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Retro Diels–Alder reaction under mild conditions: experimental and theoretical studies†

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Received 20th March 2006, Accepted 27th March 2006
First published as an Advance Article on the web 12th April 2006
DOI: 10.1039/b604063b

We describe experimental as well as theoretical results to support the role of cyclopropane in a retro Diels–Alder reaction at lower temperature.

The Diels–Alder (DA) reaction is one of the most powerful tools available to synthetic organic chemists for the construction of six-membered rings of diverse nature.[1] Despite its limited popularity, the retro Diels–Alder reaction (rDA) has evolved as a useful protocol and remains the preferred method for the preparation of several reactive olefins or metastable molecular entities.[2,3] The endothermic nature of the rDA has led to the use of flash-vacuum pyrolysis (FVP) conditions. Although the FVP method has several advantages, the end products sometimes undergo rearrangements.[4] In view of the specialized equipment needed to perform this reaction, we became interested in developing a better alternative where less than pyrolytic conditions may be employed. The rDA reaction can be driven to completion by perturbing the equilibrium, which in fact was introduced over 60 years ago by Diels and Thiele through the use of maleic anhydride as a scavenger for trapping the anthracene generated in a rDA reaction.[5] Hence the design of new strategies where expulsion of the common diene and dienophile under mild reaction conditions will enhance the application of rDA in organic synthesis. Additionally, the rDA reaction performed under mild conditions can have a direct impact in dynamic combinatorial chemistry (DCC). Recently, Lehn and co-workers have utilized the rDA reaction involving functionalized fulvenes for the development of DCC.[6]

To circumvent the problems of decomposition or polymerization of the end products, various efforts were made to achieve the rDA reaction at lower temperature.[7] Limited reports are available regarding the factors governing the rDA reaction, and hence this poses severe restrictions in designing a simple strategy for the rDA reaction. Studies by Magnus *et al.* on [2.2.1]-bicyclic DA adducts have revealed that substituents such as $-SiMe_3$ (TMS) at the C_7 position are highly effective in reducing the barrier associated with the rDA reaction, making it amenable even at lower temperatures.[8] Density functional theory (DFT) studies have shown that the ground-state geometry exhibits geometrical features such as C_1–C_5 bond elongation in the $-SiMe_3$-substituted system.[9] The σ–σ^* conjugation between $\sigma(C_7–Si)$ and $\sigma(C_1–C_5)$ [also $\sigma(C_2–C_6)$] is identified to be the key factor behind the ground-state bond elongation.[10] If orbital interaction is responsible for bringing about reduction in the activation barrier (compared with the unsubstitued case), one might anticipate that electronically active substitutions at the C_7 position could have subtle consequences on the rDA reaction profile.

However, cyclopropane offers a rich set of orbitals that are known to interact with electron-deficient centers. Along these lines, we reasoned that a spirocyclopropane moiety at the C_7 position might turn out to be an interesting substrate.[11] Herein, we describe our preliminary experimental and theoretical findings on the rDA reaction under milder reaction conditions. We believe that our observation will open up a new avenue in the rDA protocol where unstable molecules can be prepared without involvement of FVP, thereby eliminating the unwanted side-reactions. Towards this goal the required spiro[4,2]hepta-1,3-diene was prepared using micellar conditions.[12] However, side-reactions like unwanted polymerization could not be avoided in the presence of a strong base, which accounted for the poor yield of the desired diene. Then the required diene was immediately reacted with various dienophiles in a micellar medium to obtain the respective DA adducts in good yields (Table 1). Having the desired product, the next step was to screen the reaction conditions for optimized yield of the rDA reaction.‡ It was found that the yield was considerably decreased even after prolonged refluxing conditions in DCM. However, changing the solvent to acetonitrile (or toluene) markedly improved the yield of the rDA product and the reaction was completed in a much shorter time (Scheme 1). The rDA reactions required no special conditions like an inert atmosphere or FVP. These results are summarized in Table 1. In the case of adducts **2b** and **3b** the volatile nature of the dienophile

Table 1 Summary of DA and rDA reactions of spirodiene and dienophiles

	Reaction	DA		rDA	
Entry	Cycloadduct	Time/h	Yield (%)	Time/h	Yield (%)
$R_1 = H$	**2a**	4	67	24	62[a,b]
$R_1 = H$	**2b**	5	73	28	35[a]
$R_1 = H$	**2c**	8	89	10	76[c]
$R_1 = H$	**2d**	4	62	12	75[b,c]
$R_1 = H$	**2e**	12	91	8	81[c]
$R_1 = Me$	**3a**	4	81	12	67[a,b]
$R_1 = Me$	**3b**	5	84	24	49[a]
$R_1 = Me$	**3d**	8	80	24	72[a,b]
$R_1 = Me$	**3e**	4	91	8	87[c]

[a] rDA performed in toluene. [b] Yield based on starting material recovered. [c] rDA performed in acetonitrile.

