Original Scientific Paper

Semiempirical Calculations on Heterodiene-Heterocumulene Cycloadditions*

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4-Benzoyl substituted five-membered heterocyclic 2,3-diones (*e.g.* furandiones or pyrrolediones) add various heterocumulenes giving bicyclic heterocycles. The structures of the products obtained in these reactions can be rationalized by assuming an initial [4 + 2] cycloaddition between the heterodiene system formed from the benzoyl group and the endocyclic C=C double bond of the heterocyclic ring and the heterocumulene, followed by special and novel furandione rearrangements. Although some formal [4 + 2] cycloadditions of ketenes are known, their reactivity is dominated by [2 + 2] cycloadditions. For ketenimines, this reaction appears to be the first example of a [4 + 2] cycloaddition. After presenting some pertinent experimental observations semiempirical (AM1) calculations on reactants, regioisomeric products and possible intermediates are discussed. As the simplest model, cycloadditions between acrolein and ketenimine are used to locate transition states of the twelve possible peri-, site-, and regioisomeric products. Finally, the reliability of these calculations is discussed and some prospects for future work are given.

INTRODUCTION

[4 + 2] cycloadditions of heterodienes are well known and synthetically useful reactions for the formation of a great variety of heterocyclic molecules with special importance in natural product synthesis.[1,2] On the other hand, the chemistry of heterocumulenes is dominated by [2 + 2] cycloadditions,[3] although a few examples of [4 + 2] cycloadditions, especially with electron deficient dienes, are known.[4-6] The periselectivity, *i.e.* [4 + 2] *vs.* [2 + 2] cycloaddition, of these reactions strongly depends on the nature of the heterocumulenes. A typical example is given in Figure 1.[4]

The postulated formation of a [4 + 2] cycloadduct between the diazabutadiene *1a* and diphenylketene[5] was dismissed on the basis of spectroscopic evidence.[6] With monophenylketene, however, formation of the six-membered heterocycle *2b* was confirmed. Furthermore, the sterically strained diazabutadiene *1c* also adds diphenylketene in a Diels-Alder type reaction[6] (Figure 2).

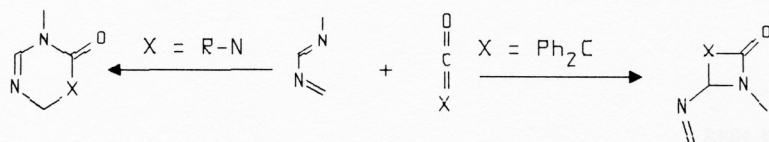* Dedicated to Prof. D. Hadži on the occasion of his 70th birthday.

Figure 1. Influence of heterocumulene structure on the periselectivty of heterocumulene – heterodiene cycloadditions.
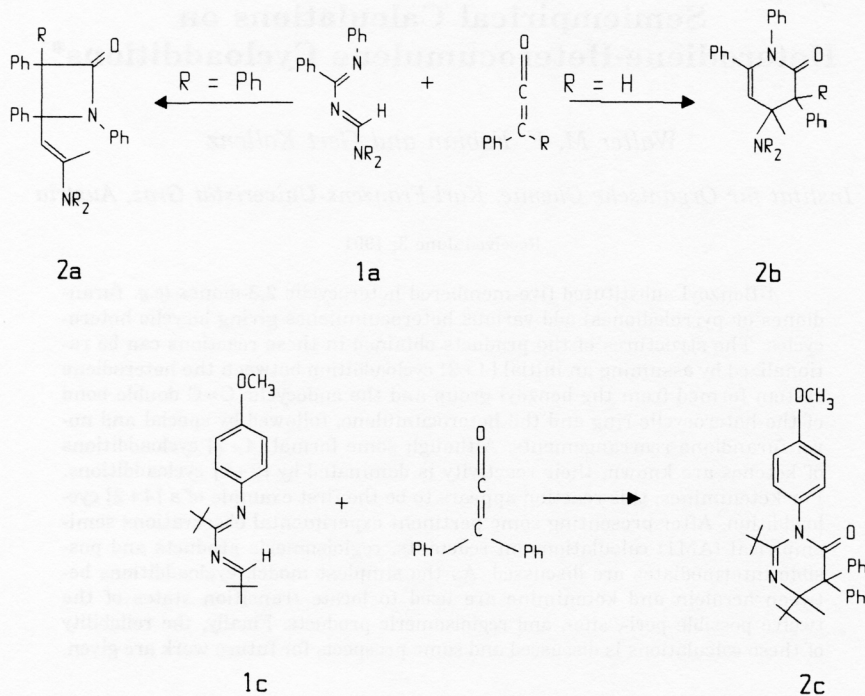

Figure 2. Influence of heterocumulene and heterodiene structure on the periselectivity of their cycloadditions.

