Peri-, Site-, and Regioselectivity in Heterocumulene−Heterodiene Cycloaddition Reactions: An ab Initio Study of the System Ketenimine + Acrolein

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Abstract: Geometries of the 12 possible cycloaddition products between ketenimine and acrolein as well as of the respective transition states have been obtained by ab initio calculations at the MP2/6-31G* level. Energies were obtained up to the MP4(SDTQ)/6-31+G* level. On the basis of product stability arguments, addition of the ketenimine C=C double bond is more favorable than reaction of the C=N double bond. Similarly, acrolein also preferentially should react via its C=C rather than C=O bond. In kinetically controlled reactions, however, participation of the ketenimine C=N bond in [4 + 2] cycloadditions across the oxa-1,3-dienic system is comparable to (**8**) or far more feasible than (**7**) reaction of the C=C bond.

Introduction

Ketenes or heterocumulenes in general have found widespread applications in organic synthesis, and reviews on all aspects of their reactivity have appeared.[1,2] In contrast to alkenes the cycloaddition chemistry of heterocumulenes is dominated by the "symmetry forbidden" [2 + 2] rather than the "allowed" [4 + 2] mode[3] even if the latter one (e.g., with cyclopentadiene)[3b,c] appears attractive. Theoretical treatments of heterocumulene cycloaddition reactions also have been largely restricted to the [2 + 2] type.[4−6] Recently, it has been shown by high-level ab initio calculations that the [2 + 2] isomer is the kinetically favored product whereas the [4 + 2] isomer is the thermodynamically more stable one.[6] Other than [2 + 2] cycloadditions have been observed in a few cases, especially with electron deficient dienes or heterodienes[5,7,8] or α-oxo-ketenes.[9−11] Generally, it is the cumulated C=C double bond which reacts in both [4 + 2] and [2 + 2] cycloadditions. Only in a few other cases has a different siteselectivity in [2 + 2] and [4 + 2] reactions been reported.[12] On the basis of ab initio calculations, frontier orbital arguments, and experimental investigations, it has been suggested recently that formation of the [2 + 2] cycloadduct between conjugated dienes and the C=C double bond of ketene in fact takes place as a two step process (not considered in ref 6a) via prior formation of the [4 + 2] cycloaddition involving the ketene C=O double bond followed by rearrangement to the thermodynamically more stable four-membered ketone.[13]

Over the past decade a considerable number of heterocumulene reactions with 4-acyl-substituted heterocyclic 2,3-diones (e.g., furandiones or pyrroldiones) leading to several novel polycyclic heteroaromatics were published by Kollenz et al.[14] The outcome of these reactions was found to depend strongly on the nature of both the heterocumulene as well as the 2,3-dione. In most cases, a cycloaddition between the heterocumulene and the oxa-1,3-diene subunit of the heterocyclic dione as the primary step, frequently followed by a series of unusual or even novel rearrangement reactions, was assumed. As a typical example, the proposed mechanism[15a] for the reaction of ketenimines with 4-benzoylfuran-2,3-dione is shown in Scheme 1. This reaction sequence is based on the fact that in one single

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Scheme 1

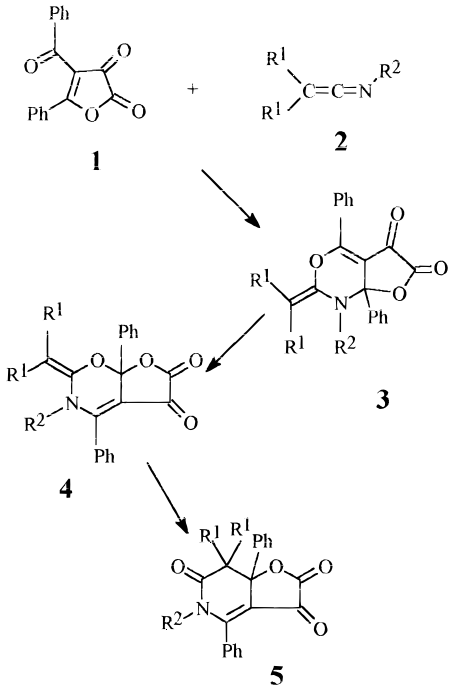
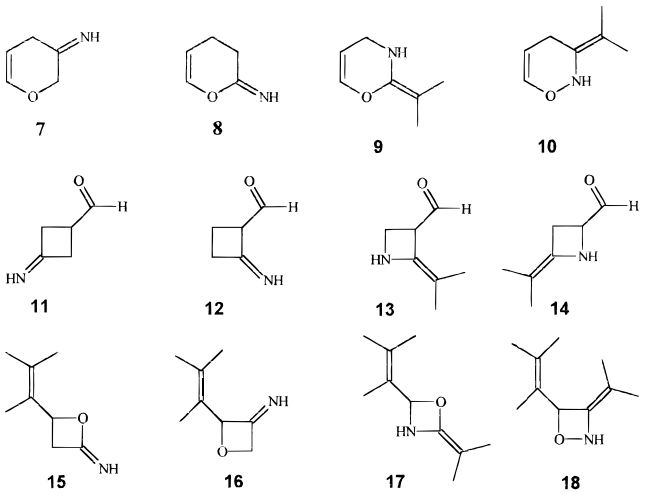


