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Evidence for a Concerted [4 + 1]-Cycloaddition between Electron-Rich Carbenes and Electron-Deficient Dienes

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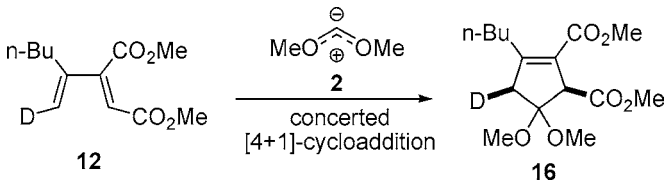
ABSTRACT

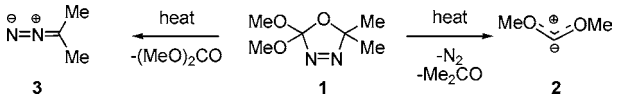


Results from the thermal reactions of deuterated dienes 12–15 provide evidence of the concertedness of the [4 + 1]-cycloaddition between dimethoxycarbene and electron-deficient dienes. Other evidence suggests that the main pathway is a concerted [4 + 1]-cycloaddition rather than a cyclopropanation followed by a vinylcyclopropane rearrangement. Ionic pathways can become competitive when steric or geometrical constraints are present.

The [4 + 2]-cycloaddition between alkenes and dienes is highly valued by synthetic chemists partly because of the high predictability of the structural and stereochemical outcomes of the reaction.[1] The concertedness of the bond forming process in the [4 + 2]-cycloaddition helps to make this reaction a predictable one. We have recently reported a series of inter- and intramolecular [4 + 1]-cycloadditions between alkoxycarbenes and electron-deficient dienes,[2] and circumstantial evidence indicated that the mechanism of the reaction may be concerted in certain cases. However, it is believed that nucleophilic electron-rich carbenes, such as 1,1-dialkoxycarbenes, generally react in a stepwise, ionic fashion with electrophiles such as vinyl ketenes,[3] vinyl isocyanates,[4] and other unsaturated systems.[5] It was thus easy to assume that the same was true with electron-deficient dienes. We now provide evidence that the mechanism of the intermolecular cycloaddition is indeed concerted in the absence of detrimental steric or geometrical factors. This finding could have a large impact on future use of this methodology.

We revisited in more detail the cycloaddition of dimethyl *trans*,*trans*-muconate **4** and dimethoxycarbene **2**, generated from oxadiazoline **1**[6] (Scheme 1). Several mechanistic pathways were considered and are displayed in Scheme 2.

Scheme 1. Generation of Dimethoxycarbene **2**



Heating **4** and **1** (5 equiv) in chlorobenzene at 132 °C gave exclusively cyclopentene *cis*-**6** (Table 1, entry 1). Intermolecular reactions give low conversion and low yields partly because of competing reactions with 2-diazopropane **3** to give products such as compounds **10** and **11** (Scheme 2). Some *trans*-**6** was formed when the heating was continued for >15 h, and it became the predominant product after 3 days of heating. Conversely, heating pure cyclopentenes *cis*-**6**

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1990. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, p 315. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(2) Spino, C.; Rezaei, H. K. Dupont-Gaudet, F. Bélanger, *J. Am. Chem. Soc.* **2004**, *126*, 9926−9927.

(3) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263−264.

(4) (a) Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848−12849. (b) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664−3670.

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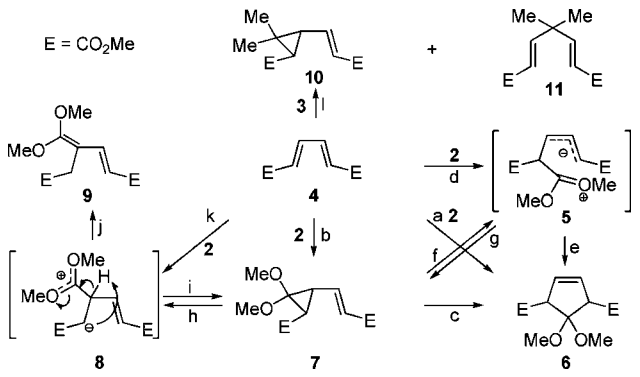
Scheme 2. Mechanistic Pathways for the Reaction between **4** and **2**



