Substituent Effects on Site Selectivity (C=C vs C=N) in Heterocumulene−Heterodiene [4 + 2] Cycloadditions: Density Functional and Semiempirical AM1 Molecular Orbital Calculations

Walter M. F. Fabian* and Gert Kollenz

Institut für Organische Chemie, Karl-Franzens Universität Graz, Heinrichstrasse 28, A-8010 Graz, Austria

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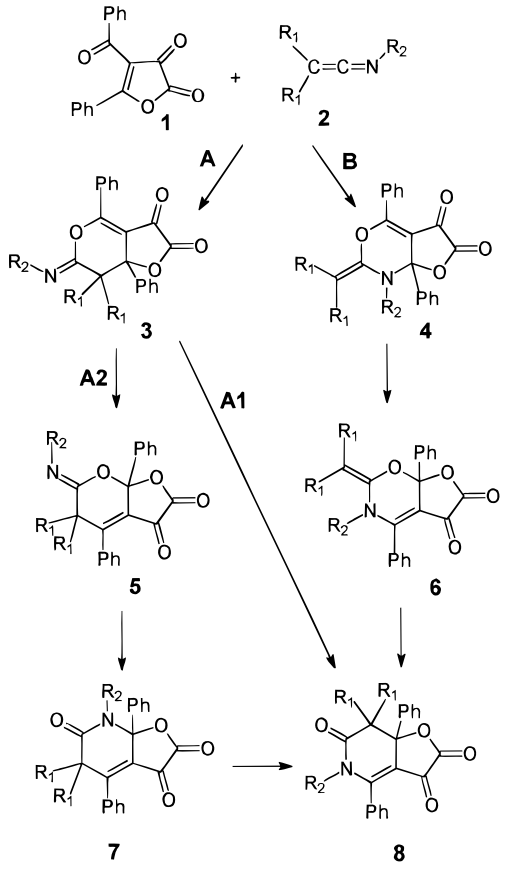
The effect of substituents on the site selectivity (C=C vs C=N) in the [4 + 2] cycloaddition between heterocumulenes (ketene imines) **2a**−**g** with heterodienes (acroleines **9a**−**n** and 4-acylfuran-2,3-diones **1a**−**d**) is treated by semiempirical AM1 molecular orbital and density functional calculations using Becke's three-parameter hybrid method (B3LYP/6-31G*). For some reactions calculations were also done at the B3LYP/6-31+G** level of theory. For reaction of the oxa 1,3-dienes with ketene imines unsubstituted at the terminal carbon invariably addition across the C=C heterocumulene double bond has a lower activation energy than addition across the C=N double bond. Substitution of methyl or especially phenyl groups at the ketene imine C-terminus leads to a reversal of the respective activation energies. Incorporation of the oxa 1,3-diene system into the heterocyclic dione **1** substantially enhances the reactivity (∼ 10 kcal mol^{-1} lower activation energies) as compared to similarly substituted acroleins. At the DFT level of theory all reactions are found to proceed via a concerted asynchronous mechanism.

Introduction

Hetero Diels−Alder cycloaddition reactions represent a versatile synthetic methodology for the construction of a variety of heterocyclic compounds, especially natural products.[1] In contrast to the normally observed [2 + 2] cycloadditions of heterocumulenes,[2−4] with heterodienes products of a formal [4 + 2] process with the C=C heterocumulene double bond acting as dienophile[1a] are obtained. Over the past decade, we have used this heterocumulene−heterodiene cycloaddition strategy for the synthesis of several novel polycyclic heteroaromatics by reaction of a variety of heterocumulenes with 4-acyl-substituted heterocyclic 2,3-diones (e.g., furandiones or pyrroldiones).[5] For instance, in the reaction of 4-benzoylfuran-2,3-dione **1** with triarylketene imines **2** (R^1 = R^2 = Ar) the furo[3,2-*c*]pyridines **8** are obtained (see Scheme 1).[6] At least three pathways leading to **8** are conceivable (Scheme 1): (i) [4 + 2] cycloaddition of the C=C double bond of the ketene imine across the oxa 1,3-dienic subunit of **1** to yield the primary cycloadduct **3**, followed by direct rearrangement to **8** (path A1 in Scheme 1); (ii) stepwise rearrangement **3** → **5** → **7** → **8** (path A2 in Scheme 1); and (iii) addition of the ketene imine C=N double bond across the oxa 1,3-diene to give the primary cycloadduct **4**, followed by a sequence of ring opening/recyclizations (**4** → **6** → **8**, path B in Scheme 1). Isotopic labeling studies[7] as well as semiempirical molecular orbital calculations[8] are inconsistent with path A1. Paths

Scheme 1



* To whom correspondence should be addressed. FAX: (Austria) 316-380-9840. E-mail: walter.fabian@kfunigraz.ac.at.