Similarly, the oxa-1,3-diene system in 4-benzoyl substituted five-membered heterocyclic diones (*e.g.* furandiones, pyrroldiones, *etc.*) 3 (see Figure 3 for structures) can undergo [4+2] cycloadditions with a variety of heterocumulenes, *e.g.* isocyanates,[7] carbodiimides,[8] or ketenimines.[9] Besides the oxa-1,3-diene subunit, the 1.4-dioxa-1,3-diene substructure of the heterocyclic dione could also be involved in [4+2] cycloadditions. Furthermore, each of the formal double bonds of 3 might participate in [2+2] cycloaddition reactions.

In the first part of this paper, some pertinent experimental results concerning the reactions of heterocumulenes with 3 will be presented. In the second part results of semiempirical AM1[10] calculations on possible intermediates and products of the reaction between ketenimine and 4-formyl-furandione as a model for 3[11] are discussed. Using the reaction between ketenimine and acrolein as the simplest possible model,

in the third part, the peri-, site-, and regiochemistry of heterodiene – heterocumulene cycloadditions will be addressed. Finally, some comments and an outlook for future work are given.
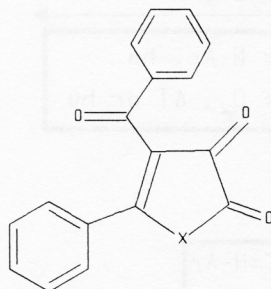
3 : X = O,NH,NR,S

Figure 3. Molecular structure of the actual heterodiene.

RESULTS

Experimental Observations

As one might expect from the introductory remarks, the outcome of the reactions between 3 and heterocumulenes depend on the nature of the latter. In addition, there are also subtle differences with respect to the heteroatom X in 3. Some typical examples[12] for the great variety and broad scope of the cycloaddition chemistry of 3 are given in Figures 4 and 5.

Generally, the primary cycloadduct cannot be isolated. Instead, it undergoes some special and even novel rearrangement reactions. The proposed mechanism for the thermal reaction between ketenimines and 4-benzoyl furandiones[9] is shown in Figure 6.

To the best of our knowledge, if this mechanism were correct, it would represent the first example of a [4+2] cycloaddition of ketenimines to the heterodienic oxa-1,3-diene system. Some support for this mechanism stems from the fact that in one single case (R' = CH$_3$) intermediate 5 could be isolated; in all other cases 6 was the only isolable product. Isotopic labelling studies using ^{17}O are also fully consistent with this reaction mechanism.[13]

