accounted for by the additional correction term for hydrogen bonding introduced into the PB-SCRF model, since frequently hydrogen-bonding energies are only poorly correlated with classical electrostatic interaction energies.[28a] Both solvent models predict a reduction of the barrier for the ring-opening reaction **A5** (**B5**) → TS6 → **A6** (**B6**). Summing up, thus, without catalysis by an ancillary water molecule not only in the gas phase but also in aqueous solution the conjugate addition of H_2O to C_5 of the heterocyclic dione and the heteroatom (N_9 (O_9)) of the 4-iminomethyl (formyl) group should be the most feasible pathway. Ring opening of the intermediate **5** formed thereby hardly should be possible. Formation of the tetrahedral intermediates **2** or **3** by an uncatalyzed addition of H_2O to $C_{2(3)}$═O is unlikely.

Catalyzed Reactions. First, as found for the uncatalyzed reactions, results obtained with the 6-31G** basis set do not differ significantly from those obtained with the 6-31G* basis. Consequently, for the larger systems (see below) this latter basis set will be used throughout.

As expected from previous work,[15,16,17a,b,18,19,21,22b,24−26] catalysis by an ancillary water molecule of the various hydration and ring opening steps generally greatly reduces the corresponding activation energies (up to >20 kcal mol^{-1}, Table 2).In contrast to the uncatalyzed 1,2-additions to the carbonyl groups (TS1, TS2) which involve unfavorable four-membered transition states, the 1,4-addition to C_5 and the heteroatom of the exocyclic double bond (TS5) is characterized by a six-membered TS. Catalysis by an ancillary water molecule requires in this latter reaction formation of an eight-membered cyclic TS with a concomitant less pronounced stabilizing effect as found for catalysis of 1,2-additions. Nevertheless, as for the uncatalyzed reactions, in the gas phase the lowest barriers are found for 1,4-addition at C_5. Generally, the trends described above for the uncatalyzed reactions are also evident for the assisted ones. With inclusion of solvent effects the differentiation between the addition to the keto (C_3═O) vs the lactone (C_2═O) carbonyl group becomes more pronounced in the case of the assisted as compared to the uncatalyzed reaction. Somewhat disturbing results are obtained with PCM solvation free energies, especially for TS5 of system **A**: here according to the PCM results the transition structure should be ∼16 kcal mol^{-1} below that of the reactants. Although apparent negative activation free energies have been found previously when the separated reactants rather than the prereaction complexes were used as reference,[17,18,25] here this effect apparently is a result of the model used for the description of solvation. In this respect, the PB-SCRF approximation seems to provide a more realistic treatment of solvent effects. Notably, for system **B** these discrepancies between the results obtained by the two solvent models for, e.g. TS2 and TS5 (Table 2), are considerably less severe. Possible reasons include specific solvent effects (e.g., hydrogen bonding, which is partly accounted for in the PB-SCRF model[28a]) or the quite large rearrangements within the prereaction complexes necessary to adopt geometries suitable for the various reaction paths.[18] Consequently, calculations with inclusion of two and three respectively additional water molecules which either act simply as solvating species or, alternatively, as nucleophile or catalyst have been performed (Tables 3 and 4).

The most notable feature of the results obtained by this supermolecule approach for solvation is that no transition states for concerted addition−ring opening (TS4, TS7) could be located. Obviously then, a stepwise mechanism involving a tetrahedral intermediate[17,19,24,25] should be more feasible than a concerted addition−elimination (i.e., ring opening) pathway. Experimentally, alkaline hydrolysis of lactones or *N*-substituted lactams has been shown to proceed indeed via tetrahedral intermediates.[11b,c] Two additional water molecules (Table 3) apparently do not significantly alter the results for the catalyzed reaction also obtained without them (Table 2). Noteworthy changes brought about by a third solvent molecule (i.e., a total of 5 H_2O molecules, Table 4) are an increase and decrease respectively of ΔG_{rel}(TS1) and ΔG_{rel}(TS2) for both the furan-2,3-dione and the pyrrole-2,3-dione. Thus, formation of adducts **A2** or **B2** should be of minor importance compared to addition at C_2. In line with these findings are experimental observations indicating that the structures of several adducts originally proposed to be of type **A2** or **B2** (i.e., **I** in Scheme 2) had to be revised.[7] Interestingly, the free energy barrier (TS3) for ring opening of adduct **A3** is increased by additional water

