Mechanism of Rearrangement Reactions of Ketenimine–4-Acylfuran-2,3-dione Cycloadducts—a Semiempirical Molecular Orbital Study

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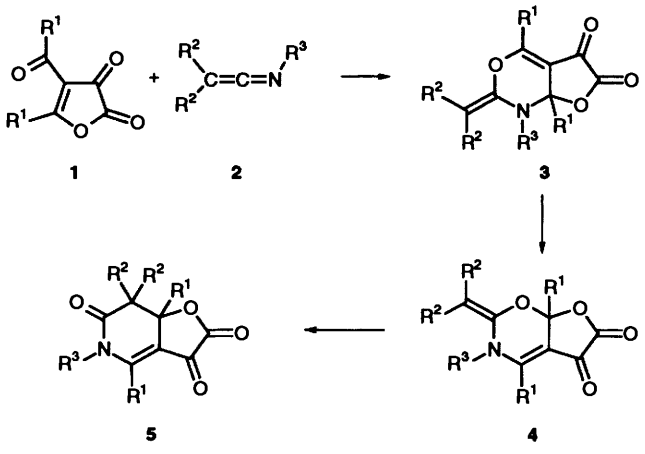
Semiempirical molecular orbital calculations (AM1) are used to explain the formation of **5** as a reaction product obtained from 4-acylfuran-2,3-diones **1** and ketenimines **2**. Rearrangement of the primary cycloadduct **3** *via* intermediate **4** is found to be the most feasible pathway. An alternative fragmentation–cycloaddition mechanism *via* iminofurandione (**9**) + ketene (**10**) is highly unlikely. Rearrangement of the regioisomeric primary cycloadduct **6** to **5** (either directly or *via* intermediates **7** and **8**) also requires significantly higher activation energies. The theoretical results are used to interpret previous findings from ^{17}O isotopic labelling investigations.

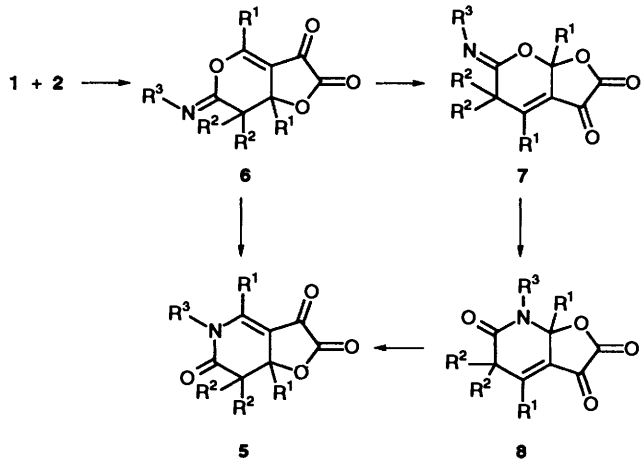
4-Acyl substituted furan- and pyrrole-2,3-diones readily add arylisocyanides or heterocumulenes to give bicyclic reaction products.[1,2] The structures of these heterocycles strongly depend on the nature of both the heterocumulene as well as the dione. For instance, the furandione **1** adds *C,C*-dimethyl-*N*-phenylketenimine **2** to yield compound **4**, whereas from reaction of **1** with triarylketenimines the furo[3,2-*c*]pyridine **5** is obtained.[2] To explain the observed reaction products an initial [4 + 2] cycloaddition between the ketenimine C=N double bond and the oxa-1,3-diene substructure of **1** to the primary cycloadduct **3**, followed by a rearrangement sequence **3** ⟶ **4** ⟶ **5** for R^2 = Ph) has been postulated.[2] The proposed reaction mechanism[2] is outlined in Scheme 1. It should be



R^1 = Ph, R^2 = Me, Ph, R^3 = Ph

Scheme 1

pointed out that formation of **3** would represent the first example for this type of reaction of ketenimines. Isolation of **4** in the case of R^2 = Me is taken as evidence in favour of the proposed reaction mechanism. In addition, semiempirical molecular orbital calculations of the stability of a number of conceivable cycloaddition and rearrangement products[3] as well as experimental isotopic labelling studies[4] also support this reaction pathway. However, the question about the detailed mechanism of such a rearrangement sequence as well as its feasibility (*i.e.* the respective activation energies) remains. Furthermore, an alternative route involving the more common [4 + 2] cycloaddition of the heterocumulene C=C double bond affording **6** as the primary cycloadduct (see Scheme 2) can be envisioned. In addition, since **5** can also be obtained by reaction

