

SEMI-EMPIRICAL CALCULATIONS ON HETEROCUMULENE-HETERODIENE CYCLOADDITION REACTIONS: KETENE + 1-AZABUTADIENE

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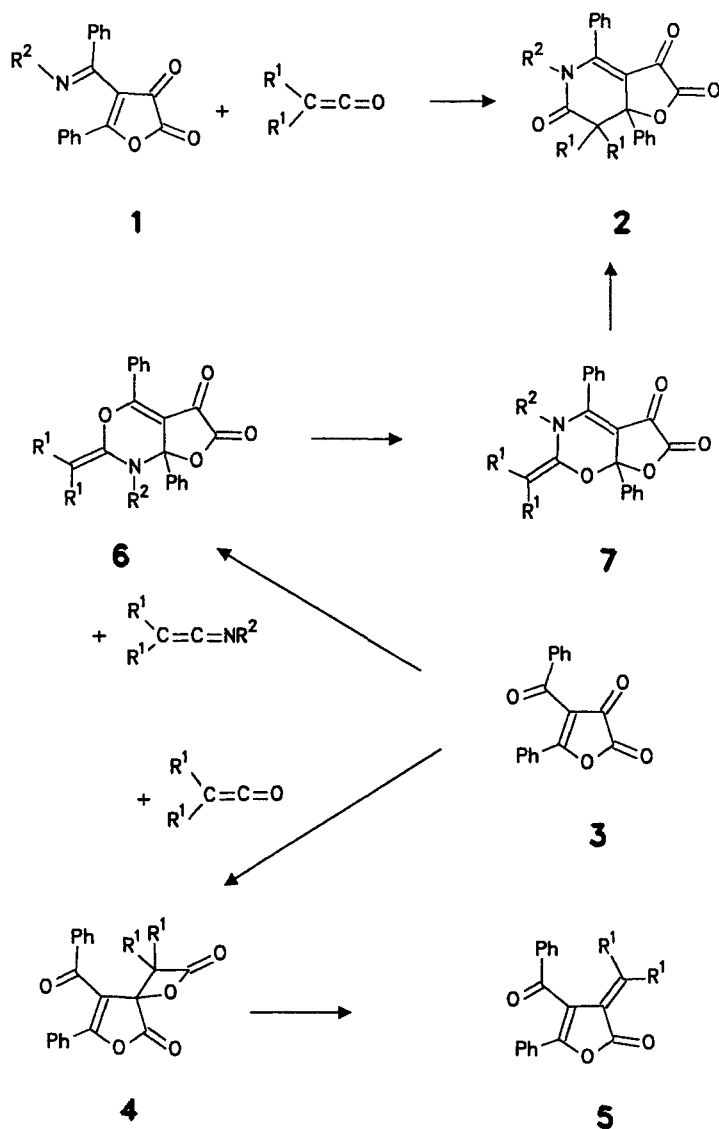
Semi-empirical (AM1) calculations on the 12 isomeric products and the corresponding transition states of ketene-1-azabutadiene [4 + 2] and [2 + 2] cycloaddition reactions as a model system for the reaction of ketenes with 4-aminobenzylfuran-2,3-diones are presented. A [4 + 2] type of reaction of the ketene C=C double bond leading to a six-membered lactam compound is found to be highly favoured both thermodynamically and kinetically. [2 + 2] Cycloadducts generally have significantly higher activation energies. Reactions involving the formation of a carbon-nitrogen bond proceed in most cases via attack of the nitrogen lone pair leading to a zwitterionic intermediate. Depending on the respective cycloadduct, both two-step and concerted, albeit asynchronous, processes were obtained. Based on the structures of the various transition states, some predictions with respect to substituent effects are made. Similarities to and differences from the analogous reaction of ketenimines with oxo-1,3-dienes are discussed.

