

Review Article

Radical Cation Initiated Cycloaddition of Electron-Rich Allenes. Evidence for a Stepwise Mechanism[†]

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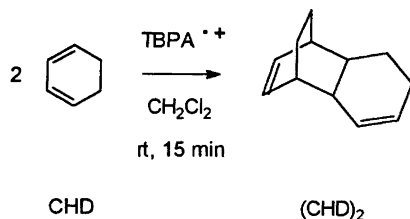
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Schmittel, M., Wöhrle, C. and Bohn, I., 1997. Radical Cation Initiated Cycloaddition of Electron-Rich Allenes. Evidence for a Stepwise Mechanism. – Acta Chem. Scand. 51: 151–157 © Acta Chemica Scandinavica 1997.

Several di- and tri-substituted allenes have been allowed to react with pentamethylcyclopentadiene in a radical cation initiated cycloaddition. Mechanistic evidence points to the occurrence of an intermediate distonic radical cation, the ring closure of which to the Diels–Alder product radical cations is controlled by the substituent at the remote end of the allene. A novel criterion for the design of stepwise radical cation cycloadditions is presented.

The last couple of years have witnessed a growing number of electron transfer (ET) promoted reactions that proceed with high selectivity. Notably, in some cases even reactions that have never been realized before by any other method have been accomplished.^{1,2} In this context, the radical cation Diels–Alder reaction has become a distinguished example for the potential of ET activation. For instance, the ET induced Diels–Alder (DA) cyclodimerization of 1,3-cyclohexadiene (CH_2Cl_2 , r.t., 15 min), triggered by the simple addition of 5–10 mol% of tris(*p*-bromophenyl)aminium hexachloroantimonate ($\text{TBPA}^{\bullet+}$), is accelerated by a factor of 10^{15} vs. the thermal reaction.^{3,4}

Based on the seminal mechanistic studies mainly undertaken by Bauld,⁵ Ebersson⁴ and Steckhan,⁶ the following mechanism may be proposed for the Diels–Alder cyclodimerization of 1,3-cyclohexadiene (CHD).⁷

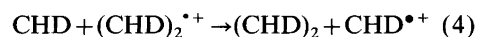
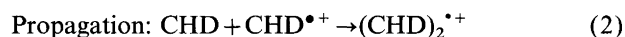
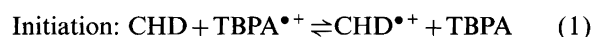


Scheme 1. ET-induced cyclodimerization of 1,3-cyclohexadiene.

[†] Lecture held at the 14th International Conference on Radical Ions, Uppsala, Sweden, July 1–5, 1996.

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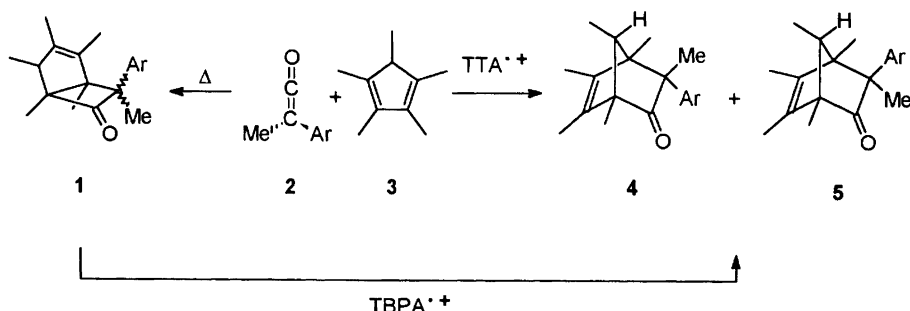
After an initiating one-electron oxidation, the endergonic equilibrium of which can be controlled on the basis of redox potential data, the cycloaddition of $\text{CHD}^{\bullet+}$ with CHD to yield the $(\text{CHD})_2^{\bullet+}$ takes place with almost zero activation barrier ($\Delta H^\ddagger = 1.6 \text{ kcal mol}^{-1}$).^{7e}