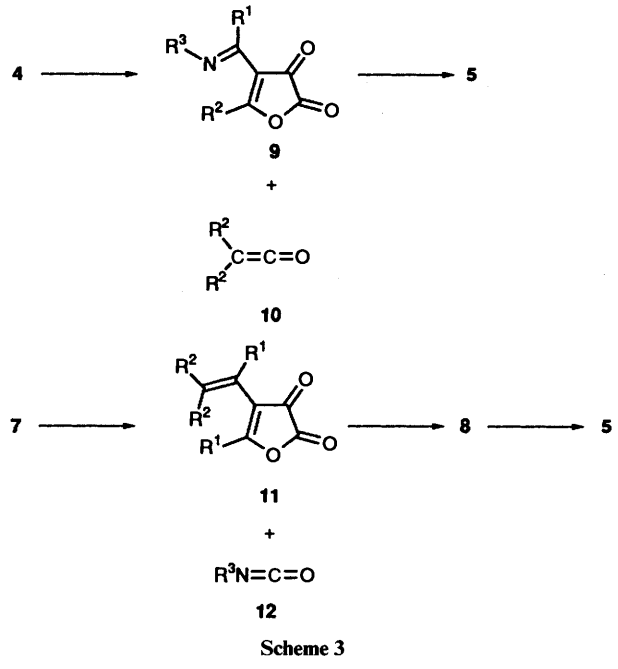


Scheme 2

of independently synthesized iminofurandione **9** (**1** + carbodiimides) with ketenes **10**,[2] a fragmentation–cycloaddition mechanism (**4** ⟶ **9** + **10** ⟶ **5** and **7** ⟶ **11** + **12** ⟶ **8**, respectively) might also operate (Scheme 3). Therefore we found it worthwhile to supplement the experimental findings with semiempirical molecular orbital calculations. Given the proven reliability and effectiveness in related problems[5] the AM1 model[6] seems to be the method of choice for this purpose. To keep the computational efforts manageable, the calculations were done with simplified model compounds (R^1 = R^2 = R^3 = H).

Results and Discussion

Formation of the Primary Cycloadducts **3** *and* **6**.—Reactions of **1** across the ketenimine C=N double bond proceeds *via* attack of the nitrogen lone pair (transition state **TS1**) rather than the π-orbital (the dihedral angle τ between C5 of **1**, N, central C and N*H* of **2** is −168.2° instead of the expected ≈90°) to give the intermediate **11**, which then cyclizes *via* transition state **TS2** to the primary cycloadduct **3**. In contrast, **6** is formed in a single step (**TS10**). Here, the dihedral angle between C5 of **1**, terminal C, central C, C*H* of **2** is close to the expected value (τ = −108.9°). Interestingly, although the calculated reaction energies should favour formation of **6** over **3** [$\Delta_R H$ = −149.8 (**6**) *vs.* $\Delta_R H$ = −77 kJ mol^{-1} (**3**), see Table 1], the differences in the corresponding activation energies are much less pronounced [39.3 (**TS10**) *vs.* 62.8 kJ mol^{-1} (**TS1**)]. Furthermore, from the structures of the respective transition states it has been



Scheme 3

Table 1 Computed reaction and activation energies,[a] E_{rel}, dipole moments, μ, and ionization potentials for the possible intermediates and transition states

	E_{rel}/kJ mol^{-1}	μ^b/D	E_i/eV	$\tilde{\nu}$/cm^{-1}
TS1	62.76	6.66	9.43	430
I1	28.87	10.35	8.76	
TS2	44.35	9.00	9.17	404
3	−77.82	4.05	9.54	
TS3	89.54	16.00	8.57	81
I2	76.99	15.83	8.70	
TS4	106.69	16.11	8.42	72
I3	85.35	17.48	8.59	
TS5	87.86	16.83	8.66	20
4	−110.88	7.38	9.50	
TS6	65.69	5.65	8.28	164
I4	51.04	4.31	7.89	
TS7	69.45	4.09	8.05	148
5	−246.02	4.49	10.17	
TS8	169.03	7.10	8.95	545
9 + 10	−2.93			
TS9	82.84	2.58	8.72	417
TS10	39.33	6.60	9.06	548
6	−149.79	4.36	10.69	
TS11	343.51	3.57	9.18	1468
TS12	117.15	13.90	8.62	66
7	−148.53	4.88	10.98	
TS13	123.43	3.87	9.88	689
11 + 12	−61.50			
TS14	137.65	5.34	9.15	377
8	−212.13	4.05	10.75	
TS15	−7.95	13.86	8.54	57