or *trans*-**6** for 3 days in chlorobenzene left them unchanged. We repeated the heating of *cis*-**6** or *trans*-**6** in the presence of DMAD, *p*-benzoquinone, H_2O, or other additives to intercept any ionic intermediate that could form during their interconversion[7] but recovered them intact. Therefore, whatever the operative pathway, the overall process is not under equilibrium. The slow epimerization of *cis*-**6** to *trans*-**6** during the reaction could originate from an enolization process caused by basic species in the reaction medium.

Importantly, when toluene was used as solvent, a significant amount of cyclopropane adduct **7** was isolated (Table 1, entry 2). The formation of cyclopropane **7** was also observed in chlorobenzene after 1 h of reaction, but its disappearance is fast (within 4 h). The cyclopropyl ring in **7** and the double bond had the *trans* geometry. When we became aware of the formation of **7**, we assumed that cyclopentenes **6** were formed exclusively from the rearrangement of **7**. However, when **7** was heated in either toluene (111 °C) or chlorobenzene (132 °C) for 17 h, the major product was compound **9** accompanied by a mixture of *cis*-**6** and *trans*-**6** (entries 3 and 4). When pure **9** was heated at 132 °C in chlorobenzene for >17 h, *it did not* revert to either cyclopentenes **6** or cyclopropane **7**: only starting material **9** and decomposition products were observed by ^{1}H NMR. Compound **9**, however, degrades quickly, with no trace of either **6** or **7** being observed when resubjected to the reaction conditions in toluene or chlorobenzene, explaining why it is never observed in any of the reactions between **4** and **2** despite careful monitoring by GCMS and ^{1}H NMR. It seems possible, therefore, that pathway b (Scheme 2) contributes only marginally to the overall formation of **6** during the reactions between **4** and **2**. Pathway b may be a competitive not a transitional one.

From this information, we speculated that, although ionic pathways (d and f) are available to this reaction, the main operative pathway is concerted—perhaps even a true concerted [4 + 1]-cycloaddition (pathway a). We prepared dienes **12**−**15** deuterated at position 4 for the purpose of resolving this question (Scheme 3). Dienes **12** and **13** were converted to cycloadducts **16** and **17**, respectively, when refluxed in toluene for 9 h in the presence of 10 equiv of **1** (Table 1, entries 5 and 6). Only a small loss of stereochemical integrity occurred in both cases. When resubjected to the reaction conditions for 9 h, pure **16** or pure **17** remained intact, with no detectable epimerization. Dienes **14** and **15** were less efficiently converted to mixtures of **16** and **17** in 19 h with a more significant loss of stereochemical information (entries 7 and 8). Compounds **18**−**20** came from the reaction of dienes **12**−**15** with **3**. Dienes **12** and **13** were separately heated in toluene at 111 °C for 9 h and were recovered in ratios of 83:17 and 82:18, respectively. This isomerization could account for the small loss in stereochemical integrity during their cycloaddition with **2**. However, heating **14** or