INTRODUCTION

The cycloaddition chemistry of heterocumulenes is largely dominated by [2 + 2] reactions.¹ In a few cases, especially with electron-deficient dienes, e.g. azabutadienes, [4 + 2] cycloaddition products could be observed.²⁻⁶ This type of reaction product may also be obtained by cation radical-initiated Diels-Alder or vinylcyclobutanone rearrangement reactions.⁷ Finally, vinylheterocumulenes and α -oxo ketenes can be used as heterodienes in [4 + 2] reactions.⁸⁻¹⁰ Theoretical work concerning heterocumulene cycloadditions so far has been almost exclusively devoted to those of the [2 + 2] type, e.g. dimerization of ketene¹¹⁻¹³ or carbodiimides,¹⁴ cycloadditions to alkenes,¹⁵⁻¹⁹ carbonyl compounds^{19,20} (in this case an [8 + 2] process also has been considered²¹) and especially Schiff bases.^{19,22-25} In contrast, calculations dealing with [4 + 2] cycloadditions of heterocumulenes are scarce.^{6,26-28} Experimentally, the heterodiene subunit of 4-benzoyl-substituted heterocyclic 2,3-diones (furan-diones and pyrrolediones) has been found to add a variety of heterocumulenes yielding bicyclic heterocyclic molecules.²⁹⁻³³ For example, Schiff bases of 4-benzoylfuran-2,3-diones (**1** in Scheme 1) readily react with diphenylketene ($R^1 = R^2 = \text{phenyl}$ in Scheme 1) to furo[3,2-*c*]pyridines (**2**)³² in agreement with other reactions of ketenes and aza-1,3-dienes.^{2-6,34-38} In

striking contrast, the parent carbonyl compound **3** (see Scheme 1) adds diphenylketene in a [2 + 2] reaction at the 3-carbonyl group to give after decarboxylation 3-diphenylmethylen-2(3*H*)-furanone (**5**).³³ The same product **5** is also obtained in photochemical reactions of **3** with ketenimines³³ ($R^1 = R^2 = \text{aryl}$ in Scheme 1), whereas in thermal reactions **2** is formed.³² As corroborated by isotopic labelling experiments,³⁹ the latter reaction most probably proceeds via a [4 + 2] cycloaddition of the C=N double bond of the ketenimine with **3** to give the primary cycloadduct **6**, followed by a rearrangement sequence **6** → **7** → **2**. Further evidence for this mechanism stems from the fact that in a single case ($R^1 = \text{CH}_3$) the intermediate **7** could be isolated. Obviously, the outcome of these reactions strongly depends on the nature of both the heterocumulene and the heterocyclic dione.

To obtain some insight into this intriguing behaviour, we have performed theoretical calculations on some simple model reactions.²⁶⁻²⁸ In this paper the main focus is on the reaction of ketenes with 4-aminobenzylfuran-2,3-diones (**1**) with special emphasis on the peri-, site-, and regiochemistry of these cycloadditions. For this purpose, as the simplest model system possible, the reaction between ketene and 1-azabutadiene was chosen. This should make it possible to delineate both similarities to and differences from the analogous reactions of ketenimines with acrolein



Scheme 1.

studied previously as a model system for the reaction $3 \rightarrow 2$.²⁶⁻²⁸

CALCULATIONS

All calculations were done by the semi-empirical AM1 method⁴⁰ using either the MOPAC⁴¹ or VAMP⁴² program packages (a copy of a Stardent version of the VAMP program was kindly provided by Dr T. Clark, Institut für Organische Chemie, Universität

Erlangen-Nürnberg, Germany). Geometries were completely optimized (keyword PRECISE). Transition states were approximately located by the reaction coordinate method, refined by gradient norm minimization (NS01A routine in VAMP) and characterized by force constant calculations. In addition, starting from transition states, downhill optimizations along both directions of the normal mode corresponding to the negative eigenvalue of the force constant matrix were performed.