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A2 and B are, however, both consistent with the ^{17}O isotope distribution in **8** obtained from differently labeled **1**.[7] Activation energies calculated by AM1 for path A2 are significantly higher than those obtained for path B.[8] Thus, this latter mechanism appears the most likely one. One major drawback of invoking mechanism B, however, concerns the feasibility of the formation of the primary cycloadduct **4**: although a few ketene imine [4 + 2] cycloadditions across the C=N double bond are known,[4,9] the reaction leading to **4** would represent the first example of this type of ketene imine cycloadditions. Rather, compounds of type **3** are those normally observed in heterocumulene−heterodiene cycloadditions.[1a] Since it never had been possible to isolate the primary cycloadduct (**3** or **4**), to answer the question whether formation of **4** really constitutes the first step leading to **8**, we have resorted to computational methods. Not unexpectedly, both semiempirical (AM1)[10] as well as ab initio[11] calculations on a simple model system (acrolein + ketene imine) indicate a considerably greater stability for the cycloadducts of type **3** as compared to that of type **4**. In striking contrast, however, there is little difference in the respective activation energies. Presumably, therefore, the substituents present in **1** and **2** easily could reverse relative activation energies leading either to **3** or **4**. Given the unusual features and the novelty of these heterocumulene−heterodiene cycloadditions, we found it worthwhile to investigate this reaction by computational methods in some detail. The size of the actual molecules involved clearly prevents the use of sufficiently high level ab initio calculations necessitating the use of semiempirical (AM1)[12] procedures. Although in related reactions the AM1 method had been reported to give quite satisfactory results,[13−17] the question about the reliability of such calculations still remains. Therefore, the semiempirical calculations will be supplemented by ab initio—specifically, the hybrid Hartree−Fock/density functional method—calculations on a series of model compounds.

Computational Methods

The semiempirical AM1[12] calculations were done by the MOPAC[18] or VAMP[19] package. Ab initio (density functional) calculations were performed with Becke's three-parameter hybrid method[20] with the Lee−Yang−Parr correlation functional[21] (B3LYP) as implemented in Gaussian 94.[22] Geometries were completely optimized with the 6-31G* and, in most cases, also with the 6-31+G** basis set. All stationary points were characterized as minima or true transition states by frequency calculations at the B3LYP/6-31G* level of theory. B3LYP/6-31G* zero point energies were scaled by 0.9806.[23] In addition, for transition structures downhill optimizations along both directions of the normal mode corresponding to the imaginary frequency were done. The B3LYP method has been shown to give results comparable to ab initio calculations at the MP2 level of theory;[24] activation energies are, however, systematically too low.[25] The electronic structures of transition states were analyzed by the natural bond orbital (NBO)[26] method (program G94NBO[27]). To allow for greater flexibility, the HF/6-311G* density was used as previously.[11]

Results and Discussion

To decipher the effect of substituents on the site selectivity (C=C vs C=N) of ketene imine−oxa 1,3-diene [4 + 2] cycloadditions a fairly systematic investigation of the reaction between differently substituted ketene imines **2** and acroleins **9** (see Scheme 2) has been undertaken. In the following text, first the results for reactions of unsubstituted ketene imine **2a** with substituted acroleins **9a**−**n**, followed by those for substituted ketene imines **2b**−**g** with acrolein **9a**, will be presented. After discussing the energetics (activation and reaction energies) of these reactions, structural features (geometrical and electronic) of transition states will be given. In addition, selected reactions between various combinations of substituted ketene imines and substituted acroleins are investigated. These calculations, thus, should allow us to assess the structural features that possibly might force the reaction depicted in Scheme 1 to proceed via the proposed[6,7] path B. Finally, to address the question whether steric strain caused by incorporating part of the heterodiene into a cyclic system will exert any effect on the site selectivity and/or reactivity, results for reaction of ketene imines **2** with 4-acylfuran-2,3-diones **1a**−**d**(see Scheme 2) will also be discussed. Products of the reactions described below will be characterized by a two-letter code, the first one indicating the ketene imine and the second one the acrolein (or 4-acylfuran-2,3-dione, e.g., **10gn** and **11gn** designate the two site-isomeric products of the reaction **2g** + **9n**.