Chart 1



case (R = Me) compound **4** was the isolable product. For all other substituents only **5** could be isolated. Isotopic-labeling studies further corroborate this scheme.[15b] It has, however, never been possible to isolate the proposed primary cycloadduct **3**. Although a few examples of ketenimine−heterodiene [4 + 2] cycloadditions are known,[16] the first step shown in Scheme 1−addition of the ketenimine C═N double bond across the oxa-1,3-diene moiety−would constitute one of the first examples of this reaction (in ketenimine [2 + 2] or 1,3-dipolar cycloaddition reactions involvement of the C═N bond is more frequently observed[17]). Given the novelty of this heterocumulene−heterodiene cycloaddition reaction outlined in Scheme 1, we found it worthwhile to address the question of peri-, site-, and regioselectivity in ketenimine−oxa-1,3-diene cycloadditions at the ab initio level. For this purpose we have chosen as a model the reaction between ketenimine (**2**, $R^1 = R^2 = H$) and acrolein (**6**). The 12 possible isomeric products resulting from [4 + 2] (**7**−**10**) and [2 + 2] (**11**−**18**) cycloadditions between these two molecules are shown in Chart 1.

Computational Methods

Ab initio calculations were carried out employing the program package Gaussian 94.[18] Geometries of reactants, products, and transition states were optimized at the closed shell MP2/6-31G* level of theory. Starting from the products, transition states were approximately located by a potential energy scan of the two bonds formed in the cycloaddition and refined by gradient norm optimization. All stationary points were characterized as minima or transition structures by the eigenvalues of the second derivative matrices. For transition structures, in addition, downhill optimizations along both directions of the normal mode corresponding to the imaginary frequency were done. MP2/6-31G* zero-point vibrational energies (ZPE) were scaled by 0.9646.[19] Single-point calculations were performed at the MP2/6-311++G** as well as the MP4(SDTQ)/6-31G* and MP4(SDTQ)/6-31+G* level of theory. The electronic structures of reactants and transition structures were analyzed by the natural bond orbital (NBO) method[20] which seeks to represent a system in terms of the best possible Lewis resonance structure. The occupancies of the strictly localized NBOs should either be near 0 or 2. In a second step, the NBOs are allowed to delocalize as little as possible so that all occupancies become strictly 0 or 2, thereby forming the natural localized molecular orbitals (NLMO). In the present case, the NBO analysis of the MP2/6-311G(d) density has been performed employing the program G94NBO.[21]

Results and Discussion

In the first part, energetic aspects (stability of the products shown in Chart 1 as well as activation energies for their formation) will be presented and discussed. In the second part structural details of the respective transition states will be given and, finally, their electronic structures will be analyzed in terms of natural charges, bond orbitals, and localized molecular orbitals.

