Trapping Intermediates in an [8 + 2] Cycloaddition Reaction with the Help of DFT Calculations
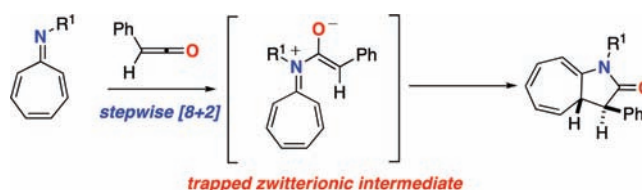
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ABSTRACT

trapped zwitterionic intermediate

DFT calculations predict that the [8 + 2] cycloaddition reaction between ketenes and 8-azaheptafulvenes occurs stepwise through antiaromatic zwitterionic intermediates. With adequate modifications of both the electronic properties of the ketene and the reaction conditions, these elusive intermediates have been successfully trapped and fully characterized (X-ray), thus confirming the predicted stepwise nature of the transformation.

Cycloaddition reactions play a pivotal role in modern organic synthesis because of their ability to increase the molecular complexity in a single synthetic step.[1] It is generally accepted that while thermal cycloadditions usually involve $(4n + 2)$ π electrons participating in the starting materials, $4n$ π electrons are required in cycloadditions occurring with photochemical activation.[2] Both type of transformations have been traditionally understood according to the Woodward−Hoffmann rules,[3] which are related to the principles of orbital symmetry.

Nowadays, the initial idea of a concerted reaction mechanism for cycloaddition reactions has evolved to a range of different possibilities, i.e., from fully synchronous and concerted transformations to highly asynchronous or even stepwise mechanisms involving biradicals or zwitterionic intermediates. For instance, the concerted or stepwise mechanism of 1,3-dipolar reactions was hotly debated in the past, but most of these reactions have been determined

to be concerted.[4] Despite many cycloaddition processes having been suggested to proceed through stepwise mechanisms, the experimental isolation of the corresponding intermediates is still challenging. The main reason underlying this difficult task is the high reactivity of these intermediate species.

(1) (a) *Cycloaddition Reactions in Organics Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2001. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002.

(2) Sankararaman, S. *Pericyclic Reactions—A Textbook: Reactions, Applications and Theory*; Wiley: Weinheim, 2005.

(3) (a) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; VCH: Weinheim, 1970.

(4) (a) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291. (b) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285. (c) Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. H.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227. (d) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (e) McDouall, J. J. W.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, H. B. *J. Am. Chem. Soc.* **1987**, *109*, 4642. (f) Hiberty, P. C.; Ohanessian, G.; Schlegel, H. B. *J. Am. Chem. Soc.* **1983**, *105*, 719. (g) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291. (h) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285. (i) Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181.

(5) Some examples of trapped or detected zwitterions in different cycloaddition reactions: (a) Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2233. (b) Quiao, G. G.; Andraos, J.; Wentrup, C. *J. Am. Chem. Soc.* **1996**, *118*, 5634. (c) Lecea, B.; Arrastia, I.; Arrieta, A.; Roa, G.; López, X.; Arriortua, M. I.; Ugalde, J. M.; Cossío, F. P. *J. Org. Chem.* **1996**, *61*, 3070. (d) Sustmann, R.; Tappanchai, S.; Bandmann, H. *J. Am. Chem. Soc.* **1996**, *118*, 12555. (e) Martelli, G.; Spunta, G.; Panunzio, M. *Tetrahedron Lett.* **1998**, *39*, 6257. (f) Panunzio, M.; Bacchi, S.; Campana, E.; Fiume, L.; Vicennati, P. *Tetrahedron Lett.* **1999**, *40*, 8495. (g) Bandini, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. A. *Org. Lett.* **2000**, *2*, 1077. (h) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (i) Machiguchi, T.; Okamoto, J.; Takachi, J.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2003**, *125*, 14446. (j) Machiguchi, T.; Okamoto, J.; Morita, Y.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2006**, *128*, 44.

