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Concerning the Reactivity of PTAD with Isomeric Dienes: The Mechanism of the Diels−Alder Cycloaddition

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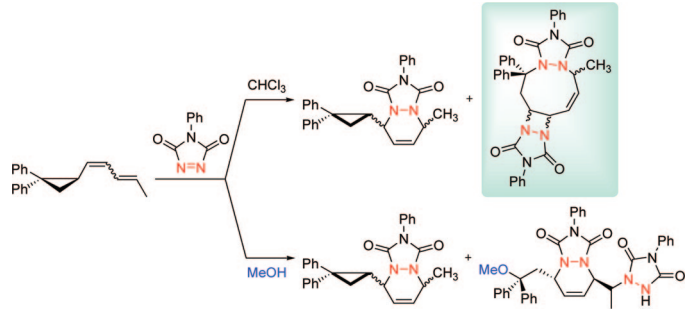
ABSTRACT



Cyclopropyl substituted dienes are employed as mechanistic probes in the triazolinedione Diels−Alder (DA) reaction. In aprotic and protic solvents, apart from the DA adducts that bear an intact cyclopropyl group, complicated and rearranged products are also obtained. These results provide solid evidence for the involvement of an open intermediate with a lifetime greater than 2×10^{-12} s.

Triazolinedione (RTAD, R = M for methyl and R = P for phenyl) is a strong electron acceptor and one of the most powerful enophiles as well as dienophiles.[1] RTADs afford ene products (*N*-allylurazoles)[2] or [2 + 2] adducts (1,2-diazetidines)[3,4] with alkenes and undergo DA reactions with conjugated dienes.[4,5] The latter class of reactions is useful in characterizing dienes,[6] protecting diene moieties,[7] isolating dienes from complex reaction mixtures,[8] and trapping unstable or volatile intermediates.[9]

The stereochemistry of the DA adducts from the reaction of RTAD with substituted 1,3-butadienes[10] is consistent with both concerted and stepwise mechanisms, depending on the substituents. For example, the addition of PTAD to the (*E*,*E*)- or (*Z*,*E*)-2,4-hexadiene was stereospecific according to the Woodward−Hoffmann rules, whereas reactions of RTAD with (*Z*,*Z*)-2,4-hexadiene and (*Z*,*Z*)-1,4-di-*tert*-butoxy-1,3-butadiene showed a lack of stereospecificity. Moreover, when RTAD reactions with the aforementioned substrates were

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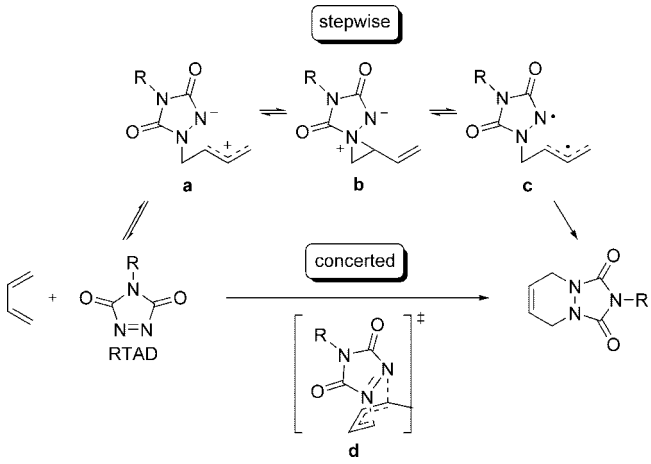
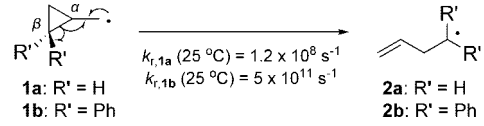
carried out in MeOH or acetone, the proposed aziridinium imide intermediate (AI; **b**, Scheme 1) was trappable affording

Scheme 1. Stepwise and Concerted Mechanistic Pathways for the Triazolinedione DA Reaction



the corresponding MeOH insertion adducts. Generally, it was concluded that dienes, which cannot easily adopt the *s-cis* conformation, react via a stepwise mechanism involving the formation of an AI intermediate in equilibrium with a 1,4-biradical or 1,4-dipolar (**a** or **c**, Scheme 1).[11] On the other hand, when the *s-cis* conformation of the diene moiety is not sterically precluded, a concerted mechanism is favored.[10a,12] Likewise, theoretical calculations with RTADs indicated that both concerted (with a highly asynchronous transition state **d**, Scheme 1) and stepwise pathways may occur, depending on the diene structure.[12b,13]