TABLE 3. Calculated Gas-Phase Relative Energies (E_{rel}) and Gibbs Free Energies (ΔG_{rel} and $\Delta G_{rel} + \Delta G_{solv}$) for the Aqueous Solution[a] of the Reaction of 4-Iminomethylfuran-2,3-dione A (4-Formylpyrrole-2,3-dione B) + 4 H_2O

	A B3LYP/6-31G*		B B3LYP/6-31G*	
	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$
TS1	20.7 (22.9)	22.1 (21.8)	22.8 (24.7)	25.0 (23.9)
2	−0.3 (0.9)	−0.1 (−6.2)	0.0 (1.2)	2.2 (−0.1)
TS2	18.8 (20.9)	16.7 (5.5)	22.1 (24.1)	24.9 (22.4)
3	−6.2 (−4.8)	−8.1 (−10.1)	3.6 (4.4)	3.7 (0.8)
TS3	11.6 (12.3)	0.7 (4.5)	26.5 (26.3)	22.3 (18.3)
4	−10.6 (−9.9)	−11.0 (−9.8)	−9.6 (−9.0)	−7.2 (−10.3)
TS5	8.1 (11.0)	6.7 (−11.5)	13.2 (15.7)	9.0 (4.2)
5	−22.7 (−20.6)	−28.6 (−31.4)	−3.5 (−1.3)	−2.9 (−10.1)
TS6	2.2 (2.8)	−9.1 (−7.3)	26.4 (28.2)	23.6 (20.1)
6	−20.0 (−19.8)	−29.1 (−25.3)	1.7 (2.7)	7.0 (1.9)
TS12	2.6 (4.7)	−4.5 (−15.4)	13.9 (16.7)	16.2 (10.6)
7	−17.0 (−17.1)	−18.7 (−19.6)	−6.3 (−5.7)	−5.8 (−10.7)

[a] ΔG_{solv} obtained by single-point Poisson−Boltzmann SCRF calculations; results from the polarizable continuum model of solvation are given in parentheses.

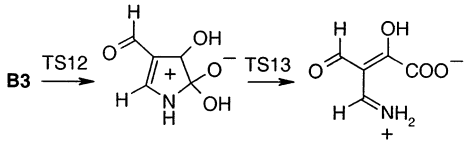
TABLE 4. Calculated Gas-Phase Relative Energies (E_{rel}) and Gibbs Free Energies (ΔG_{rel} and $\Delta G_{rel} + \Delta G_{solv}$) for the Aqueous Solution[a] of the Reaction of 4-Iminomethylfuran-2,3-dione A (4-Formylpyrrole-2,3-dione B) + 5 H_2O

	A B3LYP/6-31G*		B B3LYP/6-31G*	
	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$	E_{rel} (ΔG_{rel})	$\Delta G_{rel} + \Delta G_{solv}$
TS1	28.2 (28.0)	23.9 (23.9)	28.6 (30.3)	29.1 (29.0)
2	7.3 (6.1)	1.9 (0.0)	0.3 (1.8)	2.9 (0.3)
TS2	14.5 (16.3)	14.2 (4.6)	21.9 (24.2)	23.1 (22.5)
3	−7.5 (−6.4)	−7.2 (−8.1)	5.1 (6.0)	4.1 (2.5)
TS3	13.8 (12.9)	0.0 (3.0)	34.5 (34.8)	29.8 (26.7)
4	−6.8 (−7.1)	−11.3 (−12.2)	−2.0 (−1.7)	−2.9 (−5.3)
TS5	6.7 (7.7)	6.1 (3.4)	19.4 (20.1)	10.5 (9.6)
5	−22.3 (−22.1)	−29.3 (−29.0)	2.3 (4.2)	2.0 (−3.7)
TS6	1.1 (2.8)	−7.5 (−11.2)	31.8 (33.3)	28.2 (26.5)
6	−14.4 (−15.1)	−24.8 (−22.2)	1.4 (1.4)	3.2 (−1.9)
TS12	8.0 (9.4)	1.7 (−10.7)	16.7 (19.5)	19.1 (15.4)
7	−12.4 (−12.6)	−15.1 (−16.6)	−4.7 (−4.0)	−4.3 (−9.2)