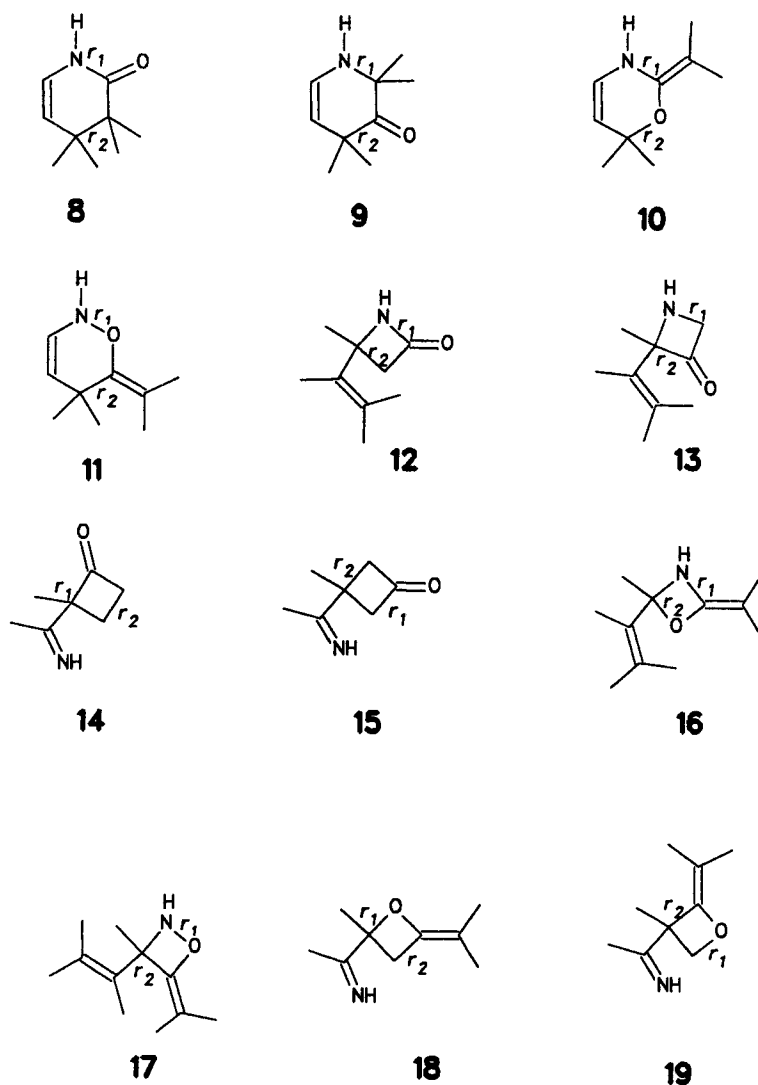
RESULTS

The possible reaction products of ketene-1-azabutadiene cycloadditions are shown in Scheme 2. Whereas for [4+2] reactions (structures 8-11 in Scheme 2) an *s-cis* conformation of the heterodiene is required, for [2+2] processes (12-19 in Scheme 2) no such restriction exists. Consequently, in the latter cases the calculations were done for both *s-cis* and *s-trans* conformations of 1-azabutadiene.

The results of the calculations [heats of reaction ΔH_R , activation energies ΔH^\ddagger (kJ mol^{-1}), dipole

moments μ (debye) for products and transition states, imaginary frequency $\tilde{\nu}$ (cm^{-1}) and distances r_1 and r_2 (pm) of the two forming bonds (for definitions see Scheme 2) are given in Table 1.

Several points are worth mentioning. For some of these model reactions a concerted mechanism, albeit with rather asynchronous transition states (11, 13, 14, 15, 17, 18, 19) are found whereas other compounds (10, 12, 16) are predicted to be formed in a two-step process via an intermediate. For 8 both a concerted [8(a)] and a two-step process [8(b)] with significantly lower activation energies are obtained by the calculations. For



Scheme 2.

Table 1. Calculated heats of reaction ΔH_R^a , activation energies ΔH^* (kJ mol⁻¹), dipole moments μ (D), imaginary frequencies $\tilde{\nu}$ (cm⁻¹) and distances r_1 and r_2 (pm) of the two forming bonds