Products. The reaction energies calculated at various levels of theory for the 12 possible isomeric products are collected in Table 1 (total energies as well as ZPE corrections are provided in Table 1 of the Supporting Information). Since for [4 + 2] cycloadditions a cis-conformation of the heterodiene is required, all reaction energies (including those for [2 + 2] additions) are referred to the cis-structure of acrolein. Although, in principle, [2 + 2] cycloadditions could take place with both the cis- and the trans-conformations, only the former one has been treated here because in the actual molecule **1** (see Scheme 1) used in the experimental investigations a trans conformation of the oxa-1,3-diene moiety is highly unlikely by steric reasons. The only exception is compound **14** for which despite several attempts no transition state leading to cis-acrolein + ketenimine could be located. Obviously, as indicated by the formyl torsional potential (Figure 1 of the Supporting Information), in the cycloadduct **14** a transoid conformation is already predetermined (both minima at τ(C4−C3−C2−O1) = 110° and τ = 240° lead

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Table 1. Reaction and (in Parentheses) Activation Energies (kcal mol^{-1}) Including MP2/6-31G* Zero-Point Energy Corrections (scaled by 0.96) for the Products of [4 + 2] (**7**−**10**) and [2 + 2] Cycloaddition (**11**−**18**) between Ketenimine and Acrolein

	I[a]	**II**[b]	**III**[c]	**IV**[d]	$\tilde{\nu}$[e]
7	−30.5 (30.6)	−29.1 (29.1)	−27.6 (33.5)	−27.4 (32.0)	612
8	−43.5 (19.8)	−40.7 (18.7)	−40.0 (22.3)	−38.6 (21.0)	513
9	−22.5 (22.3)	−21.5 (21.9)	−18.8 (24.0)	−18.7 (22.2)	546
10[f]	8.5 (25.6)	10.8 (27.0)	10.5 (27.3)	10.7 (26.0)	432
11	−30.4 (25.0)	−28.7 (22.7)	−27.1 (28.1)	−26.1 (26.5)	563
12	−30.9 (38.8)	−29.3 (35.6)	−27.4 (39.2)	−26.3 (37.2)	644
13	−18.6 (37.6)	−18.0 (33.7)	−14.9 (39.9)	−14.8 (34.7)	397
	(42.2)[g]	(39.7)[g]	(37.2)[g]	(35.2)[g]	478[g]
14[h]	24.2 (32.9)	23.6 (30.4)	20.5 (33.7)	19.4 (31.8)	708
	−19.6 (31.1)	−19.2 (30.3)	−15.9 (28.1)	−16.3 (26.3)	530
15	−25.2 (35.2)	−23.7 (33.4)	−22.3 (36.5)	−22.1 (33.6)	433
16	−7.2 (51.4)	−5.9 (51.1)	−5.0 (48.7)	−5.3 (46.1)	548
17	−5.6 (42.3)	−4.8 (41.2)	−2.6 (43.0)	−2.7 (39.0)	450
18	32.0 (94.6)	34.4 (93.0)	33.0 (94.0)	32.6 (91.0)	649

[a] MP2/6-31G*//MP2/6-31G*. [b] MP2/6-311++G**//MP2/6-31G*. [c] MP4(SDTQ)/6-31G*//MP2/6-31G*. [d] MP4(SDTQ)/6-31+G*//MP2/6-31G*. [e] Imaginary frequency (cm^{-1}) for transition states calculated by MP2/6-31G*. [f] Transition state for rearrangement **11** ↔ **10**. [g] Transition state for rearrangement **12** ↔ **13**. [h] First line: reaction and activation energy for intermediate; second line: reaction and activation energy for product.