[a] ΔG_{solv} obtained by single-point Poisson−Boltzmann SCRF calculations; results from the polarizable continuum model of solvation are given in parentheses.

molecules (ΔG_{rel}(TS3−**3**) = 12.7 (catalyzed reaction, Table 2), 17.1 (4 H_2O, Table 3), and 19.3 kcal mol^{-1} (5 H_2O, Table 4) for gas-phase complexes). With solvent effects included by the PB-SCRF model, however, these barriers are significantly reduced and the corresponding values are as follows: ΔG_{rel}(TS3−**3**) = 5.6 (catalyzed reaction, Table 2), 8.8 (4 H_2O, Table 3), and 7.2 kcal mol^{-1} (5 H_2O, Table 4). Consequently, in aqueous solution, formation of the tetrahedral intermediate **A3** (ΔG_{rel}(TS2) = 14−17 kcal mol^{-1} (Tables 2−4) is the rate-determining step for the reaction pathway **A1** → TS2 → **A3** → TS3 → **A4**. Pyrrole-2,3-dione **B1** behaves differently: here not only ΔG_{rel}(TS2) is considerably larger than for furan-2,3-dione (PB-SCRF: 23 kcal mol^{-1} vs 14 kcal mol^{-1}, Table 4) but also the tetrahedral intermediate is less stable than the starting material (PB-SCRF: ΔG_{rel} = +4 (**B3**) vs −7 (**A3**) kcal mol^{-1}, Table 4) and, finally, $\Delta\Delta G_{rel}$(TS3−**3**) values differ significantly between the pyrrole and furan derivative (PB−SCRF: 26 vs 7 kcal mol^{-1}, Table 4). Experimentally, with *N*-nucleophiles pyrrole-2,3-diones give ring-opened structures corresponding to **B4** (i.e., structure **III** in Scheme 2); in striking contrast, reaction with *O*-nucleophiles (e.g. MeOH, water) leads to formation of C_5-adducts (structures of type **II** in Scheme 2, i.e., tautomers of **B5**).[7] Not unexpectedly, however, the analogous imino enol tautomer of the furandione C_5-adduct is considerably less stable than the enaminone form **A5** (ca. 15 kcal mol^{-1} at the PB-SCRF level with 4 explicit additional solvating water molecules included). Also in line with these calculated differences between furandiones and pyrrolediones are experimental results for the alkaline hydrolysis of lactones vs lactams:[11b,c] For five- and six-membered lactones as well as β-lactams, addition of OH^- to the carbonyl group has been proposed as the rate-determining step. In contrast, for *N*-substituted γ- and δ-lactams ring fission appears to be rate determining. For both systems **A** and **B**, TS5 has the lowest free energy of activation (PB-SCRF: 6 and 11 kcal mol^{-1}, respectively). Thus, in agreement with the experimental results for pyrrolediones[7] conjugate addition to C_5 should be the preferred reaction mode. The stabilities of the resulting adducts **A5** vs **B5** are, however, very different (ca. 30 kcal mol^{-1}, Table 4). Ring opening of **A5** has a considerably larger barrier than that found for adduct **A3** (PB-SCRF: $\Delta\Delta G_{rel}$(TS3−**3**) = 7 vs $\Delta\Delta G_{rel}$(TS6−**5**) = 22 kcal mol^{-1}, Table 4). In contrast, for pyrrole-2,3-dione both barriers are almost equal (PB-SCRF: $\Delta\Delta G_{rel}$(TS3−**3**) ∼ $\Delta\Delta G_{rel}$(TS6−**5**) = 26 kcal mol^{-1}, Table 4).