Compound	ΔH_R	ΔH^*	μ^b	μ^c	$\tilde{\nu}$	r_1	r_2
8(a)	-256.5	124.3	3.05	4.19	464	279.9	171.9
8(b)		76.6 ^d		5.15	472	184.5	311.1
	56.9 ^c		7.28			152.8	303.3
		79.5 ^f		6.06	571	152.2	242.4
9	-86.6	175.5	2.65	2.20	882	187.1	232.4
10	-118.4	73.2 ^d	2.16	4.78	468	185.0	315.3
	55.2 ^c		6.94			154.0	302.6
		79.9 ^f		5.23	507	148.3	214.7
11	26.8	239.7	2.62	4.27	592	205.8	165.6
12	-74.0	71.5 ^d	3.59	5.88	448	185.6	311.2
	(-69.4)	(71.5) ^d	(3.68)	(6.22)	(446)	(185.3)	(310.6)
	50.6 ^c		8.37			152.4	294.8
	(50.2) ^c		(8.77)			(152.2)	(295.5)
		123.8 ^f		5.89	485	144.5	234.8
		(123.4) ^f		(6.07)	(488)	(144.6)	(234.5)
13	-46.9	295.8	1.94	1.97	765	237.1	165.4
	(-45.2)	(295.8)	(1.74)	(1.79)	(805)	(235.8)	(166.5)
14	-128.4	143.5	1.86	4.41	553	265.5	161.6
	(-117.2)	(170.1)	(1.84)	(6.50)	(627)	(261.1)	(163.5)
15	-130.1	171.5	1.85	4.83	535	165.3	263.5
	(-128.9)	(173.2)	(3.69)	(4.48)	(521)	(164.8)	(263.3)
16	43.1	73.2 ^d	1.68	4.79	468	184.8	247.4
	(54.4)	(82.0) ^d	(2.08)	(5.27)	(478)	(185.7)	(304.8)
	55.2 ^c		6.83			152.7	295.8
	(59.8) ^c		(7.64)			(152.4)	(286.4)
		195.0 ^f		5.51	756	144.9	206.7
		(204.6) ^f		(6.04)	(733)	(144.7)	(204.8)
17	187.4	441.8	2.60	3.23	1450	201.8	160.3
	(187.0)	(441.8)	(2.74)	(3.21)	(1452)	(201.6)	(160.7)
18^g	-12.4	227.6	1.30	3.62	820	227.5	157.2
19(a)	-11.7	253.1	2.65	4.26	1009	224.2	164.3
	(-10.5)	(257.3)	(1.66)	(4.45)	(1026)	(223.4)	(162.8)
19(b)		256.1		2.24	973	157.5	225.9
		(266.1)		(3.72)	(1201)	(162.1)	(223.7)

^a ΔH_R and ΔH^* relative to reactants ketene + 1-azabutadiene; results for [2 + 2] cycloaddition products of *s-trans*-1-azabutadiene are given in parentheses.

^b Dipole moments of products and intermediates.

^c Dipole moments of transition states.

^d First transition state.

^e Intermediate.

^f Second transition state.

^g Despite several attempts, only a transition state for [2 + 2] reaction with *s-trans*-1-azabutadiene could be found.

19 two transition states of nearly the same energy but differing in their structures [**19(a)**, $r_1 > r_2$; **19(b)**; $r_1 < r_2$] are found. Except for **18** where only a transition state for the reaction with *s-trans*-1-azabutadiene could be located, [2 + 2] cycloadducts formed from either the *s-cis* or the *s-trans* conformation of the heterodiene show only small differences in ΔH_R and ΔH^* . In all cases reaction of the *s-cis*-diene should be slightly favoured. Formation of the [4 + 2] cycloadduct **8**, which corresponds to the experimentally observed

product **2**, is calculated to be considerably more feasible than any of the [2 + 2] products **12**–**19** both under kinetic and thermodynamic control of the reaction. Interestingly, for the isomeric [2 + 2] cycloadduct **12**, which also contains a lactam structure, the first transition state and the intermediate are slightly lower in energy than those of **8**. However, the activation energy for conversion of the intermediate to the [4 + 2] product is much lower than that to the [2 + 2] product. This second transition state, therefore, is decisive for