to trans-acrolein; to give cis-acrolein, $\tau \approx 0°$ would be required). In contrast, both vinyl group rotamers of compound **15** with τ (O1−C2−C3−C4) = 130° and $\tau \approx 0°$ are stable and of nearly equal energy ($\Delta\Delta E$ (MP4(SDTQ)/6-31+G*//MP2/6-31G*) = 0.1 kcal mol^{-1}). Not surprisingly, reactions leading to the formation of a N−O single bond (i.e., compounds **10** and **18**) are endothermic. All other reactions are calculated to be exothermic. Generally, addition across the C═C double bond of the ketenimine leads to thermodynamically more stable products than reaction across the C═N double bond (e.g., **7** and **8** vs **9** and **10**; **11** and **12** vs **13** and **14**; **15** and **16** vs **17** and **18**. With respect to siteselectivity of the heterodiene, it is obvious from the data of Table 1 that [2 + 2] products resulting from addition of ketenimine onto the dienic C═C double bond are more stable than those obtained by reaction of the carbonyl group (compare compounds **11** and **12** vs **15** and **16** or **13** and **14** vs **17** and **18**). Concerning the periselectivity (i.e., the [4 + 2] vs [2 + 2] mode of addition), the [4 + 2] cycloadduct **8** is calculated to be considerably more stable (ca. 10 kcal mol^{-1}) than the most stable [2 + 2] product **12**. Compounds of the type **8** are those which are generally obtained in the known [4 + 2] cycloaddition reactions of heterocumulenes with α,β-unsaturated carbonyl compounds.[8] On purely thermodynamic grounds, in addition to **8**, formation of compound **7** should be at least competitive with [2 + 2] cycloadditions. Interestingly, however, structure **9**, which corresponds to the proposed primary cycloaddition product **3** (see Scheme 1) in ketenimine−4-acylfuran-2,3-dione reactions, is considerably less stable than the isomeric [4 + 2] cycloadducts **7** and **8**. Moreover, reaction of the ketenimine C═C double bond in the [2 + 2] fashion (**11**, **12**, and **15**) should also lead to products more stable than **9**. Unless the substituents present in **1** and **2** can induce a change of reaction energies greater than ca. 20 kcal mol^{-1} , therefore, formation of structure **9** can—if at all—only occur in a kinetically controlled process.

Activation Energies. A justification for using single-reference methods in treating heterocumulene cycloadditions has been given by Salzner and Bachrach.[6a] Moreover, for the reactions between ketene[5] or ketenimine[22] and aldehydes to give β-lactones and iminooxetanes, respectively, it has been shown that the transition state can be adequately described by a single-reference wave function. Therefore, we conclude that the energetics of the possible cycloaddition modes between ketenimine and acrolein presented here are of sufficient reliability. Activation energies are also summarized in Table 1. Any attempt to locate a transition state leading to the [4 + 2] product **10** failed. Instead, only the transition state for rearrangement between **10** and the [2 + 2] cycloadduct **11** was obtained. Formation of compound **10** via rearrangement of **11** would be even more endothermic (ΔE_{react} = 36.8 kcal mol^{-1} at the MP4-(SDTQ)/6-31+G*//MP2/ 6-31G* level) than [4 + 2] cycloaddition. Although by and large activation energies parallel product stabilities, there are some notable and important exceptions. For instance, **7** is calculated to be more stable than **9** by approximately 8 kcal mol^{-1}; the activation energy, however, is higher than that for **9** by the same amount. Also, compound **15** should by favored over **12** in a kinetically controlled reaction. Similarly, for the site-isomeric pair **12** and **13,** the latter one, which involves reaction of the ketenimine C═N double bond, has a somewhat lower activation energy than the much more stable compound **12**. Starting from compound **17**, besides **17TS1**, a second transition state (**17TS2)** of a completely different structure but only slightly higher energy was found. Upon downhill optimization, this transition state leads to a different conformation of **17** with almost equal energy ($\Delta\Delta E_{react}$ = +0.6 kcal mol^{-1} at the MP4(SDTQ)/6-31+G* //MP2/6-31G* level). The most interesting result is obtained for the isomeric pair **8** and **9**: product stability arguments alone would favor compound **8** by ≈20 kcal mol^{-1}. In striking contrast, however, the difference in activation energies barely exceeds 1 kcal mol^{-1}. For **8**, in addition to the [4 + 2] cycloaddition transition state **8TS** an even lower one (ΔE_{act} (MP2/6-31G*) = 13.1 kcal mol^{-1}) for C4−C7 bond formation and proton transfer leading to 5-hydroxy-4-pentenenitrile (enol form of glutaric aldehydenitrile) was located. The different nature of this transition state is also evidenced by the corresponding imaginary frequency ($\tilde{\nu}$ = 1970*i* cm^{-1} as compared to values of ∼400−700*i* cm^{-1} found for cycloaddition transition states). Since, however, the reactions with the heterocyclic 4-acyl-2,3-diones were performed with N-substituted ketenimines, this possibility of Michael-type 1,4-addition as an alternative mechanistic pathway was not pursued any further.