SEMIEMPIRICAL CALCULATIONS

Calculational Details

All semiempirical calculations were done by the AM1 method[10] using the PRECISE option. Geometries were fully optimized without any constraints and all stationary points were characterized by force constant calculations as either true minima or transition states. For transition states, downhill optimizations along both directions of the normal mode, corresponding to the negative eigenvalue of the force constant matrix, were also performed.
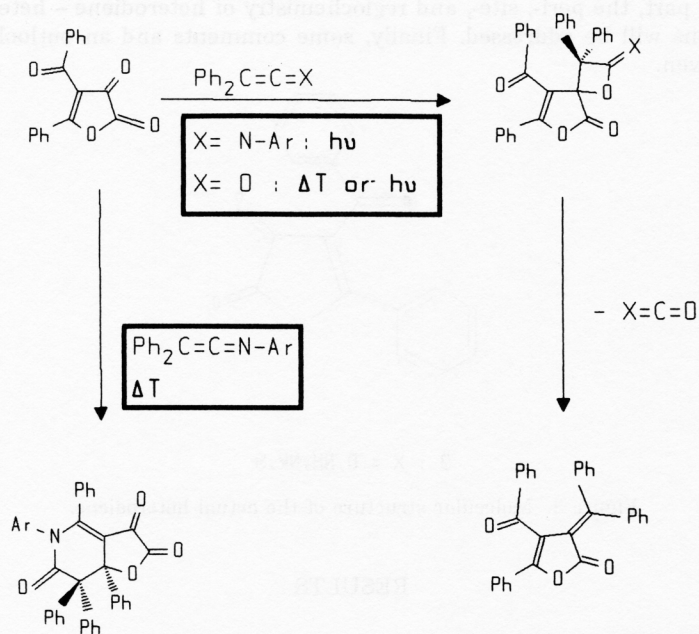
Figure 4. Influence of heterocumulene structure and the nature of heteroatom X on reactions of *3*.
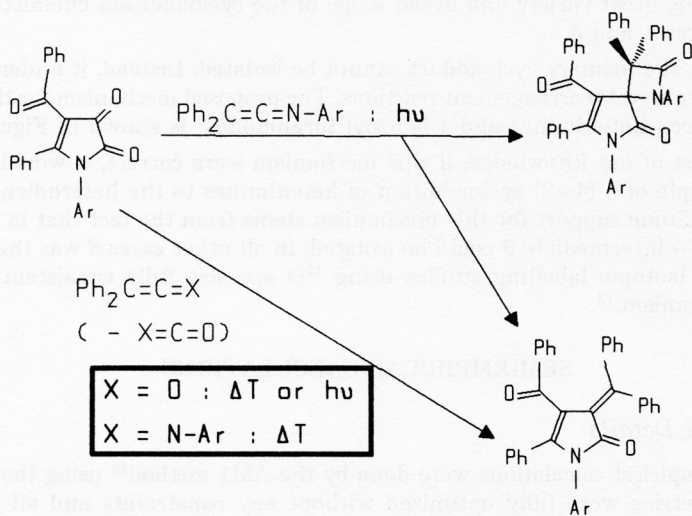

Figure 5. Influence of heterocumulene structure and the nature of heteroatom X on reactions of *3*.
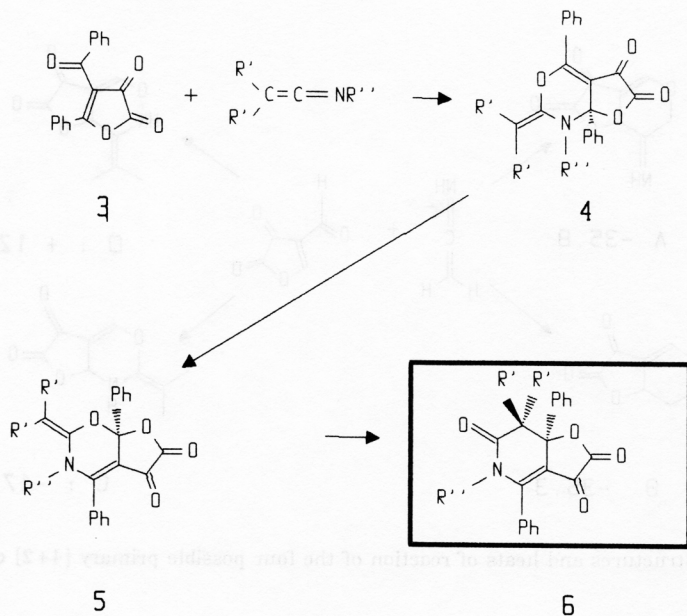
Figure 6. Proposed reaction mechanism of reactions between ketenimines and 4-benzoyl-furan-2,3-diones *3*.

Thermodynamics of [4+2] Cycloadditions

As stated in the introduction in this section, energetical aspects of [4+2] cycloadditions between ketenimine and 4-formyl- furandione,[11] as a model for *3*, will be presented. Structures and heats of reactions (kcal mol^{-1}) for the four possible isomeric primary cycloadducts are summarized in Figure 7. Rearrangements products of these four cycloadducts and their relative energies are shown in Figure 8.

From the data presented in Figures 7, and 8, the following conclusions can be drawn[11]:

i) On purely energetic grounds (*i.e.* thermodynamically controlled reactions) formation of either *A* or *B* should be highly favoured; *C* is expected to be less easily formed and *D* can be safely ruled out.

ii) Both *B* as well as *C* can rearrange to thermodynamically much more stable products and, finally, lead to the same product *F* as the most stable one.

iii) The most stable product *F* in this model reaction corresponds to structure *6* in Figure 6, *i.e.* exactly the compound that is obtained experimentally in all but one single case.