Reactions of Unsubstituted Ketene Imine with Substituted Acroleins. Computed energetics (activation and reaction energies, respectively, given relative to the separated reactants) for these reactions are collected in Table 1. First of all, with the AM1 method almost invariably for reaction of the ketene imine C=N

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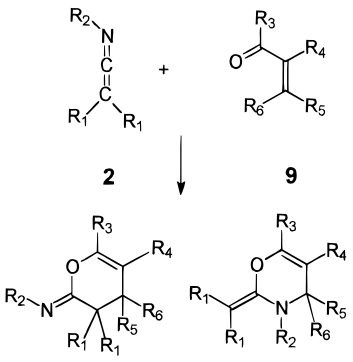
Scheme 2

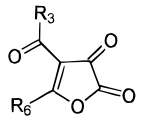


2 **9**

10 **11**

2	R^1	R^2
a	H	H
b	H	Me
c	Ph	H
d	Me	H
e	H	Ph
f	Me	Ph
g	Ph	Ph

9	R^3	R^4	R^5	R^6
a	H	H	H	H
b	H	H	H	Ph
c	H	H	Ph	H
d	Ph	H	H	H
e	H	H	H	OH
f	H	H	OH	H
g	H	CHO	H	H
h	Ph	H	OH	Ph
i	Ph	H	Ph	OH
j	Ph	CHO	H	H
k	H	CHO	OH	H
l	H	CHO	H	Ph
m	Ph	CHO	H	Ph
n	Ph	CHO	OH	Ph



1

1	R^3	R^6
a	H	H
b	Ph	H
c	H	Ph
d	Ph	Ph

double bond leading to **11**, a two-step mechanism involving a true intermediate is obtained. Depending on the substitution pattern, either one of the two transition states, i.e., that for formation of the intermediate or that for cyclization to **11**, is rate determining. In Table 1 only the higher one of these two transition states is listed. Formation of this intermediate is calculated to be endothermic, and in many cases it is barely stable collapsing or dissociating, respectively, nearly barrierless to **11** or the separated reactants. No such intermediates, however, are found by the DFT calculations. As can be seen from the data presented in Table 1, activation energies calculated by the B3LYP method are only marginally dependent on the basis set used. Inclusion of polarization functions on hydrogen atoms and diffuse functions on heavy atoms led to a slight increase (0.6−1.6 kcal mol^{-1}) of activation energies. Transition states for the two cycloaddition modes considered (**10** vs **11**) are affected in a similar manner. Conclusions regarding the effects of substituents on the propensity for formation of cycloadduct **10** or **11**, respectively, obtained at the B3LYP/6-31G* level of theory will, therefore, be of sufficient reliability. A more pronounced effect (2.0−4.5 kcal mol^{-1} decrease) of the basis set is found for reaction energies. Those of compounds **10** are somewhat more affected than compounds **11**. Thus, with larger basis sets the quite substantial difference between reaction energies for **10** vs **11**—which, depending on the substituents, amounts up to 16 kcal mol^{-1}—is slightly mediated. With respect to substituent effects on activation energies the following trends are clearly discernible: (i) the phenyl group in position 2 has virtually no (B3LYP) or only a small (AM1, <1 kcal mol^{-1}) effect; (ii) the substituents at the terminal carbon atom of acrolein (4-OH and, especially, 4-phenyl) increase E_a; (iii) the 3-CHO group leads to a substantial decrease of E_a; and (iv) these effects are found in transition states for **10** as well as **11**. A completely similar trend is also found for reaction energies with somewhat less variation in compounds **11aa**−**ag** than in **10aa**−**ag**. Most importantly, however, despite the large difference in the thermodynamical stability of compounds **10** as opposed to **11**, the differences in the respective