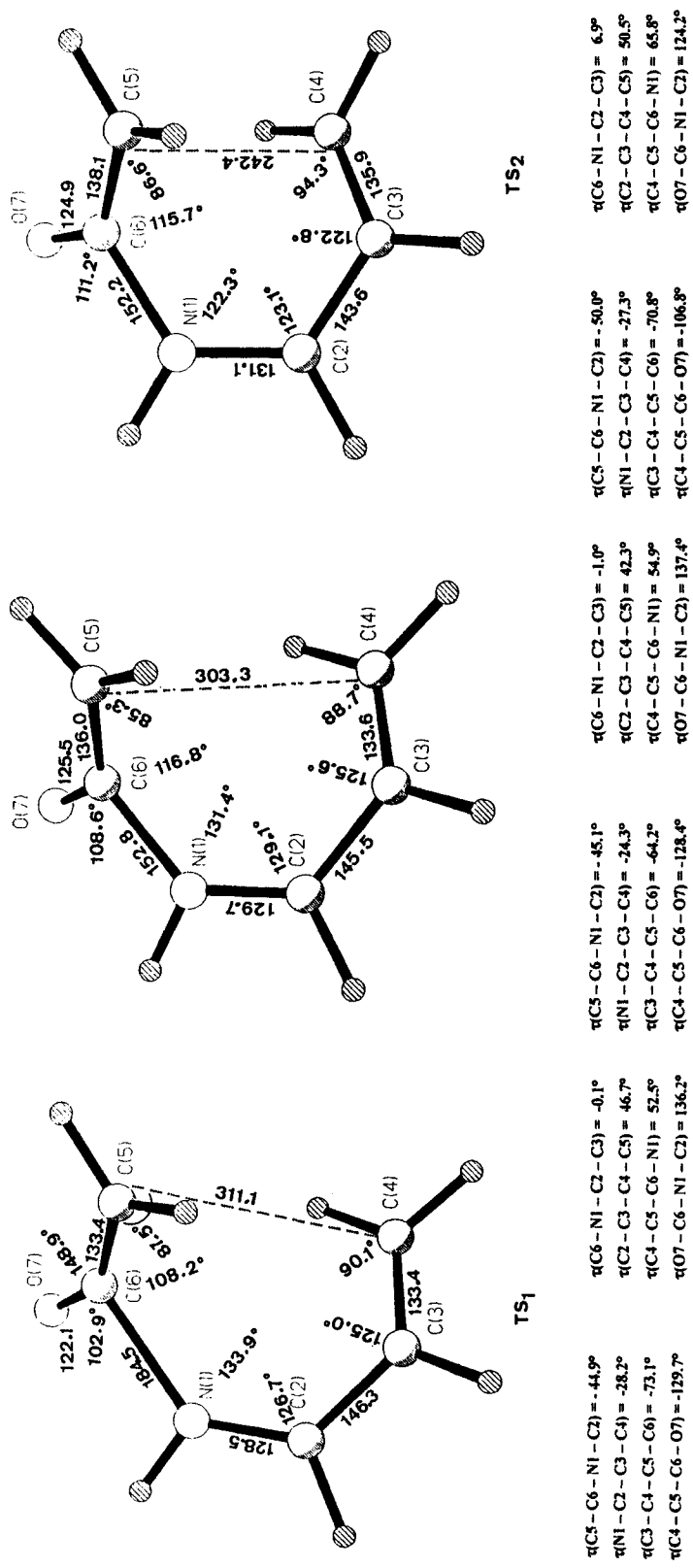


Figure 1. Calculated structures of the first transition state (TS₁), intermediate (I) and second transition state (TS₂) leading to compound 8 (distances in pm, angles in degrees)