With respect to periselectivity, the data of Table 1 indicate that the two isomeric [4 + 2] cycloaddition products **8** and **9** will be favored over all possible [2 + 2] isomers on both thermodynamic and kinetic reasons. In contrast, formation of the rather stable compound **7** should not be competitive with [2 + 2] modes of reactions leading to **11** and possibly **14** or

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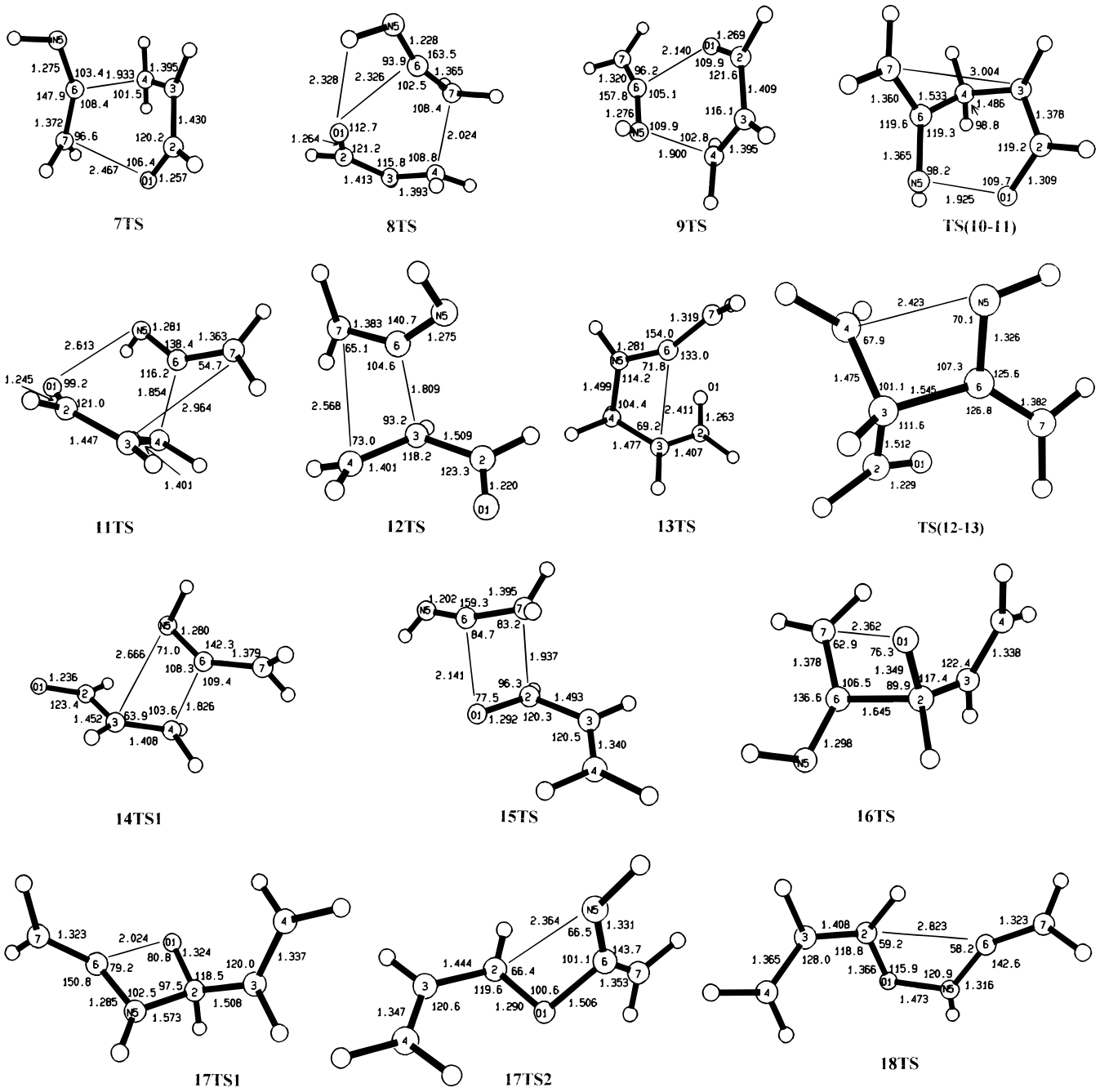

Figure 1. MP2/6-31G*-calculated transition structures (distances in angstroms, angles in degrees).