Nevertheless, the wise selection of substituents and reaction conditions has allowed the isolation and characterization of intermediates in very specific transformations.[5] However, interest in capturing intermediates in stepwise cycloadditions remains unabated.
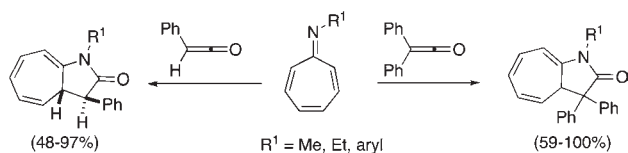
Within the context of our ongoing work in the reaction mechanims and synthetic applications of cycloaddition reactions involving organic and organometallic reagents,[6] the [8 + 2] cycloaddition reaction of 8-azaheptafulvenes and ketenes attracted our attention.[7] This process, originally described by Kanemasa and co-workers,[8a] exclusively leads to the corresponding *trans*-[8 + 2] cycloadducts at room temperature in excellent yields (Scheme 1).[8] Information about the concerted or stepwise nature of these reactions was not provided. The possibility of using very different ketenes and reaction conditions renders this transformation a good target for a combined computational-experimental study of its reaction mechanism. Reported herein is the computational (DFT) evidence of the stepwise nature of the process, which led us to the experimental isolation and complete characterization of the involved intermediates.

DFT calculations (B3LYP and M06-2X/6-311+G(d) levels)[9] were carried out to study the [8 + 2] cycloaddition reaction between phenylketene **1** and 8-azaheptafulvene **2a** (Scheme 2). Our calculations suggest that the reaction occurs stepwise through the initial nucleophilic attack of the nitrogen atom of the cyclic imine to the electrophilic carbonyl group of the ketene (via transition state **TS1**).

This process yields zwitterion intermediate **3**, which readily evolves to the final cycloadduct **4** through a ring closure (in a conrotatory process) via **TS2**, a saddle point associated with the final C−C bond formation.[10] Therefore, this process resembles the stepwise mechanism of the [2 + 2] cycloaddition reaction between ketenes and imines to form 2-azetidinones.[11]
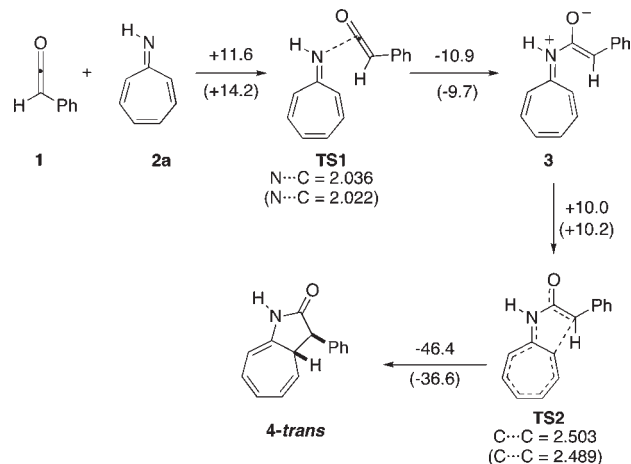
[a] Values close to the arrows indicate the computed PCM corrected free energies (ΔG_{298}, at 298 K in kcal/mol) using CH_2Cl_2 as solvent. Bond lengths are given in angstroms. All data have been computed at the M06-2X/6-311+G(d) level and B3LYP/6-311+G(d) level (in parentheses).

It has been suggested that the [8 + 2]-cycloaddition reaction between 8-azaheptafulvenes and ethynyl-Fischer carbene complexes occurs through similar zwitterionic intermediates[12] because of the significant contribution of the corresponding resonance form where the positive charge is delocalized within the ring. This species, which resembles the tropyl cation, should possess an important aromatic character and, therefore, an important degree of stability favoring the stepwise mechanism. However, the computed positive values of the nuclear independent chemical shift (NICS)[13] at the [3,+1] ring critical point of the electron density,[14] as defined by Bader[15] (NICS = +5.3 ppm), and the corresponding out-of-plane component

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(8) (a) Yamamoto, K.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1977**, *6*, 91. (b) Takaoka, K.; Aoyama, T.; Shioiri, T. *Heterocycles* **2001**, *54*, 209.