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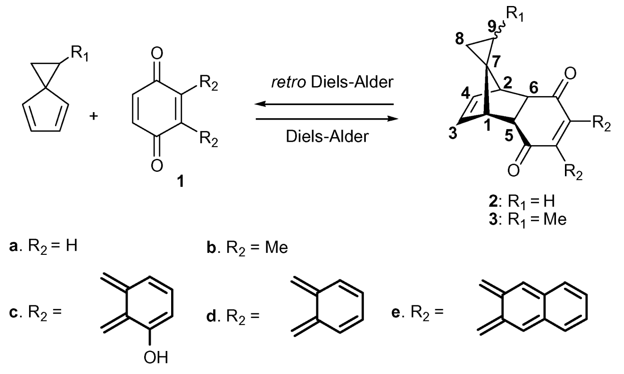
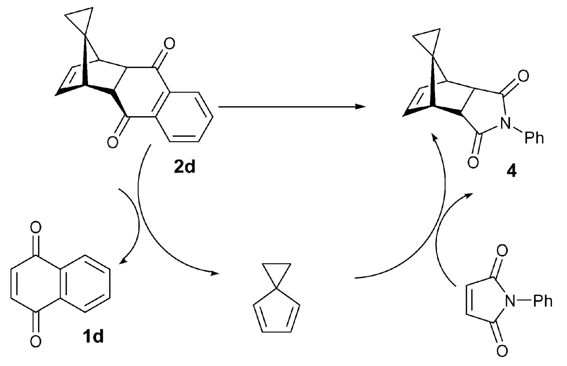
† Electronic supplementary information (ESI) available: Preparation and characterization of **2a–e** and **3a–e**, and Cartesian coordinates for optimized geometry of compounds **2a–e** and **3a–e**. See DOI: 10.1039/b604063b



Scheme 1 DA and rDA reaction of spiroheptadiene with quinones.



Scheme 2 Retro Diels–Alder reaction in the presence of a scavenger.

Table 2 Computed activation barrier for the rDA reaction of a spiro DA adduct obtained at the B3LYP/6-31G* level of theory[a,b]

Reaction	$\Delta E^{\dagger}{}_{g}$/kcal mol^{-1}	$\Delta E^{\dagger}{}_{sol}$/kcal mol^{-1} [c,d]
2a → **1a**	27.9	24.2 (25.9)
2b → **1b**	27.8	24.6 (26.4)
2c → **1c**	26.9	23.8
2d → **1d**	27.2	23.3
2e → **1e**	27.1	24.3
$\mathbf{3a_1}$ → **1a**[e]	27.8	24.6 (26.3)
$\mathbf{3a_2}$ → **1a**[f]	27.6	24.3 (25.9)
$\mathbf{3b_1}$ → **1b**	27.7	25.0 (26.6)
$\mathbf{3b_2}$ → **1b**	27.5	24.6 (26.3)
$\mathbf{3d_1}$ → **1d**	27.1	24.9 (26.4)
$\mathbf{3d_2}$ → **1d**	26.8	24.8 (25.7)
$\mathbf{3e_1}$ → **1e**	27.0	24.7
$\mathbf{3e_2}$ → **1e**	26.7	24.5

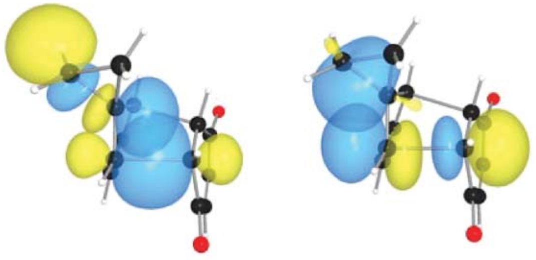
[a] Gas phase calculation at the B3LYP/6-31G* level. [b] Single-point energies in acetonitrile computed using Tomasi's PCM (polarized continuum model) method[13] in combination with SCRF at the same level of theory and basis set. [c] Values in parentheses indicate single-point energies in toluene. [d] Activation barrier values for TMS-substituted and unsubstituted systems in acetonitrile are 22.9 and 27.1 kcal mol^{-1}, respectively. [e] Subscript 1 represents the –Me group at the 9th position. [f] Subscript 2 represents the –Me group at the 8th position.

was responsible for low yield of the rDA reaction. However, in the presence of a scavenger, the yield of the rDA reaction increased considerably (Scheme 2). The use of the scavenger has the advantage that it traps the diene and prevents the reverse DA reaction, thereby enhancing the rate of the rDA reaction.

To gain further insight on the role of cyclopropane in the rDA reaction, we have carried out a detailed investigation of the reaction profile using the DFT method. The transition states for each substrate have been precisely located with the B3LYP/6-31G* level of theory. The computed activation barriers for the rDA reaction are provided in Table 2. The experimental activation barrier for –$SiMe_3$-substituted (at C_7) and unsubstituted cycloadducts are, respectively, 24.8 ± 1 and 29 ± 1.5 kcal mol^{-1}.[8] TMS substitution has been found to be capable of bringing about a rate acceleration as high as 95 times compared to the unsubstituted system (H at C_7) under comparable reaction conditions. The computed activation barrier in the gas phase at the B3LYP/6-31G* level of theory for the TMS-substituted and unsubstituted cases are, respectively, 24.6 and 29.9 kcal mol^{-1}, a prediction in good concurrence with experimental observation. It is interesting to note that the predicted barrier for the spirocyclopropane system in general is lower than the unsubstitued case over a range of dienophiles, indicating the possibility of a relatively facile rDA reaction. Another observation pertains to the lowering of the computed activation barrier upon inclusion of solvation by single-point energy calculations in acetonitrile media using the polarizable continuum model (PCM).[13] The activation barrier is predicted to be higher in toluene than in acetonitrile, at the same level of theory. All of these predictions support the fact that the spirocyclopropane systems could undergo a faster rDA reaction compared with the unsubstituted cycloadduct. Alternatively, milder reaction conditions might be adequate enough to bring about cycloreversion in spirocyclopropane systems.