iv) In a thermodynamically reaction, thus, a mechanism involving structure *B* as the primary cycloadduct should be most probable. As pointed out in the previous section,
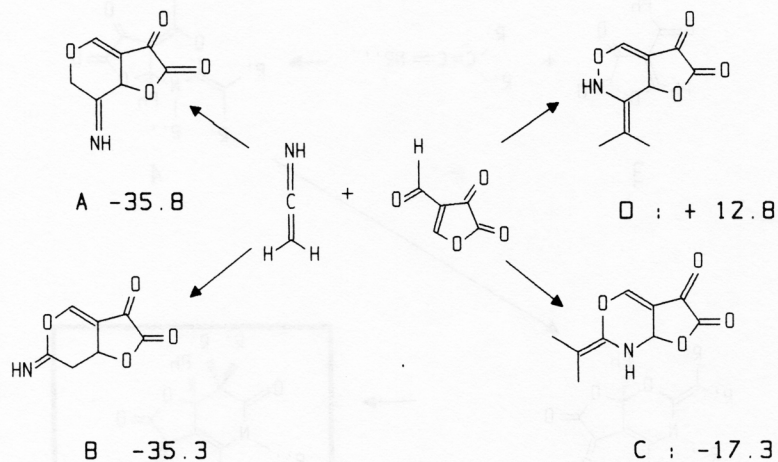
Figure 7. Structures and heats of reaction of the four possible primary [4+2] cycloadducts.
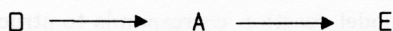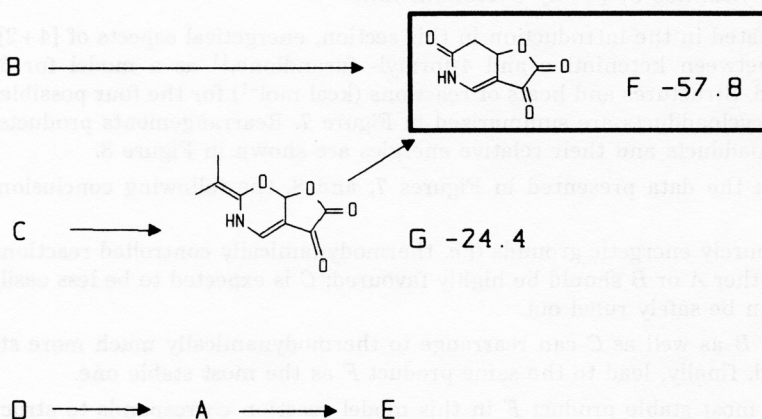

E -31.8 (endothermic !)

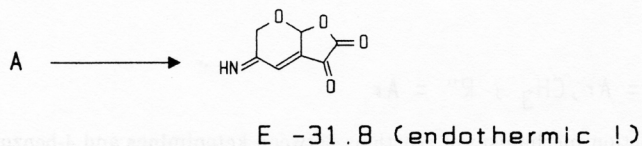Figure 8. Rearrangement reactions of the primary cycloadducts and heats of reaction.

7   8   9   10

11   12   13   14
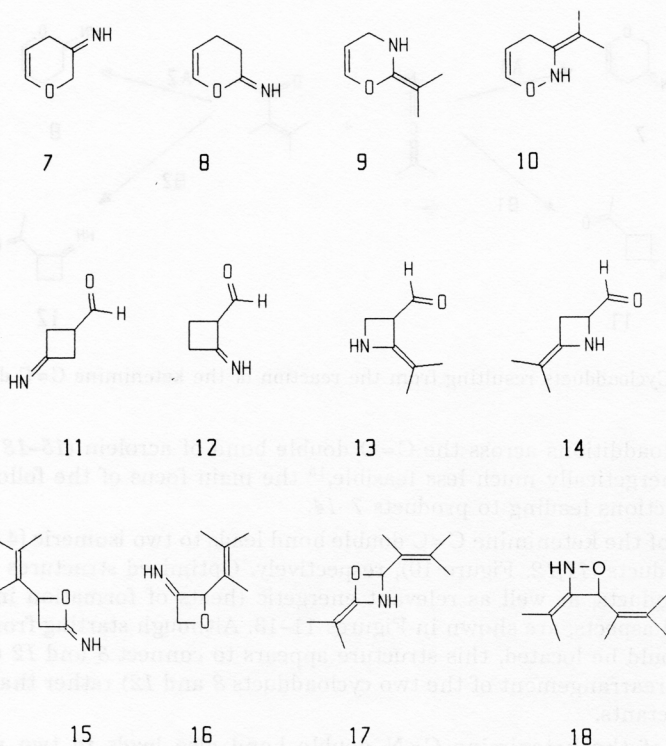
15   16   17   18

Figure 9. Structures of the possible ketenimine – acrolein cycloadducts.