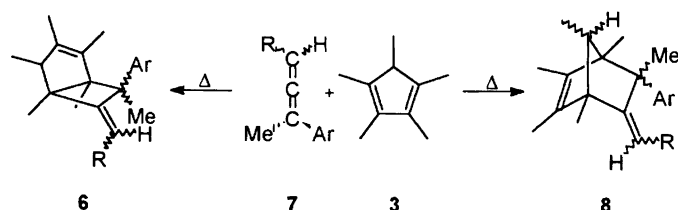
Several pieces of evidence suggest that ET reduction of $(\text{CHD})_2^{\bullet+}$ [eqn. (3)] is best effected by the reduced amine TBPA and not by 1,3-cyclohexadiene. Hence, the cycloaddition follows a conventional catalytic mechanism, but not a pure radical cation process.⁴

Several years ago, we became fascinated by the possibility of controlling the [4+2] vs. [2+2] periselectivity of cumulene/diene cycloadditions by use of radical cation catalysis, as such a strategy had successfully been used for other unsaturated substrates with high chemo-, regio- and stereo-selectivity.⁸ Indeed, one-electron oxidation allowed us to steer the ‘periselectivity’ in ketene/diene cycloadditions.² Accordingly, the [2+2] cycloadducts were formed in the thermal reaction, while in the presence of the tris(*p*-tolyl)aminium hexafluoroantimonate ($\text{TTA}^{\bullet+}$) the [4+2] cycloaddition products were afforded exclusively (Scheme 2).

Consequently, one-electron oxidation seemed to be a viable strategy to overcome the inherent problems of



Scheme 2. Periselectivity in ketene/diene cycloadditions.



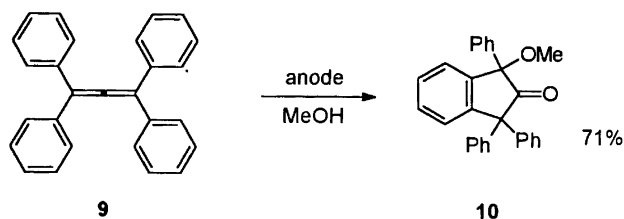
Scheme 3. Thermal allene cycloadditions leading to [2+2] and [4+2] cycloadducts.

thermal allene cycloadditions that often lead in parallel processes (Scheme 3) to [2+2] and [4+2] cycloadducts.⁹

Hitherto, only few reports have been concerned with the one-electron oxidation of allenic systems,¹⁰ although such processes may provide interesting perspectives for synthetic C–C bond formations. For instance, electro-oxidation provides a novel strategy for the cyclization of allene **9** to the 2-indanone derivative **10** (Scheme 4).¹¹

Allenes show almost no tendency to dimerize under oxidative conditions, quite in contrast with the situation with alkenes and alkynes.^{10b,c,12} So far, cycloadditions involving allene radical cations have been limited to photoinduced electron transfer (PET) conditions that do not support chain processes. In the examples by Maruyama,¹³ the allene and a photochemically excited quinone undergo ET, after which the resulting allene radical cation and the reduced acceptor combine (Scheme 5). With the sterically less hindered allene **12** the formal [2+2] cycloadduct **13** was obtained, while a crowded allenic system (**14**) led to the unexpected spiro-pyran adduct **15** as a result of a [4+2] cycloaddition followed by a [1,5] hydrogen shift. The only other example for such a PET cycloaddition was provided by Mariano in the PET oxidation of allene **17** in the presence of iminium acceptors (Scheme 6).¹⁴

Obviously, the approaches chosen by Maruyama¹³ and



Scheme 4. Anodic cyclization of tetraphenylallene.