Table 1. Calculated Relative Energies (kcal mol^{-1}) of Transition States (TS) and Products (P) for the Reaction of Ketene Imines 2 and Acroleins 9 to Cycloadducts 10 and 11

		10		**11**				**10**		**11**	
reaction	method	TS	P	TS	P	reaction	method	TS	P	TS	P
2a + **9a**	AM1[a]	21.6	−38.4	25.9	−21.2		B3LYP/6-31+G**	17.8	−31.0	23.6	−15.6
	B3LYP/6-31G*	19.8	−36.5	21.7	−19.5	**2c** + **9a**	AM1	36.0	−18.4	33.4	−20.1
	B3LYP/6-31+G**	21.3	−32.3	23.3	−16.1	**2c** + **9b**	AM1	47.6	−6.2	39.5	−16.4
	MP4[b]	21.0	−38.6	22.2	−18.7	**2c** + **9d**	AM1	36.3	−16.8	33.5	−18.5
2a + **9b**	AM1	28.6	−32.3	34.0	−15.7	**2c** + **9n**	AM1	*c*	*c*	39.8	−6.7
	B3LYP/6-31G*	25.3	−30.2	26.3	−16.8	**2d** + **9a**	AM1	29.7	−27.6	27.6	−20.2
2a + **9c**	AM1	28.2	−30.0	33.1	−12.5		B3LYP/6-31G*	21.9	−34.0	19.4	−19.7
2a + **9d**	AM1	22.3	−35.8	26.8	−19.2		B3LYP/6-31+G**	22.5	−30.4	20.2	−16.1
	B3LYP/6-31G*	19.8	−34.7	21.8	−17.9	**2d** + **9b**	AM1	38.7	−19.9	33.4	−13.3
2a + **9e**	AM1	25.9	−35.6	31.3	−16.5	**2d** + **9d**	AM1	30.0	−25.7	27.6	−18.8
2a + **9f**	AM1	26.4	−30.2	30.6	−15.2	**2d** + **9n**	AM1	43.1	−7.7	33.0	−6.2
	B3LYP/6-31G*	23.3	−25.9	23.5	−17.6	**2e** + **9a**	AM1	26.4	−36.4	34.2	−13.1
	B3LYP/6-31+G**	24.5	−23.6	25.0	−15.6		B3LYP/6-31G*	19.6	−34.6	24.1	−15.5
2a + **9g**	AM1	13.6	−39.6	19.3	−22.9	**2e** + **9b**	AM1	33.4	−31.3	40.2	−6.2
	B3LYP/6-31G*	11.6	−39.2	13.2	−23.5	**2e** + **9d**	AM1	26.4	−34.8	34.5	−11.7
	B3LYP/6-31+G**	13.0	−34.7	14.1	−19.5	**2e** + **9n**	AM1	31.5	−21.7	42.3	4.9
2a + **9h**	AM1	31.8	−25.0	38.4	−8.9	**2f** + **9a**	AM1	34.6	−26.4	36.0	−13.7
2a + **9i**	AM1	31.3	−18.7	40.5	−2.5	**2f** + **9b**	AM1	43.0	−18.8	41.7	−5.2
2a + **9j**	AM1	15.6	−37.6	20.5	−21.5	**2f** + **9d**	AM1	34.7	−24.4	36.0	−12.3
2a + **9k**	AM1	18.8	−32.5	22.4	−14.8	**2f** + **9n**	AM1	45.1	−7.1	43.6	5.3
2a + **9l**	AM1	20.3	−33.7	24.2	−15.7	**2g** + **9a**	AM1	39.9	−16.9	43.0	−10.8
2a + **9m**	AM1	25.2	−29.8	26.5	−13.1	**2g** + **9b**	AM1	51.3	−6.4	50.6	−0.5
2a + **9n**	AM1	30.0	−22.9	33.0	−8.7	**2g** + **9d**	AM1	39.8	−15.3	43.0	−8.4
2b + **9a**	AM1	22.5	−37.2	31.5	−15.4	**2g** + **9n**	AM1	54.0	5.7	48.7	7.7
	B3LYP/6-31G*	16.7	−35.4	22.7	−18.9						