experimental evidence, however, suggests involvement of a structure corresponding to *C* in the proposed reaction sequence.

v) A simple PMO treatment[14] does not support assertion of a kinetically favoured formation of *C*[11] (The argument of a kinetically controlled reaction had previously been used to rationalize the preferred formation of the thermodynamically less stable [2+2] cycloadduct, as compared to the [4+2] product in ketene – diazabutadiene reactions[6]).

vi) Inspection of molecular models suggest a sterically much more demanding transition state for formation of *B* as opposed to *C*.

Since such an effect is not taken into account in the simple PMO treatment, it appeared worthwhile to investigate the transition states of these cycloadditions in a somewhat greater detail. For this purpose, the simplest possible reactants, *i.e.* ketenimine and acrolein, were chosen.

Peri-, Site-, and Regiochemistry of Ketenimine–Acrolein Cycloadditions

Disregarding stereochemical details for the reaction of ketenimine with acrolein, twelve cycloadducts and transition states are possible (Figure 9).
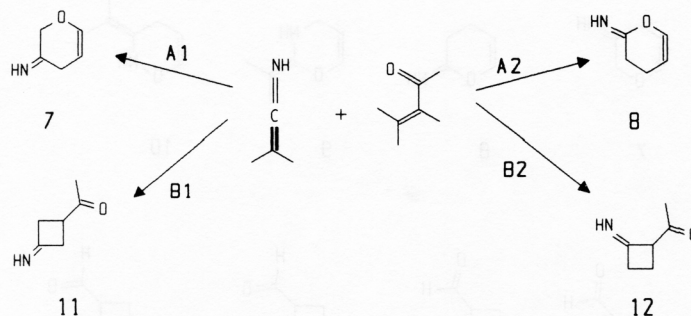
Figure 10. Cycloadducts resulting from the reaction of the ketenimine C=C double bond.

Since cycloadditions across the C=O double bond of acrolein (15–18 in Figure 9) seem to be energetically much less feasible,[15] the main focus of the following discussion is on reactions leading to products 7–14.

Reaction of the ketenimine C=C double bond leads to two isomeric [4+2] (7,8) and [2+2] cycloadducts (11,12, Figure 10), respectively. Optimized structures of transition states and products, as well as relevant energetic (heats of formation in kcal mol⁻¹) and structural aspects, are shown in Figures 11–13. Although starting from 12, a transition state could be located, this structure appears to connect 8 and 12 (i.e. a transition state for rearrangement of the two cycloadducts 8 and 12) rather than 12 and the separated reactants.

Reaction of the ketenimine C=N double bond also leads to two regioisomeric [4+2] (9, 10) and [2+2] cycloadducts (13, 14, Figure 14), respectively. Optimized structures of transition states and products for reactions A3, B3, A4, and B4 are shown in Figures 15–18. Energies relative to the two reactants, ketenimine ΔH_f = 44.3 kcal mol⁻¹) and cis-acrolein (ΔH_f = −16.3 kcal mol⁻¹), i.e. activation energies and heats of reaction, are summarized in Table I.
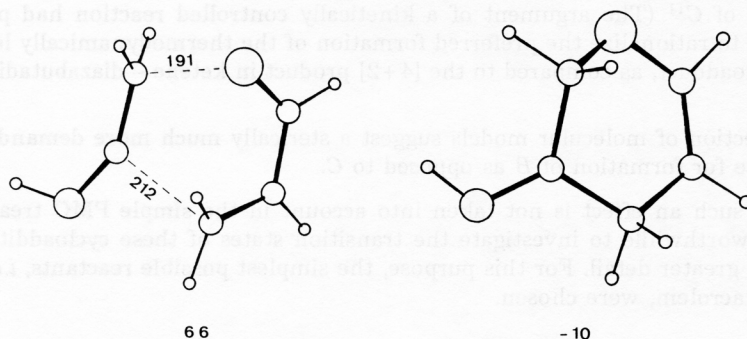

Figure 11. Optimized structures and heats of formation for the transition state and product of reaction A1.

TABLE I

Heats of reaction and activation energies (kcal mol^{-1})
for the reactions shown in Figures 10 and 14.