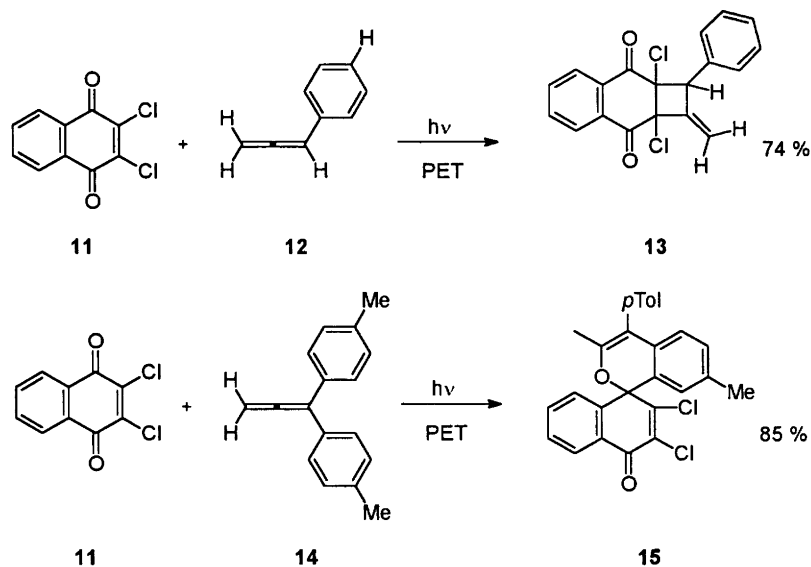
Mariano¹⁴ have some intrinsic limitations, insofar as the allene cycloaddition has to be set up with an electron-poor acceptor. Consequently, it was desirable to have a look at radical cation cycloadditions with electron-rich allenes as dienophiles and electron-rich dienes. As a prerequisite for the thermal radical cation format the allene has to carry at least one aryl electrophore in order to provide a substrate with low oxidation potential.

When allenes **20a–i** (Scheme 7) were oxidized with tris(*p*-tolyl)aminium (TTA^{•+}) salt in the presence of diene **3** (0 °C, 5 min), only two out of 32 possible isomers were formed (Scheme 8).^{15–17} The reaction is remarkably ‘periselective’ since [2+2] cycloadducts were not found at all. In addition, it shows a high facial selectivity with the diene **3** always being attacked from the less hindered side and a high chemoselectivity favoring the aryl substituted double bond of the allene system. Finally the reaction is highly stereoselective with the various groups R always ending up *E* to the bridgehead system. Last but not least, the *endo:exo* selectivity amounts to ca. 4:1 (Table 1).

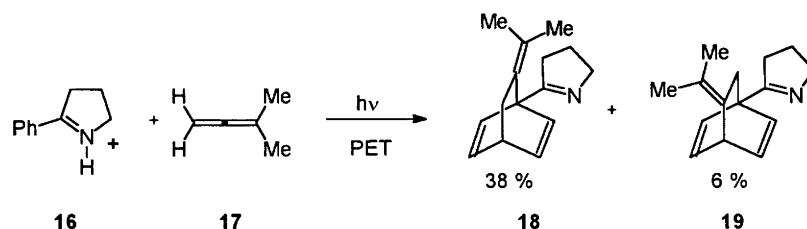
Two observations are mechanistically important. The oxidation potentials¹⁸ of all allenes **20** (Table 1) are higher than that of diene **3** indicating that the diene should be oxidized preferentially. And in addition, the yield of the cycloaddition could be increased the higher the allene: diene ratio (Table 2).^{15,16} In this respect, the mechanistic investigations unambiguously propose that the reaction proceeds by a [3+2] cycloaddition mechanism, i.e., the diene is oxidized to the diene radical cation and adds to the allene.^{15,16} Such a [3+2] mechanism is

[3+2] Mechanism:

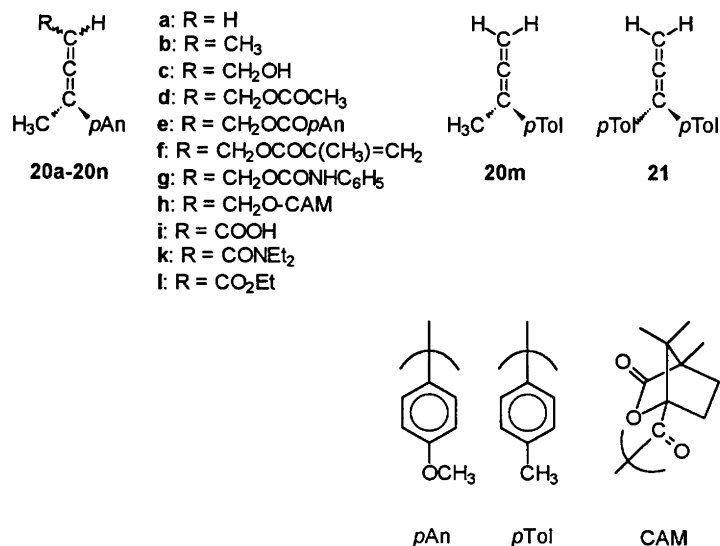




Scheme 5. PET-induced cycloaddition of allenes.