[a] Reference 10b. [b] MP4(SDTQ)/6-31+G*//MP2/6-31G* results: ref 11. [c] Only [2 + 2] cycloaddition instead of [4 + 2] was obtained.

activation energies are quite small ($\leq$2 kcal mol^{-1}). Both the 4-phenyl and even more the 4-hydroxy group lead to a lowering of this difference (for the reaction **2a** + **9f** under kinetic control both products **10af** and **11af** should be formed almost equally). It is also evident from the data of Table 1 that by and large the results of the semiempirical AM1 calculations follow the trends described above. Less satisfactory are the AM1 results for the differences in E_a for cycloadducts **10** vs **11**: obviously, here the destabilizing effects of substituents in position 4 of the oxa 1,3-diene on the transition states leading to **11** as contrasted to those for **10** are somewhat overestimated.

Reactions of Substituted Ketene Imines with Unsubstituted Acrolein. According to the B3LYP/6-31G* results either substitution at the nitrogen atom or at the terminal carbon of the ketene imine has only a rather small—generally destabilizing—influence on the stability of the primary cycloaddition products, especially for addition across the ketene imine C=N double bond. The only exception is compound **11ea**: introduction of the *N*-phenyl group causes a noteworthy decrease in the reaction energy. Calculations using the larger 6-31+G** basis set corroborate these findings (Table 1). Compared to the DFT results, the semiempirical AM1 calculations—although broadly in line—appear to overestimate the destabilizing effect on the stability of primary ketene imine C=C double bond cycloadducts **10** by C-terminal substitution, e.g., **10da**. On the other hand, the destabilizing effect of N-substitution seems to be exaggerated by AM1 for C=N addition (**11ea** in Table 1). The approximate additivity of C- and N-terminal ketene imine substitution on reaction energies is found. Activation energies for ketene imine C=C cycloaddition are, respectively, increased by C-terminal and decreased by N-terminal substitution. The unexpectedly large lowering of the activation energy for the reaction **2b** + **9a** → **10ba** might be attributed to the unusual transition-state structure indicating some sort of hydrogen bonding between the acrolein oxygen and the *N*-methyl hydrogens. Exactly the reverse substituent effects on transition-state energies for C=N reaction is evident. Most importantly, however, the DFT calculations indicate that—although reaction energies would favor reaction of the ketene imine across its C=C double bond—C-terminal substitution is predicted to reverse the respective activation energies (compare **10da** vs **11da**). At the B3LYP/6-31+G** level of theory this effect is even more pronounced. Likewise, as for the reactions of unsubstituted ketene imine with substituted acroleins, AM1 transition-state energies for ketene imine C=N addition are too high compared to those obtained by B3LYP calculations. However, in line with the DFT results, AM1 predicts an inversion of activation energies for formation of cycloadducts **10** vs **11** by C-terminal substitution of the ketene imine. Therefore, if one assumes B3LYP/6-31G* calculations to be more reliable than AM1, the conclusion is reached that whenever AM1 predicts a lower activation energy for formation of cycloadducts **11** (or **4**) than for **10** (or **3**) one can safely rely on this result.

Geometries and Electronic Structures of Transition States. B3LYP/6-31G* transition structures for the reaction **2a** + **9b** → **10ab** + **11ab** are depicted in Figure 1. Selected structural parameters for some representative transitions states for ketene imine C=C and C=N cycloadditions, respectively, are provided in Tables 2 and 3 of the Supporting Information. Some general trends