15. Thus, taken together, activation and reaction energies indicate, as the preferred cycloaddition mode in the ketenimine−acrolein reaction, the formation of compound **8**. In kinetically controlled reactions, however, cycloaddition to **9** via the previously apparently unknown [4 + 2] addition of the oxa-1,3-diene system across the ketenimine C═N double bond will be at least competitive with—if not preferred over—formation of compound **8**. Only formation of **11** possibly could compete with [4 + 2] cycloadditions. It is worth noting that in the reactions of ketenes with 1-aza-butadienes—depending on the substitution pattern—compounds analogous to **8** and **15** (with O and NH interchanged in Chart 1) are formed.[5] Similarly, with simple carbonyl compounds ketenimines react in a [2 + 2] manner to give iminooxetanes of type **15**.[17,23] The calculated activation energy for formation of **15** is close to that (∼35 kcal mol^{-1}) obtained for the reaction of formaldehyde + ketenimine.[22] The [2 + 2] cycloadducts of type **11** are formed in the reaction of triarylphosphoranylideneketenimines with maleimide[24] or of keteniminium salts with simple olefins.[25] Finally, compound **14** is the only one for which a two-step reaction involving a true intermediate was found at the MP2/6-31G* level (no such intermediate could be obtained at the RHF/6-31G* level). Formation of this intermediate rather than its ring closure to the [2 + 2] cycloadduct **14** appears to be rate determining.

Structures of Transition States. The calculated (MP2/6-31G*) structures for the various transition states are depicted in Figure 1. Not only transition states for all the [2 + 2]

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cycloadditions are highly asymmetric but also those for [4 + 2] reaction with C−O bond formation lagging behind C−C (or C−N) bond formation. In ketenimine C=C double bond additions (**7TS**, **8TS**, **11TS**, **12TS**, **15TS**, **16TS**), generally the bond to the central ketenimine carbon atom C6 is preferentially formed, the only exceptions being **8TS** and **15TS** where C6 reacts with O1 of acrolein. Another unique feature of these two transition structures concerns the length of the N5−C6 bond: in all of the transition structures but **8TS** and **15TS,** *R*(N5−C6) is longer than in ketenimine (R = 1.239 Å) itself whereas in these two structures it is shorter. Except **14TS1**, in transition states involving ketenimine C=N double bond additions, the formation of the bond to the ketenimine nitrogen atom is more pronounced. In the [4 + 2] cycloaddition transition states **7TS**, **8TS**, and **9TS**, the C3−C4 bond has already substantially lengthened whereas the C2−C3 bond has acquired significant double bond character. It is interesting to compare the structures of the transition states of ketenimine−acrolein cycloadditions with those obtained by Cossio et al.[5] for the Staudinger reaction between ketene and 1-azabutadiene giving isomeric structures of **8** and **15** (oxygen and NH interchanged). For these reactions, a two-step mechanism involving formation of a zwitterionic intermediate followed by electrocyclic ring closure as the rate determining step has been proposed,[5] although whether a concerted or a two-step mechanism is calculated depends on the method (HF or MP2) used in the computations or if solvent effects are included.[4f,5] All reactions treated here, except formation of compound **14**, appear—at least in the gas phase—to be concerted, albeit rather asynchronous. Another important difference concerns which one of the two bonds are formed first: in the reaction of 1-azabutadiene with ketenes, first the bond of the central carbon atom of the cumulene to the nitrogen of the diene is formed with essentially no bond between the terminal ketene carbon and C2 for [2 + 2] or C4 for [4 + 2] cycloaddition.[5] In the present reactions, the opposite situation (i.e., formation of the carbon−carbon bond prior to that of the C−N bond) is obtained (see structures of **8TS** and **15TS** in Figure 1). Calculations on the reaction of ketenimine + formaldehyde to give iminooxetanes predict a concerted mechanism in the gas phase, a two-step process with, however, the first transition state being rate determining, if solvent effects are included in the calculations and an asynchronous concerted mechanism for the catalyzed reaction.[22] For all three mechanisms—as we have found—formation of the C−O bond significantly lags behind C−C bond formation.