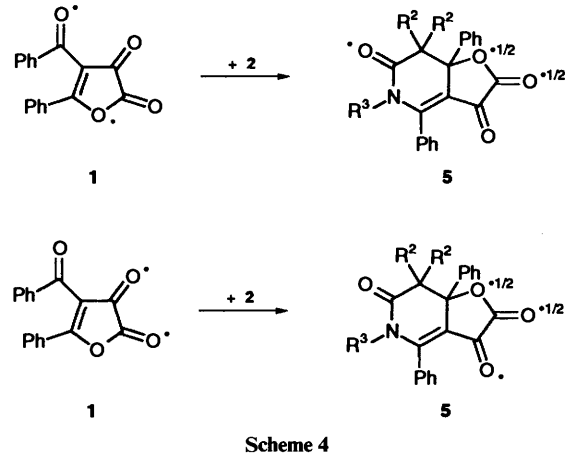
[a] E_{rel} is given relative to the energies of the separated reactants **1** + **2** (ΔH = −232.6 kJ mol^{-1}). [b] The rather large dipole moments suggest a pronounced solvent dependence of these reactions. Experimentally, the reaction was performed in anhydrous toluene, thus, only an insignificant effect by solvation is expected compared to the calculated results which refer to isolated molecules.

inferred[7] that bulky substituents, especially at the terminal carbon of the ketenimine will lower **TS1** and **TS2** relative to **TS10**. In a kinetically controlled reaction, thus, one expects formation of **3** to be at least competitive with that of **6**.

Rearrangement of **3**.—The first step is ring opening of the lactone[4] (**TS3** ⟶ **I2**), followed by rotation of the α-keto-carboxyl group (**TS4**) to the rotameric intermediate **I3** and ring closure to **4**. Opening of the six-membered ring in this compound (**TS6**, **I4**) and cyclization (**TS7**) finally yields the experimentally observed reaction product **5** (for R^2 = R^3 = Ph). The alternative pathway involving a fragmentation–cycloaddition mechanism (**4** ⟶ **TS8** ⟶ **9** + **10** ⟶ **TS9** ⟶ **I4**) is, according to the calculations, highly unlikely since the activation energies are more than twice those for the direct process (**TS7**, 69.4; **TS8**; 169.0 kJ mol^{-1}, see Table 1). It should be noted that the reaction sequence found in the calculations for the rearrangement **3** ⟶ **5** involves mainly rather exothermic steps; furthermore, the activation energies are reasonably low for such a process to be feasible. The rate determining step is found to be the transformation **3** ⟶ **4**.

Rearrangement of **6**.—Given the extremely high activation energy (E_a = 343.5 kJ mol^{-1}) a direct rearrangement **6** ⟶ **5** *via* **TS11** can be safely ruled out as a possible mechanism for formation of **5**. In contrast to the rearrangement of **3**, where both a direct mechanism as well as one—albeit less likely—consisting of a fragmentation–cycloaddition sequence could be found, here any attempts to calculate a pathway outlined in Scheme 2 (**6** ⟶ **7** ⟶ **8** ⟶ **5**) failed. Instead, the transformation **7** ⟶ **8** always resulted in a fragmentation, *i.e.* the only mechanism found (besides the unrealistic direct rearrangement) is the sequence **6** ⟶ **TS12** ⟶ **7** ⟶ **TS13** ⟶ **11** + **12** ⟶ **TS14** ⟶ **8** ⟶ **TS15** ⟶ **5** (Scheme 3). Most importantly, the activation energies involved in this reaction path (see Table 1) are substantially higher than those of the alternative mechanism **3** ⟶ **5**. Therefore, we conclude that although formation of **6** might compete with that of **3**, formation of the experimentally observed product **5** should occur *via* direct rearrangement of **3**. Mechanisms involving a fragmentation–cycloaddition sequence are rather unlikely.