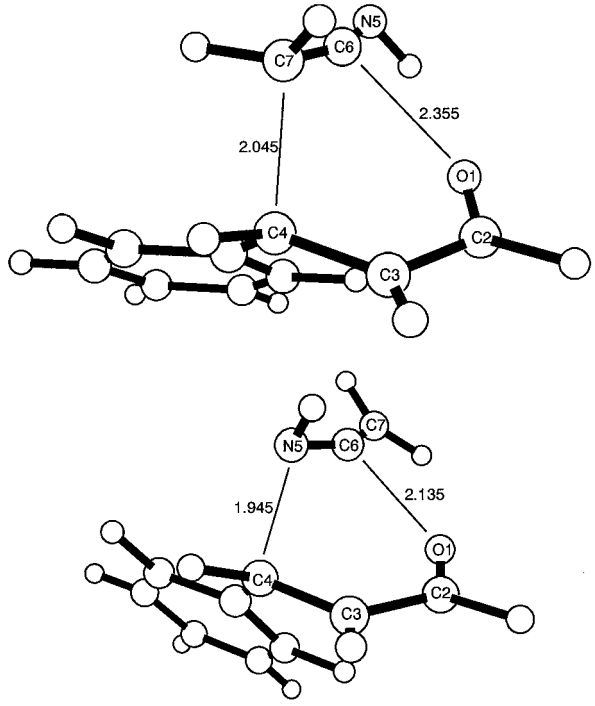


Figure 1. Calculated (B3LYP/6-31G*) transition structures for reaction of **2a** + **9b** to **10ab** (upper) and **11ab** (lower).

are clearly discernible from these data. (i) All reactions proceed through a strongly asynchronous transition state with formation of the C4−C7 (or C4−N5) bond being much more advanced than formation of that between O1 and C6. However, despite this asynchronicity, at the B3LYP/6-31G* and B3LYP/6-31+G** level of theory, no true intermediate could be found indicating a concerted asynchronous mechanism of these cycloadditions. As expected, an even larger transition-state asymmetry is calculated by AM1. (ii) There is significant bond length equalization of the C2−C3 (1.41−1.44 Å) and C3−C4 (1.41−1.42 Å) bonds of the heterodiene moiety (1.47−1.50 Å and 1.34−1.36 Å, respectively, in the reactant acrolein). (iii) In line with this acquired double bond character of the C2−C3 bond in the respective TS's an essentially planar conformation of the oxa 1,3-diene is maintained in the TS. (iv) The already quite advanced formation of the bond to C4 manifests itself also by an accompanying pyramidalization at C4 and, for addition of the terminal heterocumulene carbon, also at C7. (v) As one would expect for Diels−Alder type reactions, formation of the C4−C7 bond in TS's leading to cycloadducts **3** (or **10**) occurs via interaction of the C3=C4 and C6=C7 π-systems. In striking contrast, for addition of the C=N double bond, the improper dihedral angle τ_1 defined by the angle between the planes C6−N5−H5 and C6−N5−C4 significantly deviates from the ideal value of 90° for $\pi-\pi$-type interaction. Participation of the nitrogen lone pair in the reaction of N5 with C4 thus seems likely. (vi) Attack of the central ketene imine carbon (C6) to the heterodiene oxygen (O1) occurs in a plane only tilted by $\leq$40° with respect to the carbonyl plane. Thus, these transition states—at least partly—resemble more closely the TS's of so-called pseudopericyclic[14,28−30] reactions rather than those for traditional [4 + 2] Diels−Alder

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Table 2. Calculated (AM1) Relative Energies (kcal mol^{-1}) of Transition States (TS) and Products (P) for the Reaction of Ketene Imines 2 and Furandiones 1 to Cycloadducts 3 and 4

	3		4			3		4	
reaction	TS	P	TS	P	reaction	TS	P	TS	P
2a + **1a**	9.4 (8.0)[a]	−35.8 (−34.8)[a]	15.0 (8.5)[a]	−18.6 (−20.8)[a]	**2e** + **1a**	12.9	−34.5	20.1	−9.5
2a + **1b**	10.0	−37.6	13.3	−21.6	**2e** + **1b**	13.5	−36.2	19.8	−11.7
2a + **1c**	15.9	−25.5	21.4	−8.5	**2e** + **1c**	20.0	−25.8	28.9	1.1
2a + **1d**	17.7	−28.8	22.5	−11.4	**2e** + **1d**	21.6	−27.3	30.8	−1.2
2c + **1a**	24.4	−14.4	17.1	−17.0	**2f** + **1a**	21.0	−23.5	20.2	−9.2
2c + **1b**	25.3	−15.9	17.7	−20.5	**2f** + **1b**	21.7	−25.0	20.0	−11.0
2c + **1c**	35.7	1.9	25.4	−6.6	**2f** + **1c**	29.6	−12.4	30.1	1.7
2c + **1d**	38.9	0.7	25.5	−9.8	**2f** + **1d**	31.5	−13.7	30.5	0.1
2d + **1a**	16.5	−25.0	13.6	−18.8	**2g** + **1a**	27.6	−13.2	25.8	−5.1
2d + **1b**	17.7	−26.7	15.2	−21.9	**2g** + **1b**	28.7	−14.5	25.3	−7.5
2d + **1c**	26.1	−13.9	20.2	−7.4	**2g** + **1c**	39.0	3.3	35.5	5.0
2d + **1d**	29.5	−14.2	22.6	−10.1	**2g** + **1d**	42.4	2.2	36.6	3.8