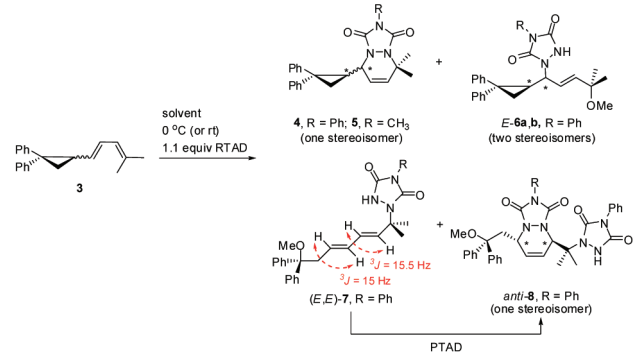
Our research aim was to reinvestigate the mechanism of this classical DA reaction between RTAD and dienes. The main focus was to ascertain precisely the possible involvement of an open biradical/dipolar intermediate in the title reaction. For this purpose, we used highly informative substrates which bear the 2,2-diphenylcyclopropyl group as a mechanistic probe. It is noteworthy that substituted cyclopropyl groups have been used as traps for other radical intermediates,[14] since they involve the rapid rearrangement of the cyclopropylcarbinyl radical (**1a**) to homoallylcarbinyl radical (**2a**) (eq 1).[15] Newcomb and co-workers reported that 2,2-diphenylcyclopropylcarbinyl radical (**1b**) rearranges rapidly with experimental rate constant of 5×10^{11} s^{-1} at rt.[16] This probe is often used as a *radical clock*[17] to quantify a radical lifetime.



(1)

In the present work, the cyclopropyl substituted dienes *Z*-**3** and *E*/*Z*-**3** were prepared (Scheme 2).[18] Notably, we were able to isolate the *Z*-**3** from the *E*/*Z*-**3** mixture by the exclusive reaction of tetracyanoethylene (TCNE) with the *E*-**3** isomer.[19] Initially, we carried out the RTAD (1.1 equiv) reactions with *E*/*Z*-**3** at 0 °C (or rt). When the reaction solvent was $CHCl_3$, apart from the formation of unidentified products, the unrearranged DA adduct **4** (R = Me) or **5** (R = Ph) was detected (entry 1, Scheme 2). Interestingly, when the same reaction was conducted in the presence of 50 equiv of MeOH, compounds **4**, *E*-**6a,b**, (*E*,*E*)-**7** and *anti*-**8** were obtained as the only products (entry 2). The *anti*-configuration of adduct **8** was confirmed by NOE experiments.[18] The above-mentioned four products were also observed when MeOH was used as a solvent (entry 3). In a similar manner,

Scheme 2



entry	substrate	solvent	conversion %[a]	yield %[a,b] 4	*E*-**6a,b**	(*E*,*E*)-**7**	*anti*-**8**
1	*E*/*Z*-**3**[c]	$CHCl_3$	>99	~25[d]	-	-	-
2	*E*/*Z*-**3**[c]	$CHCl_3$[e]	90[f]	24	27	28	11
3	*E*/*Z*-**3**[c]	MeOH	80[f]	19	21	18	22
4	*Z*-**3**	$CHCl_3$	>99	-	-	-	-
5	*Z*-**3**	MeOH	85	-	31	37	17

[a] Determined by the NMR integration of the proper hydrogen signals of the crude reaction mixture. [b] Ratio was found to be temperature independent. [c] Mixture of two isomers *E*/*Z* = 30/70. [d] Yield determined based on mass isolated product (purified by column chromatography). Similar results obtained when MTAD was used as dienophile. [e] Reaction was performed in the presence of 50 equiv of MeOH. [f] Unreacted diene was mainly the *Z*-isomer.

(11) For a stepwise mechanism, see also: (a) Yamada, S.; Hamado, K.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 2379–2382. (b) Stratakis, M.; Hatzimarinaki, M.; Froudakis, G. E.; Orfanopoulos, M. *J. Org. Chem.* **2001**, *66*, 3682–3687.

(12) For a concerted mechanism, see also: (a) Laila, A. *J. Prakt. Chem.* **1995**, 655–658. (b) Singleton, D. A.; Schulmeier, B. E.; Hang, C.; Thomas, A. A.; Leung, S.-W.; Merrigan, S. R. *Tetrahedron* **2001**, *57*, 5149–5160. (c) Roa, R.; O'Shea, K. E. *Tetrahedron* **2006**, *62*, 10700–10708.

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(18) For details, see the Supporting Information.