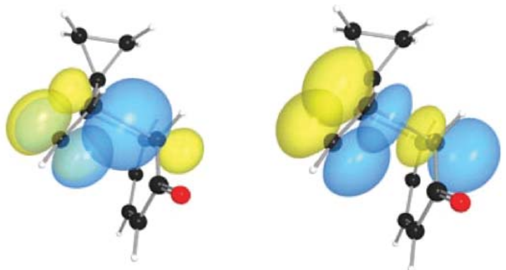
Identifying the electronic origins of the cyclopropane-promoted rDA reaction is intuitively appealing in the present context. The importance of cyclopropane orbitals in controlling the stability and conformational preferences in cyclopropylcarbinyl carbocations as well as carbenes are reported. Increased strain in the three-membered ring is known to raise the energy of the σ_{C-C} orbital, ensuring a better σ-donating ability.[14] With the help of Natural Bond Orbital (NBO) analysis we have examined important electron delocalizations in both cycloadducts and the corresponding transition states. Key sets of stabilizing electronic interactions are identified as $\sigma(C_7–C_8) \leftrightarrow \sigma^*(C_1–C_5)$, $\sigma(C_7–C_8) \leftrightarrow \sigma^*(C_2–C_6)$, $\pi(C_3–C_4) \leftrightarrow \sigma^*(C_1–C_5)$ and $\pi(C_3–C_4) \leftrightarrow \sigma^*(C_2–C_6)$ delocalizations.[15] Interestingly, increased delocalizations are noticed for the transition states compared with the cycloadduct. Two representative contour plots depicting the extent of $\sigma(C_7–C_8) \leftrightarrow \sigma^*(C_1–C_5)$ and $\pi(C_3–C_4) \leftrightarrow \sigma^*(C_1–C_5)$ at the transition state for the reaction **2a** → **1a** are provided in Fig. 1. Delocalizations of these kinds assume additional relevance due to the participation of $C_1–C_5$ (and $C_2–C_6$) bonding electrons, since depletion of occupancies will help to ease the bond-breaking process. The interactions involving cyclopropane orbitals such as $\sigma(C_7–C_8)$ as the acceptor are found to be better in the transition state compared with the cycloadduct. These delocalizations will help to reduce the barrier for the rDA reaction, making it amenable under milder reaction conditions.

In summary, we have successfully demonstrated that the rDA reaction with spirocyclopentadiene as the diene can be carried out under mild reaction conditions. The lower kinetic barrier for this reaction has been identified as arising from greater stabilization of the transition state resulting from effective orbital interactions involving the cyclopropane bond orbitals.



1.1
$\sigma(C_1\text{-}C_5) \rightarrow \sigma^*(C_7\text{-}C_8)$

1.2
$\sigma(C_7\text{-}C_8) \rightarrow \sigma^*(C_1\text{-}C_5)$



1.3
$\sigma(C_1\text{-}C_5) \rightarrow \pi^*(C_3\text{-}C_4)$

1.4
$\pi(C_3\text{-}C_4) \rightarrow \sigma^*(C_1\text{-}C_5)$

Fig. 1 3D-plots representing orbital interactions generated with natural bond orbitals at the NBO/B3LYP/6-311+G**//B3LYP/6-31G* level for the transition states (for **1a**).

We thank DST, New Delhi for financial support, Computer Centre-IITB for computing facilities. S. B. and M. P. P. thank UGC, CSIR New Delhi respectively for fellowship.

Notes and references

‡ Representative procedure for retro Diels–Alder reactions: acetonitrile or toluene (15 mL) was added to the Diels–Alder adduct **2a**–**e**, **3a**–**e** (0.40-0.80 mmol) and the solution was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under vacuum and the crude product was charged on a silica-gel column and eluted with ethyl acetate–hexane to afford the desired product. The adducts, **2a**–**e**, **3a**–**e** were used for the rDA reaction according to the above mentioned procedure.

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10 We also recognized four important orbital interactions in the bicyclo [2.2.1] cycloadduct which is responsible for C_1–C_5 elongation. Two of which are described in present text since the other two involving σ → π* and π → σ* remain constant irrespective of the nature of substituents at the C_7 position (unpublished work).

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15 Delocalizations were analysed based on second order perturbation energy values obtained at the NBO/B3LYP/6-311+G**//B3LYP/6-31G* level. Please see the ESI (Table S4, S5, S6, S7) for details on all four kinds of delocalization discussed here.