Scheme 3. Cycloaddition of Dienes **12**−**15** with Carbene **2**

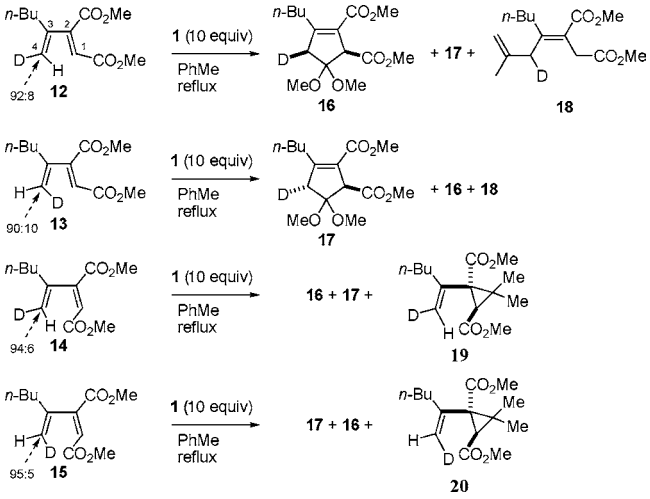


Table 1. Thermal Reactions of **4**, **7**, or Dienes **12**−**15**

entry	S.M.	*E*:*Z* ratio	solvent	temp (°C)/ time (h)	yield (%)	products (ratio)[a]
1	**4**	1:0	PhCl	132/4	38[b]	*c*-**6**, *t*-**6**, **7** (1:0:tr)
2	**4**	1:0	PhMe	111/17	42[b]	*c*-**6**, *t*-**6**, **7** (1:0:1)
3	**7**	1:0	PhMe	111/17	100[a]	*c*-**6**, *t*-**6**, **9** (8:1:40)
4	**7**	1:0	PhCl	132/17	81[b]	*c*-**6**, *t*-**6**, **9** (4:1:16)
5	**12**	92:8	PhMe	111/9	43[b,c]	**16**, **17** (86:14)
6	**13**	10:90	PhMe	111/9	44[b,c]	**16**, **17** (14:86)
7	**14**	94:6	PhMe	111/19	23[b,d]	**16**, **17** (40:60)
8	**15**	5:95	PhMe	111/19	30[b,e]	**16**, **17** (60:40)

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] +14−17% yield of **18**. [d] +24% yield of **19**. [e] +29% yield of **20**.

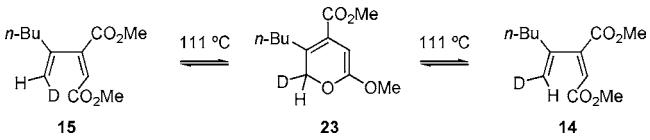
(5) For a review on many uses of such carbenes as well as mechanistic considerations, see: Warkentin, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2161−2169 and references therein.

(6) See ref 5 and: (a) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751−8752. (b) Kassam, K.; Pole, D. L.; El-Saidi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1994**, *116*, 1161−1162.

(7) Nair has intercepted ionic intermediates derived from dimethoxycarbene **2** with a variety of electrophiles. See: (a) Nair, V.; Vinod, R. A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899−907. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Balagopal, L. *Synlett* **2003**, 1446−1456. See also: (c) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295−1326.

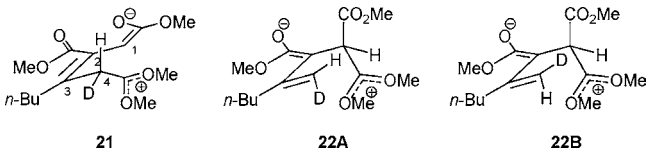
15 in refluxing toluene led to much interconversion within 9 h (see Supporting Information). Because only **14** and **15** isomerize rapidly and because only the alkene bearing the deuterium isomerizes in each case, we believe that the isomerization occurs mostly via **23** by a reversible electrocyclic reaction (Scheme 4).

Scheme 4. Isomerization of Dienes **14** and **15**



15 **23** **14**

Were an ionic mechanism operative, addition to position 4 (see Figure 1) of any of the dienes would create intermedi-



21 **22A** **22B**

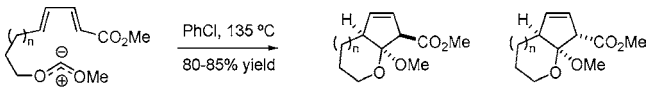
Figure 1. Purported ionic intermediates **21**, **22A**, and **22B**.

ate **21** that could not collapse preferentially to either **16** or **17**, assuming fast bond rotation.[8] If addition occurred at position 1, intermediate **22A** would be formed from either **12** or **14** and the ratio of **16**:**17** should have been the same for the reaction of **12** and **14** (the same can be said of **13** and **15** via **22B**). This is clearly not the case.