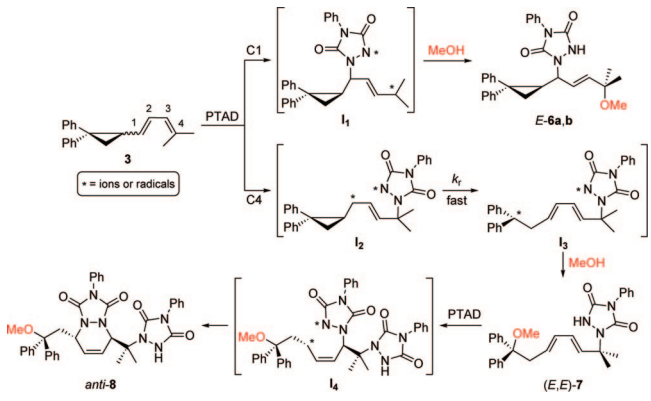
(19) O'Shea, K. E.; Foote, C. S. *Tetrahedron Lett.* **1990**, *31*, 841–844.

the reactions of PTAD with *Z*-**3** in $CHCl_3$ and MeOH were studied. When the reaction solvent was $CHCl_3$, only unidentified products were formed. Alternatively, when the reaction was carried out in MeOH, solvent-trapped products *E*-**6a,b**, (*E*,*E*)-**7** and *anti*-**8** were obtained in almost quantitative yield (entry 5).

Examining the results of the PTAD addition to dienes *Z*-**3** and *E*/*Z*-**3** in $CHCl_3$, the unidentified products (most probably polymeric materials) are plausibly formed through an open polarized biradical/dipolar intermediate. This is evident by the fact that, in the PTAD reaction with diene *E*/*Z*-**3**, a small amount of MeOH admixed to $CHCl_3$ intercepted the open intermediate forming the MeOH-trapped products and minimizing the amount of polymeric materials (compare entries 1 and 2). Moreover, because the PTAD reaction with diene *Z*-**3** in $CHCl_3$ furnished only unidentified products (entry 4), it is obvious that product **4** is exclusively formed from diene *E*-**3** (entry 1).

The formation of MeOH-trapped adducts [*E*-**6a,b**, (*E*,*E*)-**7** and *anti*-**8**] doubtlessly points to the existence of an open polarized biradical or dipolar intermediate. The possible mechanism that could account for their formation is outlined in Scheme 3. There are two distinct possibilities depending on

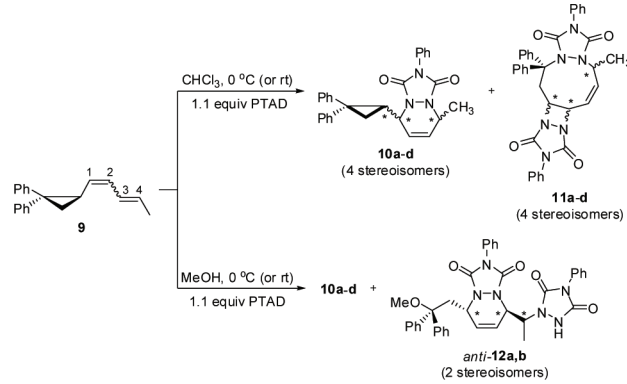
Scheme 3. Plausible Mechanism for the Formation of MeOH-Trapped Products **6**, (*E*,*E*)-**7** and *anti*-**8**



which carbon atom the enophile is added to. The addition of PTAD at C1 furnishes the open intermediate $\mathbf{I_1}$. Subsequently, the tertiary polarized radical or carbocation (at C4) is trapped by MeOH affording product **6**. An intact cyclopropyl moiety in the product is expected in this case, as found. Alternatively, the addition of PTAD at C4 affords the open intermediate $\mathbf{I_2}$. Notably, the lifetime of $\mathbf{I_2}$ must be greater than 2×10^{-12} s (at rt), which is the lifetime of 2,2-diphenylcyclopropylcarbinyl radical.[16] Thus, the initially formed secondary polarized radical or carbocation (at C1) undergoes ring opening to the more stable dibenzyl polarized biradical or dipolar intermediate $\mathbf{I_3}$. Then, $\mathbf{I_3}$ is trapped by MeOH forming the observed product (*E*,*E*)-**7**. This diene further reacts with another molecule of PTAD to form stereospecifically the *anti*-**8** adduct. To confirm the formation of *anti*-**8** from the precursor (*E*,*E*)-**7**, the reaction of the isolated (*E*,*E*)-**7** with PTAD in $CHCl_3$ was studied. Indeed, compound (*E*,*E*)-**7** afforded the thermodynamically more stable bisadduct *anti*-**8** (isolated yield >90%). In case of a concerted [4 + 2] addition, the *syn*-**8** would have been expected. This result indicates that the reaction proceeds via an open polarized biradical or dipolar intermediate $\mathbf{I_4}$ as shown in Scheme 3.