As a completely new feature, for the systems with 4 or 5 water molecules, ring opening of **A3** (**B3**) via a proton-transfer network involving two rather than just one water molecules also has been found. Interestingly, in this pathway proton transfer (TS12, see Scheme 4 and Tables 3 and 4) occurs to the C_3=O keto group rather than to the ring oxygen O_1 (nitrogen N_1). For the furan derivative, proton transfer and ring opening is a concerted process leading directly to structure **A7**, i.e., the C_3-enol tautomer of **A4**. Both in the gas phase and with inclusion of solvent effects (PB-SCRF model, n = 4 and 5 H_2O) the stability of the three tautomeric forms of the ring-opened structures increases in the order **A4** < **A7** < **A6** (Tables 3 (n = 4 H_2O) and 4 (n = 5 H_2O)). For n = 4 H_2O (Table 3), concerted proton transfer to C_3=O and ring opening (**A3** → TS12 → **A7**) is calculated to have a lower barrier (PB-SCRF: $\Delta\Delta G_{rel}$(TS12−**3**) = 3.6 kcal mol^{-1}) than ring opening via transfer of the proton to O_1 (**A3** → TS3 → **A4**, $\Delta\Delta G_{rel}$(TS3−**3**) = 8.8 kcal mol^{-1}). With inclusion of an additional explicit solvating water molecule both barriers are almost equal (PB-SCRF, Table 4). Pyrrole-2,3-dione behaves also differently for this pathway in several aspects. First, the calculations indicate a stepwise rather than concerted mechanism with proton transfer to the C_3=O keto group prior to ring opening of the resulting zwitterionic intermediate. This ring opening occurs either with a quite small free energy of activation (TS13, ∼5 kcal mol^{-1}, PB-SCRF, n = 5 H_2O) or even almost barrierless (n = 4 H_2O). Second, ring opening is also accompanied by proton transfer from the C_2−OH group toward N_1 leading to a zwitterionic structure of **B7**:



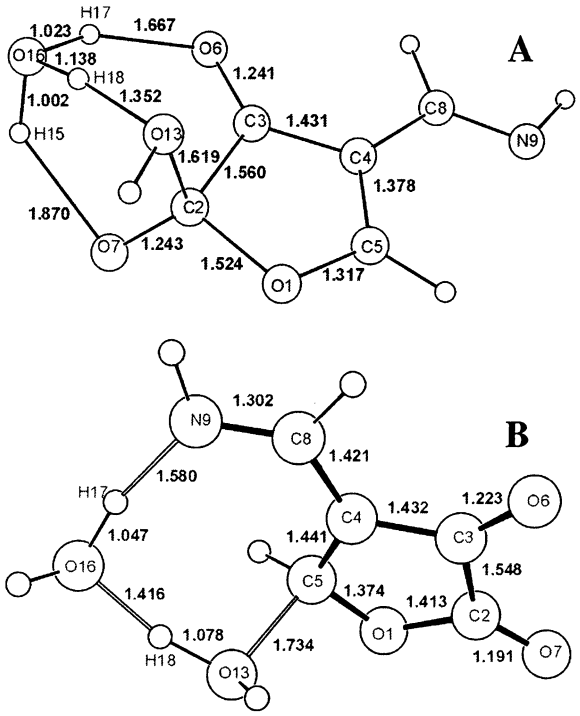


FIGURE 1. Calculated (B3LYP/6-31G*) structures for transitions states TS2 (**A**) and TS5 (**B**) of the addition of H_2O to furandione **A1**.

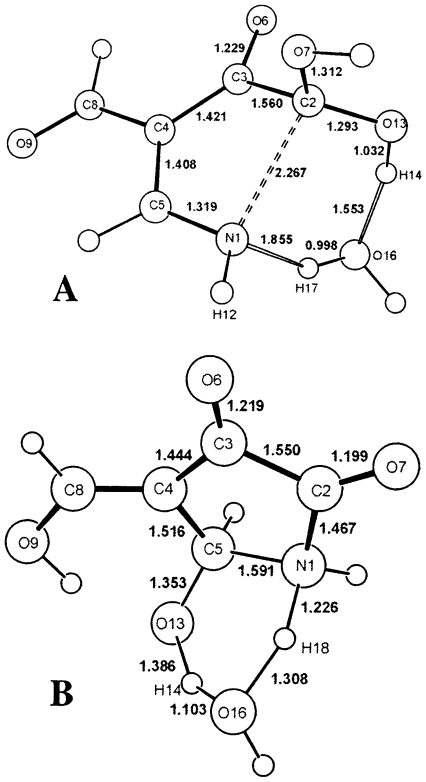


FIGURE 2. Calculated (B3LYP/6-31G*) structures for transitions states TS3 (**A**) and TS6 (**B**) for the ring fission of adducts **B3** and **B5**.