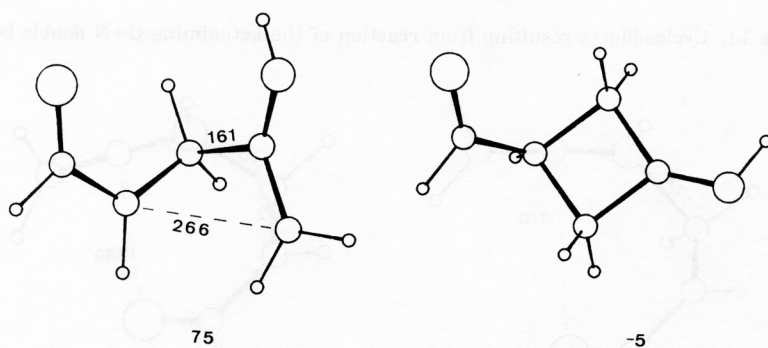| Reaction	TS1	E_{rel} INT	TS2	Product
A1	37.8	–	–	–37.6
B1	47.0	–	–	–32.5
A2	21.6	–	–	–38.4
B2	(20.1)	–	–	–32.1
A3	25.9	25.0	25.6	–21.2
B3	27.7	27.0	36.3	–12.2
A4	60.9	–	–	+6.3
B4	55.5	–	–	–12.7

75   -5

Figure 12. Optimized structures and heats of formation for the transition state and product of reaction *B1*.
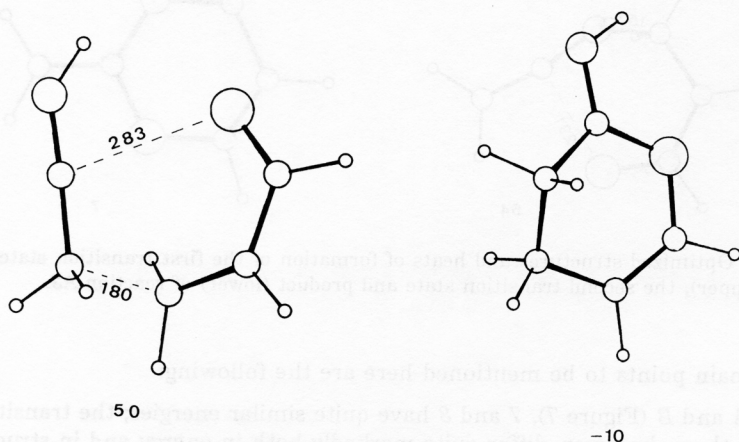

5 0   -10

Figure 13. Optimized structures and heats of formation for the transition state and product of reaction *A2*.
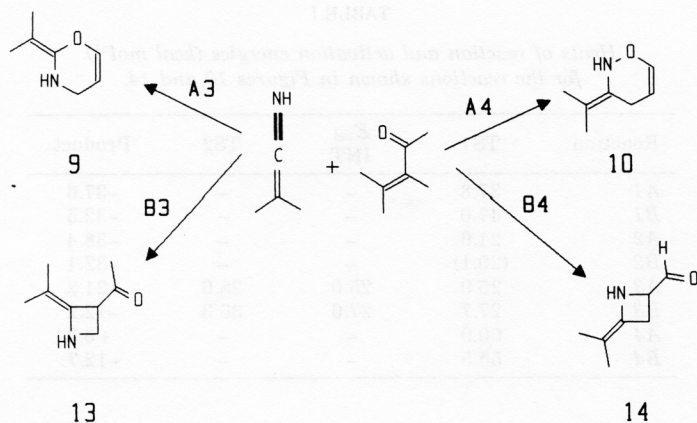
Figure 14. Cycloadducts resulting from reaction of the ketenimine C=N double bond.

Figure 15. Optimized structures and heats of formation of the first transition state and intermediate (upper), the second transition state and product (lower) of reaction *A3*.

The main points to be mentioned here are the following:

i)   Like *A* and *B* (Figure 7), *7* and *8* have quite similar energies; the transition states leading to them, however, differ quite markedly both in energy and in structure (Figure 11 and 13).