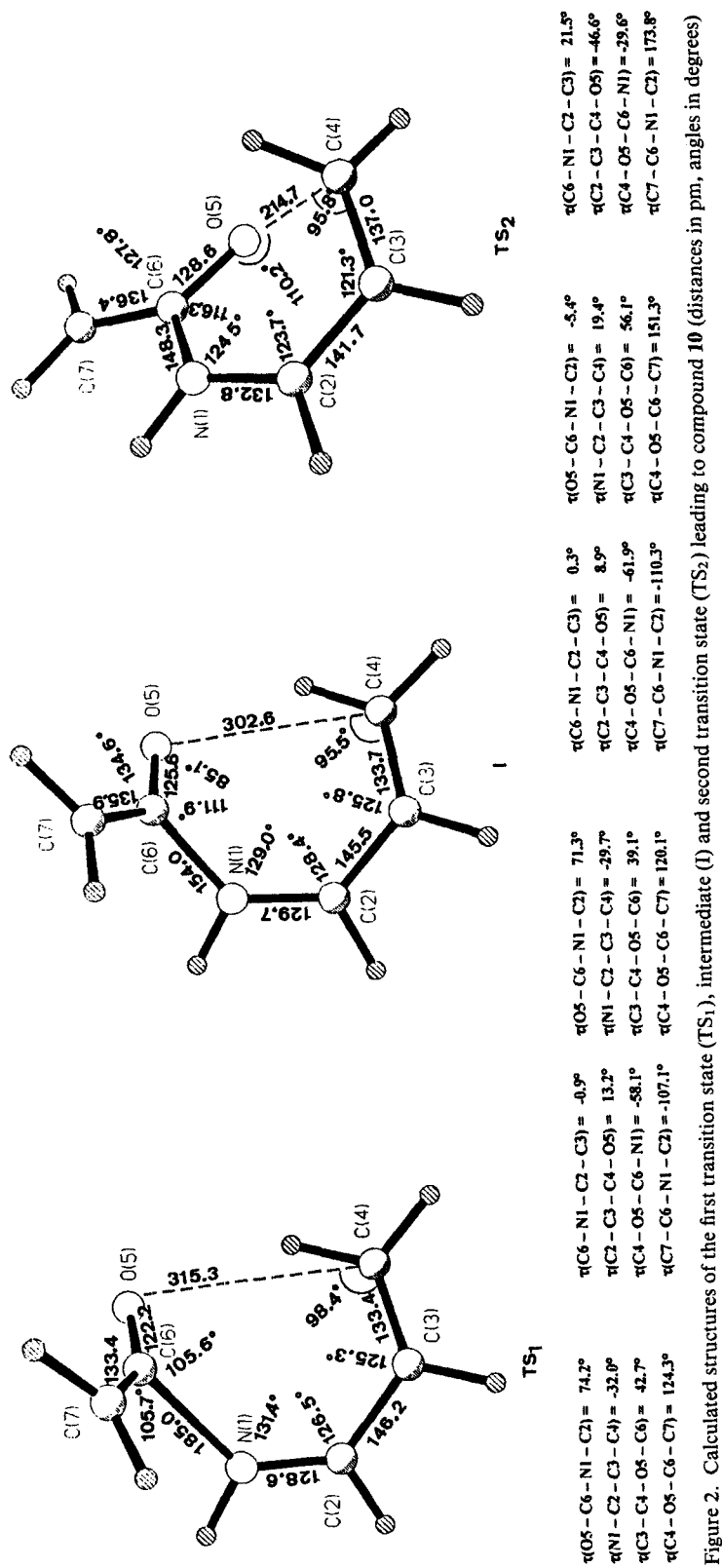
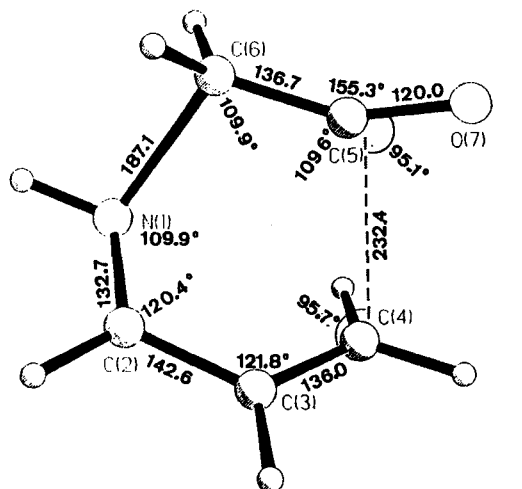


Figure 2. Calculated structures of the first transition state (TS₁), intermediate (I) and second transition state (TS₂) leading to compound 10 (distances in pm, angles in degrees)

the outcome of the reaction. [2 + 2] Cycloadditions involving the ketene C=O double bond (16–19) generally are disfavoured as compared with reactions of the ketene C=C double bond (12–15). In contrast, under kinetic control the [4 + 2] cycloaddition of the ketene C=O double bond leading to 10 should prevail even over [2 + 2] processes yielding the thermodynamically more stable products 14 or 15. Compounds involving the N–O bond (11, 17) are highly disfavoured since formation of both molecules is predicted to be an endothermic process and the activation energies are much higher than for any other reaction considered.