Third, whereas for **A3** the two pathways via TS3 or TS12 have comparable free energies of activation (see above), for **B3** ring opening via TS12 clearly is more feasible: $\Delta\Delta G_{rel}$(TS12−**3**) = 15.0 vs $\Delta\Delta G_{rel}$(TS3−**3**) = 25.7 kcal mol^{-1} (n = 5 H_2O, PB-SCRF, Table 4).

Structural Features. Some pertinent geometrical parameters of transition states TS1, TS2, and TS5 for the water-assisted reaction and hydrates thereof are summarized in Table S8 of the Supporting Information. Representative structures are shown in Figure 1. According to these data the transition structures for 1,2-addition to the carbonyl groups C_3═O_6 (TS1) and C_2═O_7 (TS2) significantly differ from those for conjugate addition to C_5 (TS5). First of all, catalyzed 1,2-additions involve six-membered cyclic transition states. In contrast, for conjugate 1,4-addition, it is the uncatalyzed reaction that has this arrangement. In the assisted 1,4-addition reaction occurs via an eight-membered cyclic array. Undoubtedly, in this latter TS, the distance of the newly forming bond C_5−O_{13} is comparable to the analogous distances r(C_3−O_{13}) and r(C_2−O_{13}) calculated for TS1 and TS2. However, in contrast to both TS1 and TS2, proton transfer from the reactant water molecule to the ancillary H_2O and from this water molecule to N_9 (O_9 in **B**) is considerably less pronounced here. As a consequence, the geometry of TS5 resembles a hydrated H_2O adduct of the heterocyclic dione whereas the geometries of both TS1 and TS2 might be interpreted in terms of a H_3O^+ complex of the dione−OH^- adduct. NBO analyses[30,31] of the electronic structures of TS1, TS2, and TS5 by and large corroborate this interpretation. For instance, according to the NBO analysis, the TS2 of the water-assisted reaction of both systems **A** and **B** can be described by a "complex" $C_5H_4NO_4$ + H_3O with charges of −0.6 and +0.6 on the two units. Addition of the nucleophile to the lactone carbonyl carbon atom C_2 of the furandione results in a substantial elongation of the C_2−O_1 bond from ca. 1.4 Å in **A1** to ca. 1.52 Å in TS2. Interestingly, the C_2−O_1 distance in TS2 is longer than that in the adduct **A3** itself (ca. 1.47 Å, see Table S9 in the Supporting Information). In the pyrroledione this elongation of the C_2−N_1 bond is considerably less pronounced and the value of r(C_2−N_1) in TS2 is comparable to that found in the adduct **B3**. In contrast to addition at the carbonyl carbon, conjugate addition to C_5 does not lead to any significant lengthening of the C_5−O_1(N_1) distance.

The two transition states TS3 and TS6 for ring opening also have quite different structural features (see Figure 2 and Table S9). In TS3 the water-assisted proton transfer from the OH group at C_2 to the ring oxygen (nitrogen in **B**) significantly lags behind elongation of the ring bond C_2−O_1 (N_1). As a consequence, the natural charges on O_1 and C_2 are quite substantial, e.g. −0.7 and +0.8 for the TS3 of **A**. In the corresponding transition state TS3 for ring opening of **B3**, both elongation of the C_2−N_1 and proton transfer are less pronounced (e.g., r(C_2−N_1) = 2.27 Å and r(N_1−H_{17}) = 1.86 Å compared to r(C_2−O_1) = 2.68 Å and r(O_1−H_{17}) = 1.56 Å, Table S9). Otherwise ring opening transition states TS3 of C_2-adducts **A3** and **B3** are quite similar. On the contrary, the transition states TS6 for ring opening of the C_5-adducts differ rather substantially depending on whether

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(31) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO* Version 3.1; Madison, WI, 1988.