A more likely explanation is that dienes **12** and **13** react with **2** in a concerted symmetry-allowed[9] [4 + 1]-cycloaddition. There are very few examples of [4 + 1]-cycloadditions involving carbenes believed to be concerted, and they do not have general utility, working only with special dienes and carbenes.[10] We cannot rule out a cyclopropanation followed by a concerted rearrangement, though results from the rearrangement of **7** cast doubts on this possibility. Careful monitoring of the reactions with dienes **12**−**15** failed to reveal the formation, at any time, of dimethoxycyclopropane adducts or their derivatives. However, because the mixtures formed during the reactions are complex, it is possible that we could not detect small amounts. Ionic pathways may become competitive in the case of **14** and **15** because the *s-cis* conformation required for a concerted [4 + 1]-cycloaddition is higher in energy, which could explain the partial loss of stereochemical integrity. Note that the observed results represent a worst-case scenario since the thermal isomerization of **14** and **15** may account for some or all of the loss in stereochemical integrity. When the reaction of **14** with **2** was monitored in time, the ratio of **17**:**16** was 70:30 after 6 h of reflux and slowly degraded to 65:35 (12 h) and 60:40 (19 h). The ratio of recovered **14**/**15** also changed and was 55:45 after 19 h.

This hypothesis also explains our previous results from the much higher yielding intramolecular cycloadditions, which was difficult to interpret in terms of a purely ionic mechanism (Scheme 5).[2] Indeed, in the case of compound

Scheme 5. Intramolecular [4 + 1]-Cycloadditions



24a n = 0
24b n = 1
24c n = 2

25a n = 0 5:95
25b n = 1 70:30
25c n = 2 >95:5

26a n = 0
26b n = 1
26c n = 2

24a having a short tether, conformational constraint forced an ionic mechanism that resulted in a *trans* configuration of the ester and the ring (**26a**). However, as the tether becomes longer and the conformational constraint eases up, *cis*-adducts **25b** and **25c** become the major compounds. The difference is best explained by a change over to a concerted [4 + 1]-cycloaddition mechanism.

We have thus provided evidence that the main mechanism of the intermolecular [4 + 1]-cycloaddition between dimethoxycarbene and electron-poor dienes is concerted. This may have far reaching implications for organic synthesis in general. Although we still do not yet know the full scope of this reaction, chemists may now wish to consider using such a [4 + 1]-cycloaddition in their synthesis knowing the stereochemical integrity of their diene may be preserved. Remarkably, we have performed intermolecular [4 + 1]-cycloadditions that yielded up to 68% cycloadduct, and the intramolecular version usually gives good to excellent yields of cycloadducts.[2] The ionic mechanism is, however, close in energy and can operate when there are constraints to the concerted pathway. The intramolecular version of the reaction is believed to follow the same rule. It appears that cyclopropanation can be a competitive pathway and not one that leads necessarily to the cyclopentene. Future studies may help establish a more thorough understanding of the factors influencing the mechanism of this reaction.

Acknowledgment. We thank the Université de Sherbrooke, CRSNG Canada, and FQRNT Québec for financial support.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) We wish to note that, if these cycloadditions were proceeding via ionic intermediates, such as **21**, that would collapse before any bond rotation occurred, the stereochemical result would be equivalent to that of a concerted reaction. Proving or disproving "true concertedness" will require many more experiments and calculations, and it is beyond the scope of this study.

(9) Fujimoto, H.; Hoffmann, R. *J. Phys. Chem.* **1974**, *78*, 1167−1173.

(10) There are few examples of [4 + 1]-cycloadditions involving carbenes believed to be concerted. See: (a) Burger, U.; Gandillon, G. *Tetrahedron Lett.* **1979**, *20*, 4281−4284. (b) Le, N. A.; Jones, M., Jr.; Bickelhaupt, F.; de Wolf, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 8941−8943. (c) Kraakmna, P. A.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1989**, *111*, 8534−8535 and references cited therein.