(9) See the computational details in the Supporting Information.

(10) The corresponding reaction path leading to the *cis* isomer was also computed. Our calculations indicate that selection occurs in the initial attack of the cyclic imine to the ketene. This is similar to the process involving ketenes derived from Fischer carbene complexes. See: Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *J. Am. Chem. Soc.* **2008**, *130*, 13892.

(11) For a recent review, see: (a) Cossío, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925. Selected computational studies on the mechanism of the Staudinger reaction: (b) Sordo, J. A.; González, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (c) Cossío, F. P.; Ugalde, J. M.; López, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (d) Assfeld, X.; Ruiz-López, M. F.; González, J.; López, R.; Sordo, J. A.; Sordo, T. L. *J. Comput. Chem.* **1994**, *15*, 479. See also ref 5c.

(12) Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A. L.; Tomás, M. *Chem.—Eur. J.* **2009**, *15*, 8800.
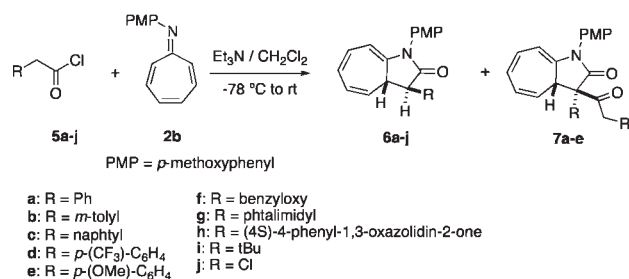
(13) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842.

(14) NICS values have been computed at the (3,+1) ring critical point of the electron density due to its high sensitivity to diamagnetic effects and its unambiguous character to define the "center" of a ring in terms of electron density.

(15) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Clarendon: Oxford, 1990.

(NICS(1)$_{zz}$ = +7.4 ppm) clearly reflect the antiaromatic nature of intermediate **3**.[16]

a: R = Ph
b: R = *m*-tolyl
c: R = naphtyl
d: R = *p*-(CF$_3$)-C$_6$H$_4$
e: R = *p*-(OMe)-C$_6$H$_4$

f: R = benzyloxy
g: R = phtalimidyl
h: R = (4S)-4-phenyl-1,3-oxazolidin-2-one
i: R = tBu
j: R = Cl

The combination of an antiaromatic intermediate and a favorable ring closure makes the isolation or trapping of the zwitterionic intermediates **3** unpromising. However, as stated above, the initial reagents are easily modifiable in their reactivities, and reaction conditions can be also tuned to achieve the desired endeavor. To this end, we first performed the reaction between *N*-*p*-methoxyphenyl-8-azaheptafulvene **2b** and phenylketene at −78 °C. An additional equivalent of ketene (generated in situ from phenylacetyl chloride and Et$_3$N at −78 °C) was used to quench the corresponding intermediate by avoiding the easy ring closure which leads to the [8 + 2] cycloadduct. Thus, the reaction of 2 equiv of acyl chloride **5a** and 1 equiv of azafulvene **2b** produced a mixture of two compounds in a 38:62 molar ratio (Scheme 3 and Table 1). The first compound was characterized as the expected *trans* [8 + 2] cycloadduct **6a** by comparison of its spectroscopic data with those reported in the literature.[7,8] Single crystals of the new compound **7a** suitable for X-ray diffraction analysis were grown in hexanes/ethyl acetate solution (Figure 1). Compound **7a** contains two molecules of ketene and one imine and can be viewed as the result of the trapping of zwitterionic intermediate **3**, which reacts with the excess of