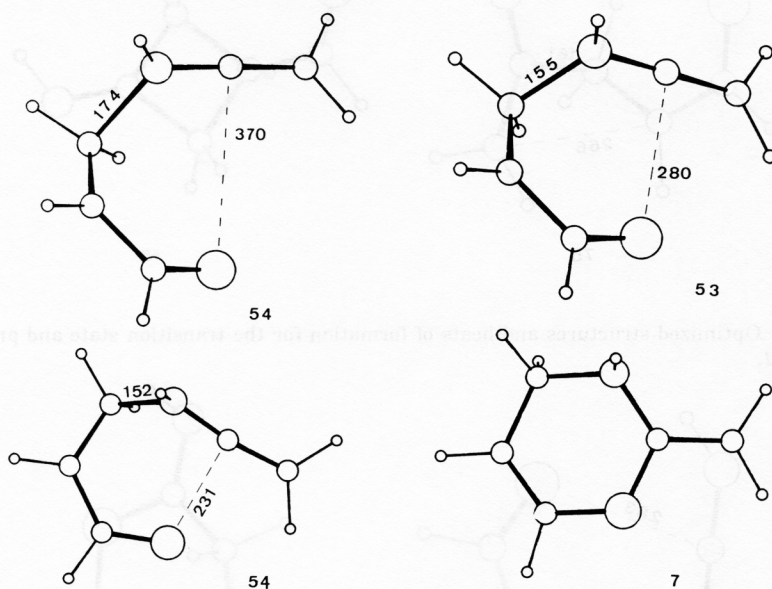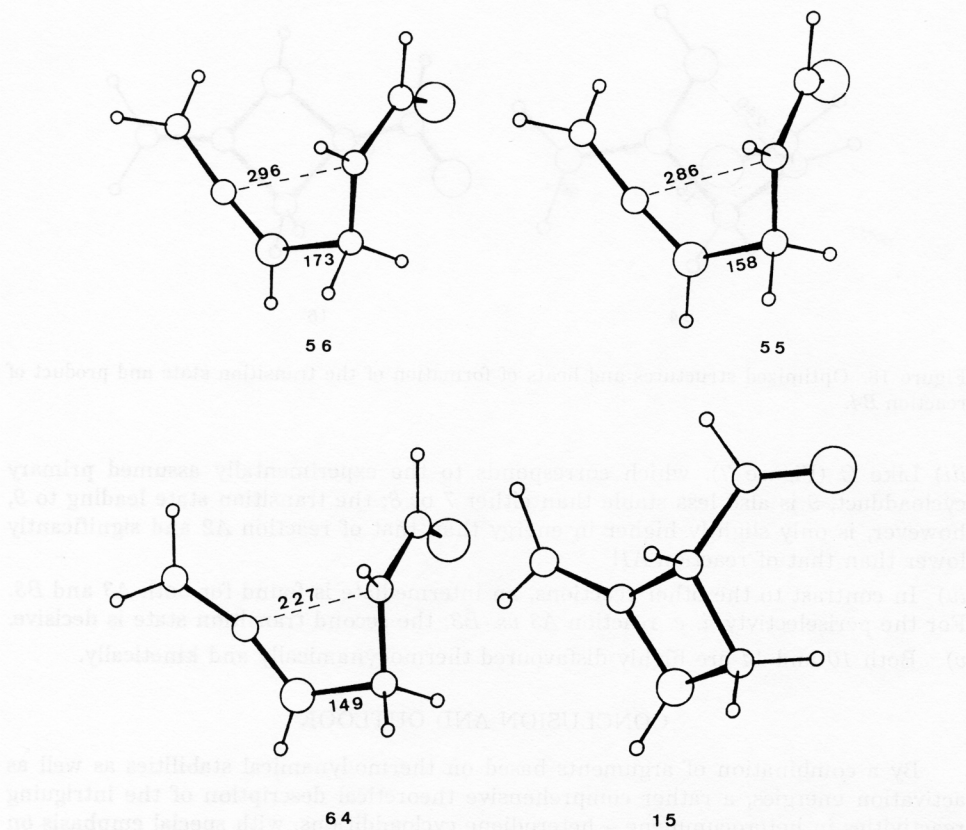*ii)*   Formation of the [2+2] cycloadduct *11* should be considerably less favourable.