Comparison to Isotopic (^{17}O) *Labelling Studies*.—The experimental[4] results using different isotopically (^{17}O) labelled **1** are outlined in Scheme 4. The isotopic distribution within



Scheme 4

the products is consistent with either mechanism described above except the direct rearrangement **6** ⟶ **5**. Exactly this process is characterized by an extremely high activation energy thus lending support to the reliability of the calculations. Based on the computational results now a decision among the various possibilities can be made: the most likely mechanism for formation of **5** is given by the reaction sequence **1** + **2** ⟶ **TS1** ⟶ **I1** ⟶ **TS2** ⟶ **3** ⟶ **TS3** ⟶ **I2** ⟶ **TS4** ⟶ **I3** ⟶ **TS5** ⟶ **4** ⟶ **TS6** ⟶ **I4** ⟶ **TS7** ⟶ **5**, as briefly described in Scheme 1. The structures and selected geometrical data of the transition states found for this pathway are given in Fig. 1.

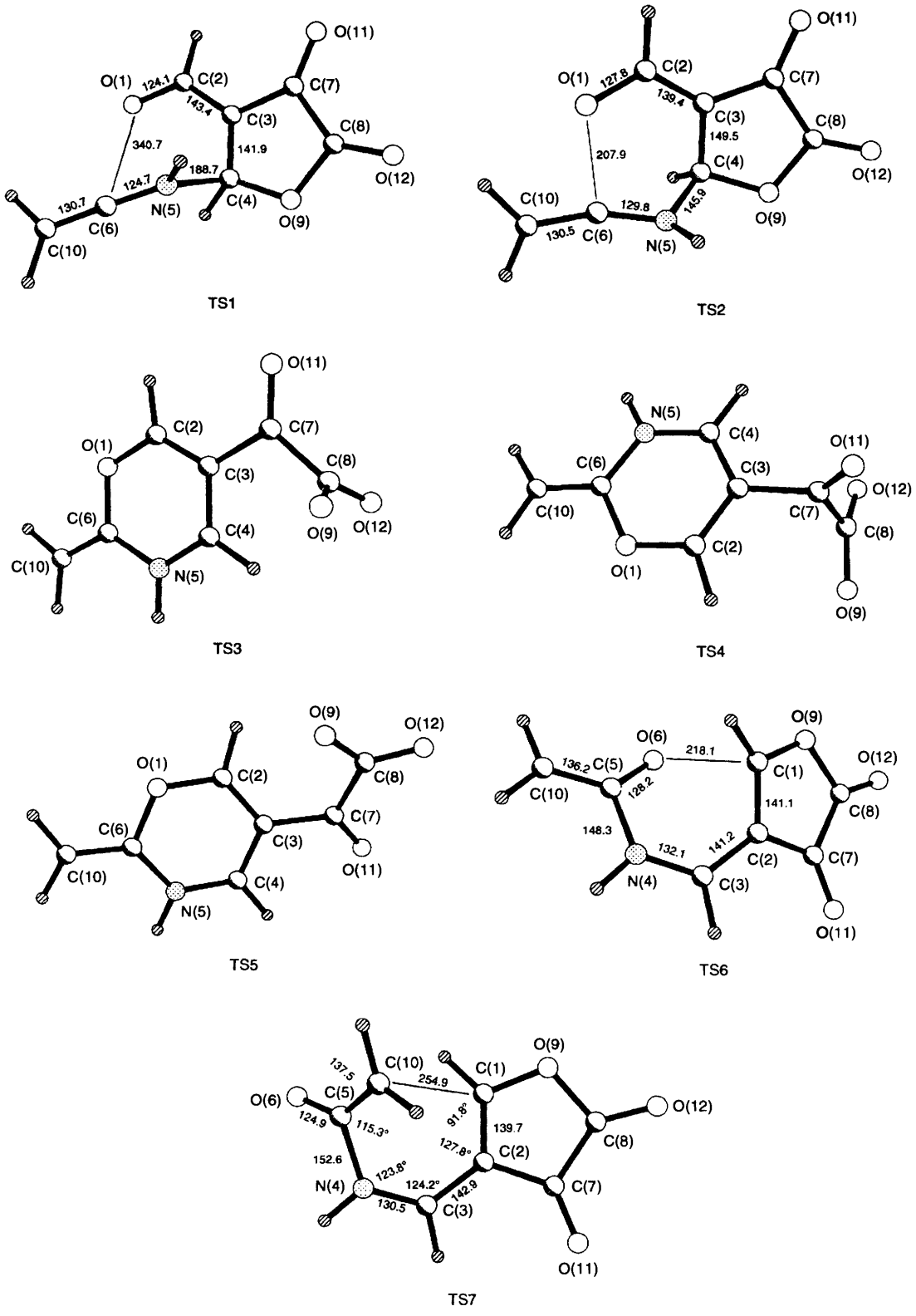


Fig. 1 Structures and selected geometrical data for the transition states found for the proposed reaction mechanism (**TS1**–**TS7**; distances/pm, angles/deg.). **TS1**: ∠(O1–C2–C3) = 123.5°, ∠(C2–O1–C6) = 97.8°, ∠ (O1–C6–N5) = 77.5°, ∠(C3–C4–N5) = 103.9°, ∠(C4–N5–C6) = 122.3°, τ(C3–C4–N5–C6) = 104.9°, τ(C4–N5–C6–N*H*) = 168.2°, τ(C6–O1–C2–C3) = 30.7°, τ(O1–C6–N5–N*H*) = 120.7°. **TS2**: ∠(O1–C2–C3) = 122.7°, ∠(C2–O1–C6) = 114.1°, ∠(O1–C6–N5) = 103.2°, ∠(C3–C4–N5) = 109.8°, ∠(C4–N5–C6) = 117.4°, τ(C3–C4–N5–C6) = 69.0°, τ(C4–N5–C6–N*H*) = −149.2°, τ(C6–O1–C2–C3) = 11.8°, τ(O1–C6–N5–N*H*) = 101.5°. **TS3**: *r*(C4–O9) = 315.2, *r*(C4–O12) = 315.3, *r*(C2–O9) = 