ketene by nucleophilic attack of the enolate carbon atom. Subsequent H-abstraction of the highly acidic hydrogen atom at the central carbon atom of the dicarbonyl moiety (either by the base present in the reaction or by the formation of the corresponding enol) promotes the final ring closure forming **7a**.[17]
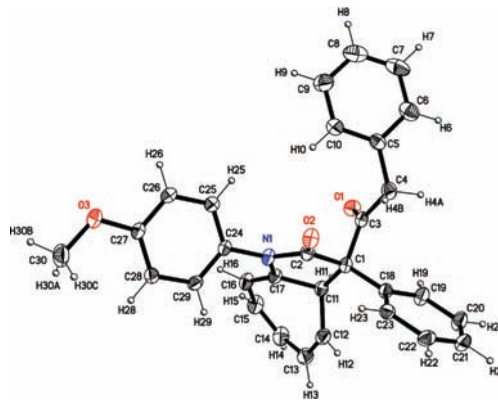

Figure 1. ORTEP diagram of compound **7a**.

To discard the possibility of the formation of **7a** by the base-promoted nucleophilic addition of the enolate of **6a** to the additional ketene equivalent, the isolated [8 + 2] cycloadduct **6a** was reacted under reaction conditions identical to those forming **7a** (Et$_3$N/CH$_2$Cl$_2$ and **1a** at −78 °C to rt). Compound **6a** was recovered unaltered (together with some minor decomposition products of unknown structure), and no traces of compound **7a** were observed in the crude reaction mixtures. This control experiment rules out the possibility of this alternative process. Therefore, the isolation of this new compound **7a** nicely confirms the computationally predicted stepwise nature of the cycloaddition reaction between azaheptafulvenes and ketenes.

To check the generality of this finding, different acyl chlorides were tested as starting reactants against **2b** (Scheme 3).[18] From the data in Table 1, it is clear that

Table 1. Cycloaddition Reactions of Acyl Chlorides **5** and 8-Azaheptafulvene **2b**

| entry	acyl chloride	6/7 ratio	yield^a (%)	others
1	**5a**	40:60	42 (17:25)	
2	**5b**	68:32	44 (30:14)	
3	**5c**	95:5	26 (21:5)	
4	**5d**	76:24	42 (32:10)	
5	**5e**	20:80	80 (16:64)	
6	**5f**	100:0	6	*cis*-**6f** (3%)
7	**5g**	100:0	59	*cis*-**6g** (6%)
8	**5h**	100:0	78	
9	**5i**	100:0	43	amide (25%)
10	**5j**	100:0	74	

^{a} The first value indicates the combined yields. In parentheses, the first value corresponds to the isolated yield of **6** whereas the second one indicates the isolated yield of **7**.

(16) The antiaromaticity of **3** (nonplanar) is in part responsible for the computed endergonicity of its formation (+0.7 kcal/mol) and the high exergonicity (−36.4 kcal/mol) computed for the final ring-closure step.

(17) It is thought that compound **7a** may be the result of the trapping of the intermediate **3** by a molecule of acid chloride. However, the reaction conditions used (−78 °C, acid chloride/Et$_3$N, the so-called "direct addition") ensure the complete transformation of the acid chlorides into the corresponding ketenes. See: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers, Inc.: New York, 1992; Chapter 6.