Figure 16. Optimized structures and heats of formation of the first transition state and intermediate (upper), the second transition state and product (lower) of reaction *B3*.
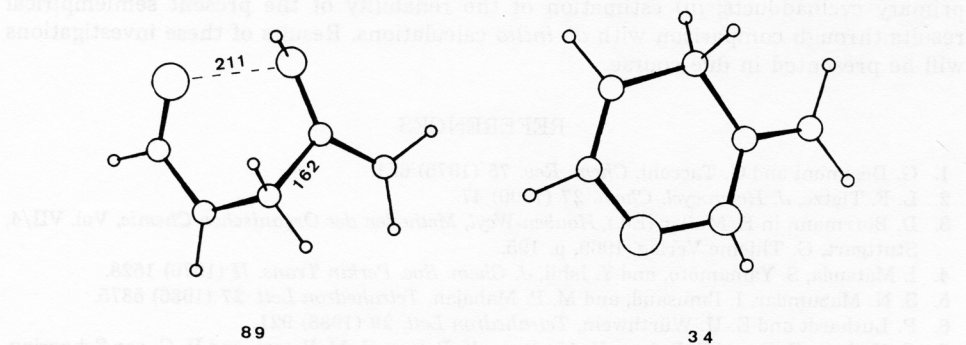

Figure 17. Optimized structures and heats of formation of the transition state and product of reaction *A4*.
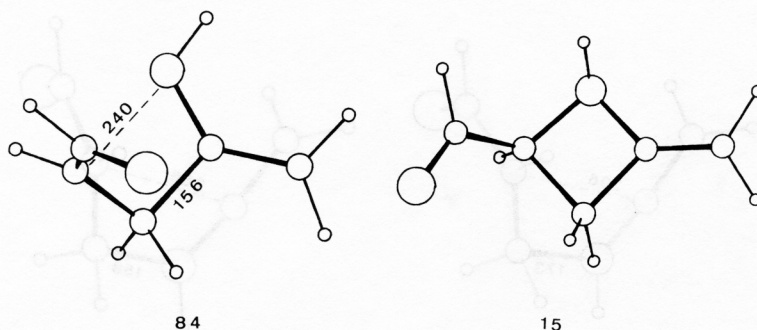
84   15

Figure 18. Optimized structures and heats of formation of the transition state and product of reaction *B4*.

iii) Like *C* (Figure 7), which corresponds to the experimentally assumed primary cycloadduct, *9* is also less stable than either *7* or *8*; the transition state leading to *9*, however, is only slightly higher in energy than that of reaction *A2* and significantly lower than that of reaction *A1*!

iv) In contrast to the other reactions, an intermediate is found for both *A3* and *B3*. For the periselectivty, *i. e.* reaction *A3 vs. B3*, the second transition state is decisive.

v) Both *10* and *14* are highly disfavoured thermodynamically and kinetically.

CONCLUSION AND OUTLOOK

By a combination of arguments based on thermodynamical stabilities as well as activation energies, a rather comprehensive theoretical description of the intriguing reactivities in heterocumulene – heterodiene cycloadditions, with special emphasis on their peri-, site-, and regiochemistry, can be given. Further work currently in progress concentrates on the following issues: *i*) effect of substituents on the structures and energies of transition states, especially with respect to steric effects; *ii*) influence of the post-SCF methods; *iii*) transition states for possible rearrangement reactions of the primary cycloadducts; *iv*) estimation of the reliability of the present semiempirical results through comparison with *ab initio* calculations. Results of these investigations will be presented in due course.

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15. W. M. F. Fabian, unpublished results.

SAŽETAK

Semiempirijski proračuni cikloadicije heterodien-heterokumulena

Walter M. F. Fabian i Gert Kollenz

4-Benzoil-supstituirani peteročlani heterociklički 2,3-dioni (npr. furadioni ili piroldioni) adiraju različite heterokumulene dajući heterocikle. Strukture produkata dobivenih u ovim reakcijama mogu se protumačiti početnom cikloadicijom [4+2] između heterodienskog sustava nastalog iz benzoilne skupine i endiciklične strukture veze C=C heterocikličkog prstena i heterokumulena, za kojom slijedi posebna, nova furadionska pregradnja. Premda su neke formalne cikloadicije [4+2] poznate, njihovom reaktivnošću dominiraju cikloadicije [2+2]. Za ketenimine, čini se da je ova reakcija prvi primjer cikloadicije [4+2]. Nakon prikaza nekih relevantnih eksperimentalnih zapažanja i semiempirijskih proračuna (AM1) na reaktantima, razmatraju se regioizomerni produkti i mogući međuprodukti. Kao najjednostavniji model, cikloadicije između akroleina i ketenimina korištene su da bi se locirala stanja dvanaest mogućih peri-, položajnih i regioizomernih produkata. Napokon, razmatra se pouzdanost ovih proračuna i neki izgledi za budućnost.