NBO Analysis. On the basis of natural population analysis (NPA)[20] derived atomic charges (details are given in Table 2 of the Supporting Information), the nature of the various transition structures can be seen to occur from some zwitterionic character (**13TS** (0.38 e transferred), **15TS** (0.34 e), **17TS1** (0.29 e), **18TS** (0.29 e), **8TS** (0.26 e), **17TS2** (0.25 e)) to rather modest charge transfer (**9TS** (0.14 e)) to no zwitterionic character at all (**7TS** (0.04 e), **11TS** (0.00 e), **12TS** (0.06 e), **14TS1** (0.03 e), **16TS** (0.05 e)). In all transition structures except **12TS** and **17TS2**, the ketenimine fragment acts as the donor and the acrolein moiety as the acceptor. The amount of charge transfer in a transition structure is mainly controlled by the steric arrangement of the educts. In particular, the oxygen in acrolein accepts electronic charge from its nearest neighbor if possible on the basis of electronegativity. Relevant NBOs for which the occupancy significantly deviates from 2 or 0, and the NLMOs derived therefrom are collected in Table 3 of the Supporting Information. For the transition structures the NBO analysis resulted in widely differing bonding patterns. Without going into detail, therefore, only a few prominent features will be presented. Generally, there are three main types of the electronic structure of the transition states: First are those with only very little interaction between the ketenimine and acrolein fragment (**7TS**, **9TS**) and electron reorganization mainly within the two fragments. The second extreme is provided by most of the [2 + 2] cycloaddition transition structures, where one of the two bonds can already be described by a σ single-bond NBO (**12TS**, **13TS**, **15TS**, **16TS**, **17TS1**, **18TS**) with bond orders in the range of 0.5−0.9, whereas the second bond is virtually not yet existent. The third type of transition structures contains three-center bonds (**9TS**, **11TS**, **14TS1**, **17TS2**) involving C3 and C4 of **6** and either the terminal (**8TS**) or the central (**11TS**, **14TS1**) carbon atom of **2**, thus bearing some resemblance to the carbenoid transition structures proposed by Houk.[4b] It is tempting to speculate that the presence of such three-center bonds will lead to low barriers (e.g., **8TS**, **11TS**). Structure **17TS2** is a very special case, since here the three-center bond is between atoms which do not become bonded in the product. For its formation, therefore, this three-center bond has to be broken; hence, the large activation energy for compound **17**. The relatively high energy of **14TS1** might be attributed to a significant biradicaloid character of this structure. In line with this interpretation is also the fact that formation of **14** is the only one calculated to proceed via a two-step mechanism.

Since the reactants of the present reactions are rather polar, electrostatic effects also may play a role. On this basis, the high barrier for the [4 + 2] cycloadduct **7** compared to that of its isomers **8** and **9** can be understood: The transition structure **7TS** is unfavorable due to the approach of the two electron-rich atoms O1 and C7. At the transition structure a significant portion of electronic charge is removed from C7 to the electron-poor centers C4, C6, and C2 to overcome the interaction between the two negatively charged centers O1 and C7. No such rearrangement is necessary at the transition structures **8TS** and **9TS**. The [4 + 2] cycloaddition via **7TS**, therefore, would require an energetically costly rearrangement of electronic charge.

Conclusion

From the results presented above the following main conclusions with respect to peri-, site-, and regioselectivity of ketenimine cycloadditions with α,β-unsaturated carbonyl compounds can be drawn: (i) on both thermodynamic as well as kinetic grounds the [4 + 2] cycloadduct **8** should be the preferred product in these reactions; (ii) among the [2 + 2] products, compound **11**, formed from addition of the ketenimine C=C double bond across the acrolein C=C double bond, is the most favored structure; (iii) the [4 + 2] cycloadduct **9**, which is thermodynamically less stable than its isomers **7** and **8** by ∼10 and ∼20 kcal mol^{-1}, respectively, has a 10 kcal mol^{-1} lower activation energy than that for **7** and an approximately equal one to that for formation of **8**. On the basis of these results, the assumed reaction mechanism for the addition of ketenimines to 4-acylfuran-2,3-diones depicted in Scheme 1, where such a cycloaddition mode has been proposed as the primary mechanistic step, appears completely reasonable.

Supporting Information Available: Tables of total energies and ZPE corrections for reactants, transition structures, and products at different levels of theory, NPA-derived atomic charges, results of NBO and NLMO analyses, and a plot of the formyl torsional potential for compound **14** (15 pages). See any current masthead page for ordering and Internet access instructions.

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