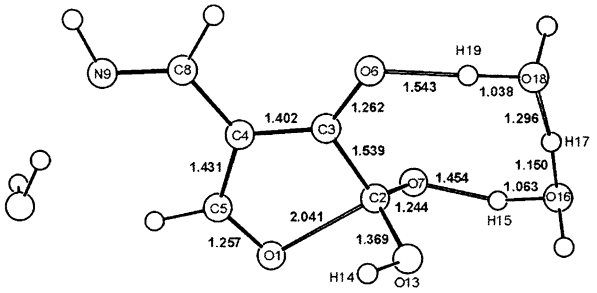

FIGURE 3. Calculated (B3LYP/6-31G*) structures for transitions state TS12 (**A**, $n = 4$ H_2O).

the heteroatom is oxygen (O_1) or nitrogen (N_1). In case of TS6 for reaction of **A5**, proton transfer from the OH group at C_5 toward O_1 is considerably less advanced than stretching of the C_5-O_1 bond ($r(C_5-O_1) = 1.95$ Å, $r(O_1-H_{18}) = 1.35$ Å). As evidenced by the NBO analysis, therefore, this transition state can be regarded as a $C_5H_4NO_4 + H_3O$ complex with quite substantial charges (±0.7) on the two subunits. In contrast, ring opening of **B5** occurs with proton transfer preceding ring opening (Figure 2 and Table S9).

Relevant structural data for TS12 are collected in Table S10 of the Supporting Information (see also Figure 3). Although adding another water molecule to TS12 for ring opening of **A3** ($n = 4$ H_2O) apparently retards breaking of the C_2-O_1 bond (see Table S10: $r(C_2-O_1) = 2.04$ ($n = 4$ H_2O) and 1.69 Å ($n = 5$ H_2O)), this process is clearly more advanced in case of system **A** than for system **B**. The structural data, as well as the NBO analysis, indicate that TS12 can be regarded as a complex between a hydrated ($n = 2$ or 3) partially negatively charged ($q = -0.7$) heterocyclic subunit $C_5H_4NO_4(H_2O)_n$ and H_3O^+ ($q = +0.7$).

Conclusions

The site of nucleophilic addition to 4-iminomethyl (acyl)-substituted furan- and pyrrole-2,3-diones has been investigated by density functional theory (B3LYP) calculations with water as a neutral nucleophile. Reactions considered include 1,2-additions to a lactone (lactam) carbonyl group with a concomitant hydrolysis (ring opening) and an activated keto (α-oxo-carboxyl) and conjugate 1,4-addition to C_5 of the heterocycle and the exocyclic 4-iminomethyl (formyl) group. Uncatalyzed additions/eliminations and catalysis of these reactions by an ancillary water molecule were treated. Solvent effects (aqueous solution) were approximated by the polarizable continuum model and the Poisson−Boltzmann SCRF method. For the present systems, this latter procedure is found to lead to a more reliable description of solvation, especially for transition states TS2 and TS5. In addition, specific solvation is accounted for by considering explicit water molecules. Apart from the two H_2O molecules acting as nucleophile and catalyst, respectively, three additional solvating water molecules were found to be necessary for a proper description of the energetics of the various reactions. Water-assisted conjugated 1,4-addition to C_5 is calculated to have the lowest activation free energy. Ring opening of this adduct, however, has a quite substantial barrier and appears to be less feasible than the analogous reaction of the C_2-adduct. Opening of the lactone (lactam) ring evidently is a stepwise process with C_2- and/or C_5-adducts as tetrahedral intermediates. Only in the case of uncatalyzed reactions could the transition states for concerted addition/elimination be located. Besides reactions catalyzed by one ancillary water molecule, ring opening of the C_2-adducts via a proton-transfer array involving two H_2O molecules and the C_3═O keto group as acceptor appears to be a feasible mechanism. Finally, reaction of the keto carbonyl with the nucleophile should be the least probable pathway.

Computational Details

All computations were done by the Gaussian 98 program suite,[32] using Becke's three parameter hybrid Hartree−Fock DFT procedure[33] with the Lee−Yang−Parr[34] correlation functional (B3LYP). The 6-31G* and in some selected cases the 6-31G** basis set was used throughout. Stationary points were characterized as minima or transition states by frequency calculations. In addition, for most TS's intrinsic reaction coordinate (IRC) calculations were performed. Zero-point energy (ZPE) corrections are unscaled. Solvent effects (aqueous solution) were estimated by the polarizable continuum model (PCM)[29] and the Poisson−Boltzmann SCRF approximation (PB-SCRF)[28] as implemented in the Jaguar program.[35]

Supporting Information Available: Tables of total energies, zero-point energy corrections and solvation free energies, pertinent structural parameters, as well as B3LYP/6-31G* optimized Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026142O

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