Scheme 6. PET-induced allene cycloaddition in the presence of iminium acceptors.

Scheme 7. Allenes **20a-m** and **21** used in the cycloaddition with diene **3**.

interesting in the light of the theoretical prediction that such a cycloaddition is formally symmetry forbidden, in contrast with the formally allowed [4+1] cycloadditions.¹⁹

With electron withdrawing substituents at the remote end of the allene functionality (**20i-l**) the cycloaddition constitutes only a minor reaction path,¹⁵⁻¹⁷ but notably

the low yields cannot be rationalized on the basis of Steckhan's criterion.⁶ These guidelines for the rational set-up of radical cation reactions emphasize that in order to react two electron-rich components they should not differ in their oxidation potentials by more than about 0.5 V. In our examples, however, the large oxidation potential differences between the two reactants, $\Delta E_{pa} =$

Table 1. Yields^a for the aminium salt initiated cycloaddition of **20a–m** and **3** providing cycloadducts **23a–m**, **24a–m** (ratio **20**:**3**:TTA^{•+} = 5:1:1, base **22**).

Allene	E_{pa}/V	Yield (%)		
		Base 22	23	24
20a	0.94	+	67	13
20a	0.94	—	31	6
20b	0.83	+	63	9
20b	0.83	—	43	9
20c	0.87	+	68	13
20d	0.93	+	38	8
20e	0.94	+	42	8
20f	0.95	—	22	5
20g	0.89	+	17	5
20h	0.93	+	35	4
20m	1.23	+	48	12

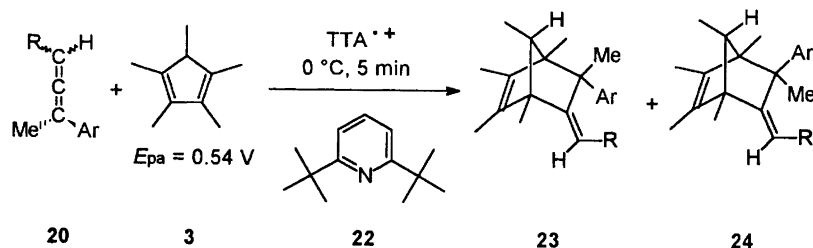
^a Yields determined by ¹H NMR spectroscopy with acetophenone as an internal standard.

Table 2. Influence of the allene **20a**:diene **3** ratio on the yield of cycloadducts **23**, **24a**.

20a : 3	Oxidant	Base	Yield (%)	
	TTA ^{•+}	22	23	24
1:1	25 mol%	+	10	2
3:1	25 mol%	+	25	5
5:1	25 mol%	+	30	6

$E_{pa}(\mathbf{20i} \text{ or } \mathbf{20l}) - E_{pa}(\mathbf{3}) = 0.54$ or 0.57 V, respectively, do not play a decisive role, since with 1-tolyl-1-methylallene (**20m**) a satisfactory yield of 60% was obtained despite $\Delta E_{pa} = E_{pa}(\mathbf{20m}) - E_{pa}(\mathbf{3}) = 0.69$ V (Table 3).

Likewise steric effects in the cycloaddition of **20i–l/3** are of negligible significance as large groups R were compatible with the radical cation reaction (e.g., **20e–h**). Pure electronic effects exerted by the substituents R = COOH and COOEt at the remote end of the allene system, however, should play only a minor role in a concerted pathway, since the forming C–C bonds develop almost perpendicular to the exomethylene group. As a consequence, the observed low yields with **20i** and **20l** provide strong evidence for the cycloaddition proceeding via a stepwise mechanism, which would allow the various functionalities R at the exomethylene group to interfere at the stage of the distonic radical cation **25**^{•+}. The following reaction course is thus proposed in Scheme 9.



Scheme 8.

Table 3. Yields of cycloadducts with electron-withdrawing substituents.