[a] B3LYP/6-31G* results in parentheses.

cycloadditions. The conclusions derived from geometrical features of the various transition states are corroborated by their respective electronic structures as revealed by a NBO-analysis (for details, see Table 4 of the Supporting Information). First of all, there is no indication at all of any bonding interaction between O1 and C6. In striking contrast, development of a significantly populated C4−C7 or C4−N5 bond orbital for addition of the C=C or C=N ketene imine double bond, respectively, is found in the corresponding TS's. For cycloaddition leading to compounds of structure **10** (or **3**) this bonding is accomplished either by a σ-type interaction of the p(C4)−p(C7) orbitals (**TS-10aa**, **TS-10ea**) or a three-center-bond involving C4−C7−C6 (**TS-10ab**, **TS-10da**) or, alternatively, C7−C4−C3 (**TS-10ag**, **TS-3aa**). The C4−N5 bonding in transition states leading to structures **11** (or **4**) is provided by a σ-type NBO formed from a p-orbital at C4 and a sp$^{2.5}$ hybrid at N5. The lone pair at N5 of the parent ketene imine, thus, plays an essential role in the formation of the C4−N5 bond as anticipated from the geometrical arrangement of the C6−N5−R plane relative to the acrolein moiety.

Reactions of Substituted Ketene Imines with Substituted Acroleins. Apart from the above-mentioned deficiencies of activation energies calculated by the semiempirical AM1 method the following conclusions regarding the combined influence of substituents on both the heterocumulene and the heterodiene are evident from the data of Table 1: most important, C-terminal substitution of the ketene imine almost invariably leads to a preferential stabilization of the transition state for C=N over that for C=C addition. This effect is most pronounced for C4-substituted oxa 1,3-dienes, whereas the 2-phenyl group has only little influence. Suitable substitution, therefore, indeed will lead to a reversal of the site selectivity in these cycloadditions. Reaction energies, especially for the more heavily substituted derivatives, are quite low and, in fact, even may become endothermic. In addition, calculated activation energies are rather high. Cycloadditions involving such highly substituted acroleins and ketene imines, thus, should require quite drastic experimental conditions. Therefore, the question arises whether incorporation of the oxa 1,3-diene system into the heterocyclic furan-2,3-dione moiety could sufficiently lower the respective activation energies to explain the experimentally observed[6] feasibility of these reactions.