Despite these interesting findings, the existence of an intermediate in the triazolinedione DA reaction in nonpolar solvents with a diene, which can easily adopt the *s-cis* conformation, remains particularly elusive. To shed more light on this issue, we synthesized and assayed the less-substituted dienes (*Z*,*E*)-**9** and (*E*,*E*)/(*Z*,*E*)-**9** (Scheme 4).[18] Unlike substrate

Scheme 4



entry	substrate	solvent	conversion %[a]	yield %[a,b] 10a–d	11a–d	*anti*-12a,b
1	(*E*,*E*)/(*Z*,*E*)-**9**[c]	$CHCl_3$	85[d]	67	18	-
2	(*E*,*E*)/(*Z*,*E*)-**9**[c]	$CHCl_3$[e]	85[d]	68	-	17
3	(*E*,*E*)/(*Z*,*E*)-**9**[c]	MeOH	65[d]	25	-	40
4	(*Z*,*E*)-**9**	$CHCl_3$	88	75[f]	13	-
5	(*Z*,*E*)-**9**	MeOH	72	41[f]	-	31

[a] Determined by the NMR integration of the proper hydrogen signals of the crude reaction mixture. [b] Ratio was found to be temperature independent. [c] Mixture of two isomers (*E*,*E*)/(*Z*,*E*) = 35/65. [d] Unreacted diene was mainly the (*Z*,*E*)-isomer. [e] Reaction was performed in the presence of 50 equiv of MeOH. [f] Only two diastereoisomers were formed.

3, diene **9** bears one alkyl substituent on each double bond carbon C1 and C4, correspondingly. In the trasition state, both double bonds are almost electronically equivalent and therefore equally competitive for the RTAD addition. In the case of an open biradical/dipolar intermediate, a secondary radical/carbocation in both C1 and C4 carbons would be formed. This intermediate is expected to form products derived from both sides of the diene moiety.

The reactions of PTAD (1.1 equiv) with (*E*,*E*)/(*Z*,*E*)-**9** at 0 °C (or rt) were initially studied. When $CHCl_3$ was the reaction solvent, four DA adducts **10** and four rearranged PTAD-bisadducts **11** were isolated and characterized (entry 1, Scheme 4). Noteworthy, when the same reaction was conducted in the presence of 50 equiv MeOH in $CHCl_3$, DA adducts **10** (four stereoisomers) and rearranged MeOH-trapped adducts *anti*-**12** (two stereoisomers) were isolated (entry 2). These six products were also detected when MeOH was used as a solvent (entry 3). Likewise, the reactions of PTAD with (*Z*,*E*)-**9** in $CHCl_3$ and MeOH were studied. When the reaction solvent was $CHCl_3$, two stereoisomers of **10** and four stereoisomers of **11** were detected (entry 4). According to previous studies,[10] we expected

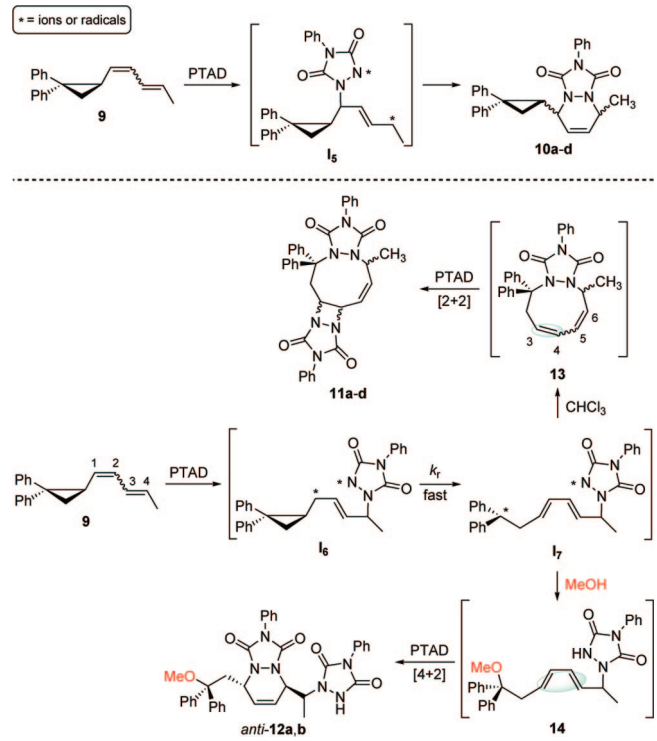
to observe the exclusive formation of DA adducts **10** with an *anti*-configuration. Suprisingly, (*Z*,*E*)-**9** gave a mixture of two stereoisomers of **10** (85:15); the major and minor isomers had the *anti*- and *syn*-configuration, respectively. The stereochemistry of these products was confirmed by NOE experiments.[18] Moreover, when we used 0.8 equiv of PTAD, the same products, mentioned above, were obtained. Attempts to isolate any rearranged PTAD-monoadduct were unsuccessful. Ultimately, when the reaction was carried out in MeOH apart from the formation of DA-adducts **10** (both *anti*- and *syn*-stereoisomers), two rearranged MeOH-trapped adducts *anti*-**12** were also isolated (entry 5). It is noteworthy that in this case no rearranged PTAD-bisadducts **11** were formed.