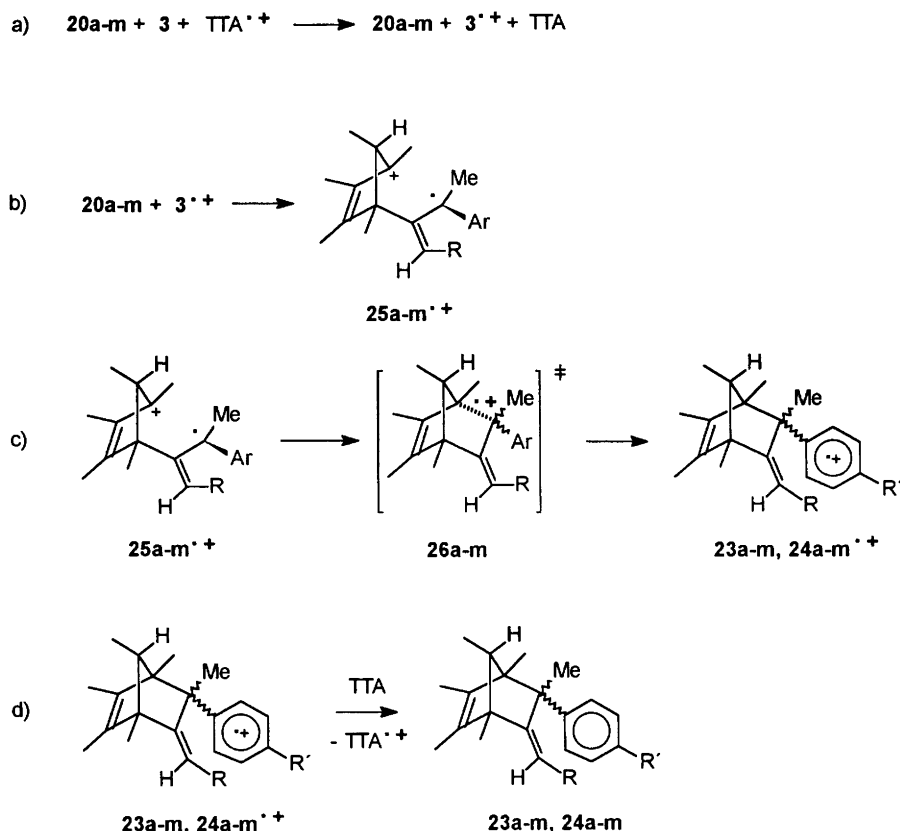
Allene	E_{pa}/V	Yield (%)		
		Base 22	23	24
20m	1.23	+	48	12
20l	1.11	+	4	1
20l	1.11	—	10	1
20i	1.08	—	10	1
20k	0.99	—	—	—

Accordingly, in order to optimize the radical cation cycloaddition, the energetics and kinetics now have to be fine-tuned for a whole series of individual events:^{15,17} (a) initial ET oxidation of diene **3**; (b) reaction of **3**^{•+} with the neutral allene **20**; (c) ring closure of **25**^{•+} to the formal DA radical cation **23**, **24**^{•+} via the transition state **26** which is best characterized by the formation of the two-center one-electron bond; (d) ET reduction of the product radical cation.

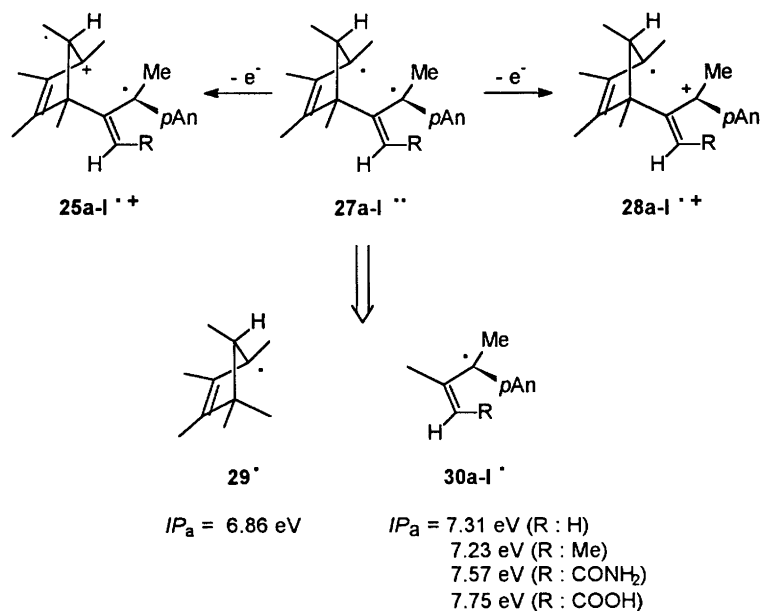
For all these reaction steps except (c) helpful criteria have been developed for the rational design of radical cation cycloadditions. For instance, it has been recommended that the electron transfer oxidation (a) begin in an endergonic equilibrium ($5 \text{ kcal mol}^{-1} < \Delta G_{ET} < 10 \text{ kcal mol}^{-1}$) using an appropriate oxidant.^{2–5} Thereby, the stationary concentration of the radical cations is kept rather low and, in addition, sufficient driving force for the reduction step (d) is provided. As mentioned above, reaction (b) is best set up using Steckhan's criterion (see above).⁶