(18) Typical procedure: To a solution of the corresponding acid chloride **5** (2.2 equiv) in CH$_2$Cl$_2$ (3 mL/ mmol) at −78 °C was added Et$_3$N (5 equiv) dropwise. The mixture was stirred at −78 °C for 20 min, after which a solution of azaheptafulvene **2b** (1 equiv) in CH$_2$Cl$_2$ (1.5 mL/mmol) was slowly transferred via cannula (dropwise) to the generated ketene. The resulting mixture was stirred at −78 °C for 30 min and then warmed to room temperature overnight. The solvent was then evaporated in vacuo and the crude mixture purified by flash column chromatography using the mixture of eluents indicated for each case (see the Supporting Information) rendering a mixture of compounds **6** and **7**.
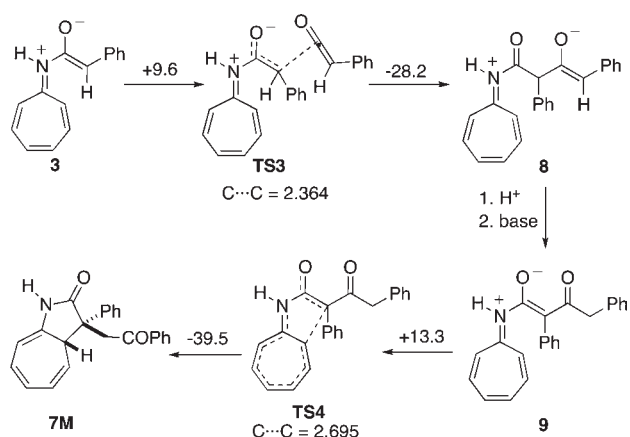
the zwitterionic intermediate can be trapped only when R = aryl substituent (entries 1−5). Alkyl- or heteroatom-substituted compounds (entries 6−10) produce the expected *trans* [8 + 2] cycloadduct and, strikingly, also the elusive *cis* [8 + 2] cycloadduct for R = benzyloxy or phtalimidyl (albeit in very low reaction yields). These results clearly reflect the crucial role of the electronic properties of the ketene (and azafulvene) in trapping the zwitterionic intermediate **3**, as we had initially envisaged. Electron-donating groups (such as OMe) placed in the para position of the phenyl group increase the overall yield of the process and strongly favor the formation of species **7**. Although these experiments have been planned to check the predicted stepwise nature of the [8 + 2] cycloaddition, the latter result indicates that the new heterocycle can indeed be produced in good yields. In contrast, the absence of π-donor groups or the presence of electron-withdrawing groups (such as CF_3) lead only to moderate overall reaction yields (up to 44%, entry 2, Table 1) and mainly to the formation of cycloadduct **6**. Moreover, hetereoatom-substituted ketenes as well as sterically hindered terbutylketene failed to trap intermediate **3**. The reasons for this behavior are not clear, but probably the more reactive (derived from heteroatom substituted ketenes) or sterically hindered (*tert*-butyl)

intermediates make the reaction with a second ketene molecule more difficult.

In order to fully understand the formation of **7**, we have computationally explored the nucleophilic attack of zwitterion **3** to the additional ketene equivalent (Scheme 4). Our calculations indicate that the transition state associated with this process (**TS3**) lies 1.3 kcal/mol below **TS2**, which is associated with the formation of the [8 + 2] cycloadduct (Scheme 2). Therefore, the formation of **7** should be kinetically favored. Although both processes are essentially different, i.e., one is intermolecular whereas the other is intramolecular, and obviously the reaction rate depends on the concentrations of the involved species, it can be suggested that there is a competition between both processes rendering a mixture of products (as experimentally observed) in view of the low barrier energy difference of both transformations. Finally, intermediate **9**, formed from zwitterion **8**, leads to the observed cycloadduct **7** through a similar ring-closure step via **TS4** (activation barrier of 13.3 kcal/mol).

In summary, we have computationally predicted that the [8 + 2] cycloaddition reaction between ketenes and azaheptafulvenes occurs in a stepwise manner through an antiaromatic zwitterionic intermediate. With adequate modifications of both the electronic properties of the ketene reagents and the reaction conditions and stoichiometry, we were successful in trapping this elusive intermediate. The zwitterion was trapped as a 2:1 ketene/azafulvene adduct formed by reaction of the enolate carbon atom of **3** with a second molecule of ketene followed by base-promoted ring closure. The stepwise nature of the [8 + 2] cycloaddition reaction between ketenes and 8-azaheptafulvenes is therefore confirmed. The computational−experimental quest for additional examples of nonconcerted cycloaddition reactions is underway in our laboratories.

Supporting Information Available. Experimental details and NMR spectra of isolated compounds, computational details, Cartesian coordinates (in Å), and free energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.