Due to the fact that three stereogenic centers are present in compound **11**, a maximum of eight stereoisomers (four enantiomeric pairs of diastereomers) are expected to be formed. Gratifyingly, we were able to separate these diastereomers, namely **11a**−**d**, by flash column chromatography. This separation was crucial since our goal was to precisely elucidate the structure of compound **11**. The structure was established through various 1D/2D NMR techniques as well as ESI-MS spectroscopy.[18] Efforts to crystallize compounds **11a**−**d** were unsuccessful.

Since the reaction of PTAD with diene (*Z*,*E*)-**9** in both $CHCl_3$ and MeOH solvents furnished an *anti*- and a *syn*-stereoisomer of product **10**, it is obvious that the other two diastereomers (an *anti* and a *syn*) are exclusively formed from diene (*E*,*E*)-**9**. Because these reactions proceeded without stereospecificity (predicted for a concerted DA reaction according to symmetry orbital rules), we strongly suggest that DA adducts **10a**−**d** are formed via an open polarized biradical or dipolar intermediate $\mathbf{I_5}$ (Scheme 5). Additionally, cyclopropyl rearranged compounds **11a**−**d** and *anti*-**12a**,**b** are derived from an open polarized biradical or dipolar intermediate. A plausible mechanism that could account for the formation of these products is represented in Scheme 5. In particular, the addition of PTAD at C4 affords an open intermediate $\mathbf{I_6}$, with a lifetime greater than 2×10^{-12} s (at rt).[16] As expected, this intermediate rapidly undergoes ring opening leading to the more stable dibenzyl polarized radical or cation intermediate $\mathbf{I_7}$. At this point, there are two possibilities depending on the reaction solvent. In $CHCl_3$, this intermediate can undergo intramolecular cyclization to yield rearranged PTAD-monoadduct **13**. Then, a second molecule of PTAD is added regioselectively through a [2 + 2] cycloaddition to the C3−C4 double bond of **13** forming compounds **11a**−**d**. On the other hand, when the reaction solvent is MeOH, intermediate $\mathbf{I_7}$ is trapped by one molecule of the solvent forming the rearranged product **14**. Ultimately, a second molecule of PTAD is added stereoselectively through a [4 + 2] cycloaddition furnishing two *anti*-stereoisomers *anti*-**12a**,**b**.

As already mentioned, compound **13** could not be isolated. Moreover, due to steric hindrance the C3−C4 double bond of **13** is more accessible than the C5−C6. Two possible pathways for the PTAD addition to the C3−C4 double bond of **13** could be considered: (a) through an ene reaction and (b) via a [2 + 2] cycloaddition. It is generally accepted that the RTAD ene reaction proceeds via the rate-limiting formation of an AI intermediate (**b**, Scheme 1) which leads directly to ene products.[2,20] In our case, due most probably to steric interactions, no ene adducts were observed. Alternatively, an extended tandem sequence of 1,4-dipolar cycloaddition of PTAD to (*E*,*E*)/(*Z*,*E*)-**9**, cyclopropyl rearrangement, cyclization and then [2 + 2] cycloaddition of PTAD to the C3−C4 double bond of **13** are likely to occur as found.

Scheme 5. Plausible Mechanism for the Formation of Products **10a**−**d**, **11a**−**d** and *anti*-**12a**,**b**



In conclusion, a hypersensitive mechanistic probe was used for the investigation of a triazolinedione DA reaction with simple acyclic dienes in both aprotic and protic solvents. The lack of [4 + 2] stereoselectivity in nonpolar solvents (for the diene **9**) as well as the formation of cyclopropyl rearranged PTAD-bisadducts and MeOH-trapped products provide strong evidence for the involvement of an open polarized biradical or dipolar intermediate in the aforementioned reaction. The lifetime of this intermediate is estimated to be greater than 2×10^{-12} s.

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Supporting Information Available: Detailed experimental procedures, spectral data, 1D and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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