Recent work^{2,4} emphasizes that, indeed, the last reduction step (d) may be pivotal in the reaction sequence thus underlining the importance of considering redox potentials and reorganization energies of both reactants and products. However, in a comparison of the cycloadditions of **20a–l**, the driving force for the last ET step is almost identical since it is best represented by the one-electron reduction of a *p*-alkylanisole radical cation [Scheme 9(d)].

Let us return to the postulated stepwise cycloaddition between **20a–l** and **3**. Interestingly, for all substituents Ar and R studied so far AM1 calculations¹⁷ propose a clear preference for the charge distribution shown in **25**^{•+} (Scheme 10). Hence, there is no charge reversal in the distonic ion **25**^{•+}, compared with **28**^{•+}, despite



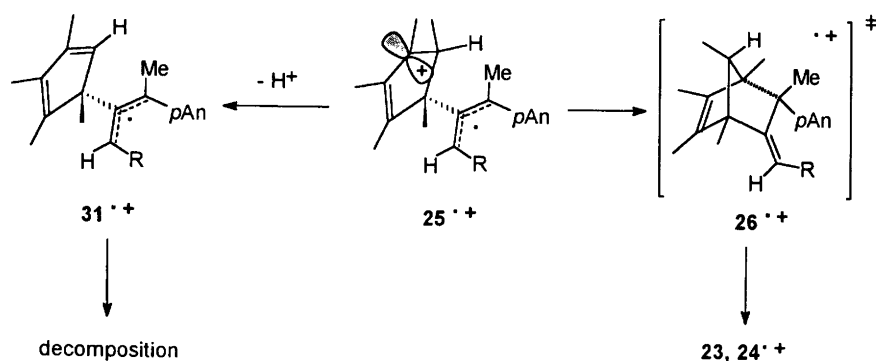
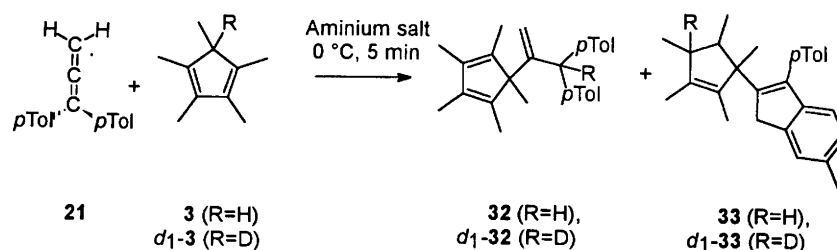
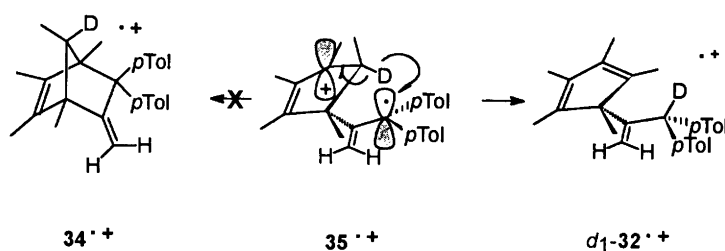
Scheme 9. Cycloaddition via the distonic radical cation $25a-m^{+\bullet}$.