443.8, *r*(C2–O12) = 443.9, τ(C4–C3–C7–C8) = 0.0°, τ(C3–C7–C8–O9) = −86.0°, τ(C3–C7–C8–O12) = 86.1°. **TS4**: *r*(C4–O9) = 418.0, *r*(C4–O12) = 349.2, *r*(C2–O9) = 332.0, *r*(C2–O12) = 407.3, τ(C4–C3–C7–C8) = −90.8°, τ(C3–C7–C8–O9) = −85.2°, τ(C3–C7–C8–O12) = 89.7°. **TS5**: *r*(C4–O9) = 404.2, *r*(C4–O12) = 487.2, *r*(C2–O9) = 249.3, *r*(C2–O12) = 412.6, τ(C4–C3–C7–C8) = −154.0°, τ(C3–C7–C8–O9) = 8.1°, τ(C3–C7–C8–O12) = −171.9°. **TS6**: ∠(C1–O6–C5) = 108.9°, ∠(C1–C2–C3) = 125.7°, ∠(C3–N4–C5) = 124.6°, ∠(C5–O6–C1) = 108.9°, ∠(O6–C1–C2) = 92.6°, ∠(C2–C3–N4) = 123.6°, ∠(N4–C5–O6) = 115.1°, τ(C1–C2–C3–N4) = 15.9°, τ(C3–N4–C5–06) = 11.0°, τ(C5–O6–C1–C2) = 58.9°, τ(C2–C3–N4–C5) = 14.6°, τ(N4–C5–O6–C1) = −43.4°. **TS7**: ∠(C1–C10–C5) = 88.3°, τ(C2–C3–N4–C5) = 2.1°, τ(N4–C5–C10–C1) = 65.1°, τ(C1–C2–C3–N4) = −18.8°, τ(C3–N4–C5–C10) = −49.5°, τ(C5–C10–C1–C2) = −65.3°.

Computational Details. All calculations were performed with the semiempirical AM1 method [6] using the VAMP program package.[8] All geometries were completely optimized using the keyword PRECISE. Transition states were approximately located either by the SADDLE routine or the reaction coordinate method. In all cases several reaction coordinates were tried. After refinement by gradient norm minimization (NS01A routine in VAMP) and force constant calculations to characterize a structure as true transition state, downhill optimizations along both directions of the normal mode corresponding to the imaginary frequency were performed.

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Paper 4/04222K
Received 11*th July* 1994
Accepted 17*th November* 1994