For 10 both the first transition state and the intermediate are slightly lower in energy than those for 8 (probably because of their *trans*- as opposed to the *cis*-amidic structure 8). In both reactions the second transition states differ only marginally in their energies. Under kinetic control formation of the thermodynamically less stable molecule 10 therefore might compete with that of 8. This result resembles that obtained for the analogous reaction between ketenimine and acrolein.^{27,28} However, there are significant differences in transition-state structures: in the two ketenimine–acrolein [4 + 2] cycloadducts corresponding to 8 and 10 (with NH and O interchanged) r_1 was calculated to be much longer than r_2 .^{27,28} Therefore, it was proposed that substituents would stabilize the sterically less demanding transition state for reaction of the C=N as opposed to the C=C double bond.^{27,28} In contrast, for 8 and 10 (see Figures 1 and 2) r_1 is significantly shorter than r_2 , rendering the transition state leading to 10 more prone to steric crowding. Hence substituents should additionally favour the formation of 8, in complete agreement with the experimental findings.

The lactam structure of 8 apparently represents a unique feature which largely favours this compound. Despite some superficial similarities to ketenimine–acrolein cycloadditions, the lack of such a structure in products obtained in this latter reactions results in a less pronounced differentiation between the various cycloadducts. Generally, in reactions leading to products with a carbon–nitrogen bond, in the respective transition states the formation of this bond is considerably more advanced than formation of either a carbon–carbon or carbon–oxygen bond, thus leading to a highly dipolar or zwitterionic intermediate, as can be inferred from the high dipole moments of these structures (see Table 1). The only exception to this generalization is 13, where $r_1 > r_2$. An alternative transition structure with $r_1 < r_2$ also found here, however, does not lead to 13 but rather to elimination of carbon monoxide. Further, from structures of the transition states an attack of the nitrogen lone pair rather than the C=N π -orbital can be inferred [e.g. for 8 a torsional angle τ (C-6-N-1-C-2-C-3) = 6.9° implies interac-



τ (C-6-N-1-C-2) = 52.4°	τ (C-6-N-1-C-2-C-3) = -60.4°
τ (N-1-C-2-C-3-C-4) = -6.2°	τ (C-2-C-3-C-4-C-5) = 54.2°
τ (C-3-C-4-C-5-C-6) = -48.2°	τ (C-3-C-4-C-5-O-7) = 132.6°
τ (C-4-C-5-C-6-N-1) = -0.6°	τ (N-1-C-6-C-5-O-7) = 177.4°

Figure 3. Calculated transition state for compound 9 (distances in pm, angles in degrees)

tion in the C=N plane rather than perpendicular to it; for numbering see Figure 1]. Previous theoretical^{22–25} and experimental^{36,43} investigations of [2 + 2] cycloadditions between ketenes and Schiff bases led to a similar conclusion. The transition state leading to 9 is unique since it resembles more closely a structure expected for a Diels–Alder reaction (see Figure 3 and the values of r_1 and r_2 given in Table 1).

CONCLUSIONS

The results of the semi-empirical calculations presented here provide a basis for a rationalization of the intriguing dependence on the structure of both the heterocumulene and the heterodiene in cycloadditions of (heteroanalogous) 4-carbonyl-substituted heterocyclic 2,3-diones. Based on the calculated activation energies the formation of the [4 + 2] cycloadducts 8 and 10 should be highly favoured over all other possible isomers. The greater stability of 8 than 10 is expected additionally to favour 8. From the structures of the various transition states one might infer this to be even more so in substituted derivatives (e.g. reaction 1 → 2 in Scheme 1). This is in striking contrast to the analogous ketenimine–acrolein cycloaddition, where substituents are predicted to favour reaction of the ketenimine C=N instead of the C=C double bond (e.g. reaction 3 → 6 in Scheme 1).

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