Scheme 10. AM1-calculated ionization potentials of fragments 29^{\bullet} and 30^{\bullet} .

varying R from an electron-releasing to an electron-withdrawing substituent. Consequently, we have to ask whether R has an effect on the kinetic barrier of ring closure of $25^{\bullet\bullet}$ to 23 , $24^{\bullet\bullet}$. Indeed, AM1 calculations by Kikuchi²⁰ propose that in the transition state the

positive charge has to be accommodated by the two carbon fragments that form the two-center one-electron bond. The ability of both centers to accommodate the positive charge, however, can be derived from the ionization potential IP of the two radical centers in the putative

Scheme 11. Reaction pathways of the intermediate distonic radical cation $25a-1^{\bullet+}$.Scheme 12. Formation of (deuteriated) products **32** and **33**.Scheme 13. Hydrogen (deuterium) transfer in $35^{\bullet+}$.

biradical $27^{\bullet\bullet}$ or, in a simplified version, from the enthalpy difference $\Delta H_f^\circ(28^{\bullet+}) - \Delta H_f^\circ(25^{\bullet+})$ (Scheme 10).¹⁷

We have calculated this enthalpy difference by AM1²¹ after having introduced another simplification. Accordingly, the ionization potentials* of both radical centers in $27^{\bullet\bullet}$ were approximated by the adiabatic ionization potentials of the fragment radicals 29^\bullet and 30^\bullet . Interestingly, while for systems **a-h** the enthalpy difference $\Delta H_f^\circ(28^{\bullet+}) - \Delta H_f^\circ(25^{\bullet+})$ is of the order of 0.37–0.45 eV, it is substantially increased to 0.71–0.89 eV for systems containing electron-withdrawing groups R as in **i-l**. This observation lends support to our postulate of a stepwise mechanism, as ring closure should be retarded with increasing $\Delta H_f^\circ(28^{\bullet+}) - \Delta H_f^\circ(25^{\bullet+})$.¹⁷

Assuming that ring closure of the distonic radical cation intermediate $25^{\bullet+}$ is slowed, a plausible reaction to replace cyclization would be the deprotonation at the cyclopentenyl cation site (Scheme 11). Indeed, we observe an interesting reactivity difference between

donor- and acceptor-substituted allenes in the radical cation cycloaddition. While for **20a,b** addition of a base increases the DA product yield,^{15,†} it is decreased for **20i-l** (Table 3). This observation suggests that the latter cycloadditions are diverted from the cycloaddition route through base-induced deprotonation, presumably at the stage of the distonic radical cation $25^{\bullet+}$ (Scheme 11).¹⁷

While these conclusions are certainly speculative and open to discussion, since no direct proof for the intermediacy of distonic radical cations of type $25^{\bullet+}$ has been established so far, we have found another interesting piece of evidence in support of the stepwise mechanism. When we tried to react the diaryllallene **21** in the radical cation cycloaddition with **3** (Scheme 12) we obtained two products, one of which (**33**) was derived from an acid-catalyzed pathway.¹⁵ Product **32**, however, was derived from a radical cation route and it was shown that in the reaction with deuteriated **3-d₁** the deuterium

* For the following discussion we assume similar solvation energies for both cations.

† Addition of 2,6-di-*tert*-butylpyridine in the cycloaddition of **20a,b** with **3** suppresses the acid-catalyzed rearrangement of **23, 24a,b** to the corresponding nortricyclanes.

label showed up exclusively in the benzhydryl position of **32-d₁**.

Again, as before, the intermediacy of a distonic radical cation allows us to formulate a plausible reaction pathway to **32-d₁**. Accordingly, the ring closure of **35^{•+}** to the DA product radical cation **34^{•+}** is inhibited for steric reasons, which allows now for a hydrogen (or deuterium) transfer reaction to yield **32-d₁^{•+}** (Scheme 13).

In conclusion, we have developed the radical cation Diels–Alder reaction of electron-rich allenes with pentamethylcyclopentadiene as a highly peri-, facial, chemo- and stereo-selective cycloaddition. Several pieces of evidence point to the occurrence of a stepwise process, the outcome of which is controlled by the fate of the distonic radical cation **25^{•+}**. This observation may give renewed attention to the question of whether the formally forbidden [3+2] cycloadditions are stepwise in general.

Acknowledgements. Financial support from the DFG and the VW-Stiftung is gratefully acknowledged. C.W. thanks the Fonds der Chemischen Industrie for a stipend.

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Received July 1, 1996.