Reactions of Ketene Imines with 4-Acylfuran-2,3-diones. According to the activation energies calculated by AM1 (see Table 2) compounds **1** indeed appear to be considerably more reactive than the similarly substituted acroleins **9**, e.g., for **2a** + **1a** → **3aa** and **2a** + **1a** → **4aa** activation energies of 9.4 and 15.0 kcal mol^{-1} are obtained compared to values of 18.8 and 22.4 kcal mol^{-1}, respectively, for the corresponding reactions **2a** + **9k** → **10ak** and **2a** + **9k** → **11ak** (Table 1). DFT (B3LYP/6-31G*) calculations on the parent system **2a** + **1a** → **3aa** and **2a** + **1a** → **4aa** appear to corroborate the AM1 results. For reactions of the substituted derivatives the increase in reactivity is even more pronounced (see, e.g., **2f** + **1d** → **3fd**, **4fd** (Table 2) vs **2f** + **9n** → **10fn**, **11fn** (Table 1)), where a decrease in activation energy of ∼13 kcal mol^{-1} is not uncommon. Replacement of the 4-formyl by the 4-benzoyl group present in the molecules actually used in the synthetic work[6] has only little influence on the energetics of the reaction. C-Terminal substitution of the ketene imine leads to a preference for formation of type **4** cycloadducts over type **3** ones, especially when the furandione bears the 5-phenyl (C4 in the numbering scheme of Figure 1) group. Substitution at the ketene imine nitrogen atom has the reverse effect on AM1 activation energies. Most importantly, except for the reactions of unsubstituted ketene imine **2a** itself and the *N*-phenyl derivative **2e**, here even with AM1 a preference for formation of **4** as opposed to **3** in a kinetically controlled reaction is predicted. Since in these reactions (compare the AM1 results for the reaction **2a** + **1a** with those obtained by B3LYP/6-31G*, Table 2) activation energies for formation of **4** seem to be even more overestimated by the AM1 method, the calculated substituent-induced reversal of the transition-state energies leading either to cycloadduct **3** or **4**, respectively, is completely reasonable. Geometrical features of the corresponding TS's are in line with those involving acroleins. According to the NBO analysis, in **TS-3aa** bonding between C4 and C7 (for consistency the same atom numbering as in the acrolein + ketene imine systems is used) is accomplished by a C7−C4−C3 three-center-bond (C4−C7 bond order ≈ 0.6). Formation of this bond requires breaking of the C7−C6 π-bond; the remaining p-orbital at C6 interacts with the nitrogen lone pair to form an additional π(N5−C6) bond with a concomitant shortening of r(N5−C6) (B3LYP/6-31G*: 1.197 Å in **TS-3aa** as compared to 1.230 Å in ketene imine). As in all TS's for ketene imine C=N additions, a σ-type p(C4)-sp$^{2.5}$ (N5) bond, accompanied by creation of a lone pair at C3 with almost equal amount of delocalization to C2 and C4,

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represents the key electronic features of **TS-4aa**. Again, no indication of a bond O1−C6 is found in line with the quite different distances of the two forming bonds. Finally, it should be mentioned that the calculated reaction energies—as also described above for the reaction of substituted ketene imines with substituted acroleins—are quite low or even predicted to be endothermic. This fact might explain why it has never been possible experimentally to isolate these primary cycloadducts but only their thermodynamically much more stable rearranged products **8** (or, in some cases, **6**).

Conclusions

Density functional calculations at the B3LYP/6-31G* level of theory for reactants, transition states, and products for heterocumulene−heterodiene [4 + 2] cycloadditions are obtained. The effects of substituents on either the ketene imine and/or the oxa 1,3-diene on the site selectivity (C=C vs C=N addition of the heterocumulene) are discussed. Although for the unsubstituted parent compounds (**2a** + **9a**) addition across the ketene imine C=C double bond to **10aa** is highly favored over addition across the C=N bond to **11aa** for thermodynamical reasons, activation energies for these two processes are only slightly different. Substitution at the C-terminus of the ketene imine leads to a reversal of the site selectivity, i.e., preferential formation of cycloadducts involving reaction of the ketene imine C=N rather than the C=C double bond, especially for 4-substituted acroleins. Incorporation of the oxa 1,3-diene system into heterocyclic systems, e.g., 4-acylfuran-2,3-diones, leads to an enhanced reactivity. For the reaction of *C*,*C*-dimethyl-*N*-phenyl- or triphenylketene imine with 4-benzoyl-5-phenylfuran-2,3-dione, which had been investigated experimentally,[6] even with the semiempirical AM1 method, which is found to overestimate activation energies for C=N vs C=C addition, preferential formation of the cycloadduct **4** rather than the more common **3** (Scheme 1) is predicted. At the B3LYP/6-31G* level of theory all cycloadditions described above appear to proceed in a concerted, albeit highly asynchronous, fashion. With AM1, addition across the C=N heterocumulene double bond is calculated to involve a true, although barely stable intermediate. Formation of the bond between the terminal heterodiene carbon and the terminal heterocumulene carbon or nitrogen atom, respectively, is considerably more advanced than development of bonding between the heterodiene oxygen and the central carbon of the ketene imine (according to the NBO analysis of the electronic structures of the various transition states there is essentially no bonding between these two centers). The present theoretical results clearly establish path B in Scheme 1 as the most likely mechanism for formation of furo[3,2-*c*]pyridines **8**.

Supporting Information Available: Tables of B3LYP total energies, selected structural data for transition states, and results of the NBO analysis (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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