# Electron Transfer Catalyzed [2 + 2] Cycloreversion of Benzene Dimers

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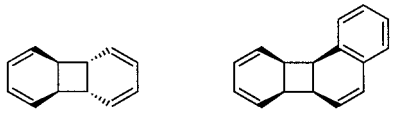
The catalysis of the [2 + 2] cycloreversion of the *anti-o,o′*-benzene dimer **1** and the *syn-o,o′*-naphthalene-benzene dimer **2** through thermal and photoinduced electron transfer is studied using experimental and computational methods. The reaction of the radical cations formed by electron transfer is at least $10^5$ times faster than the thermal background reaction. It is demonstrated that the photoinduced electron transfer catalyzed reaction proceeds via an electron transfer sensitized pathway and that the observed inverse secondary deuterium isotope effect of 0.91 ± 0.02 on the reaction is due to the equilibrium isotope effect on the electron transfer step. The relevance of these findings on the mechanism of the electron transfer catalyzed [2 + 2] cycloreversion of the biologically important *cis,syn*-cyclobutane-thymine dimer is also discussed.

The catalysis of the symmetry forbidden [2 + 2] cycloreversion of cyclobutane derivatives through electron transfer (ET) is one of the most important pericyclic reactions of radical ions. It was the first class of pericyclic reactions that was recognized as electron transfer catalyzed.[1] The cyclodimerization of styrenes and other electron rich alkenes can be catalyzed by thermal or photoinduced electron transfer and is thought to proceed via a radical cation chain process.[2] Despite detailed studies of the reaction mechanism, the question whether the reaction is concerted[3] or stepwise involving an acyclic intermediate[4] is, however, still unresolved. More recently, the electron transfer catalyzed [2 + 2] cycloreversion of cyclobutane pyrimidine dimers, which is part of the skin cancer protection mechanism in many organisms, attracted much attention.[5]

As part of our ongoing studies of the relationship between pericyclic reactions of radical cations and their neutral counterparts, we investigated the ET catalyzed cycloreversion of the *anti-o,o′*-benzene dimer **1** and the *syn-o,o′*-benzene-naphthalene dimer **2**, shown in Figure 1 together with their activation parameters for cycloreversion under thermal conditions**.** These energy-rich molecules can be considered as simple all-carbon analogues of the cyclobutane pyrimidine dimers and have been studied in considerable detail because of their unique topology and high internal energy.[6] As a result



| **1** | **2** |
|---|---|
| $\Delta H^{\neq}$ = 24.1±1.0 kcal/mol | 27.5 kcal/mol |
| $\Delta S^{\neq}$ = -2.2±2.3 e.u | -2.0 e.u |
| $\Delta G^{\neq}$ = 24.8±1.6 kcal/mol (298 K) | 28.2 kcal/mol (348 K) |

**Figure 1.** Activation parameters for cycloreversion of *anti-o,o′*-benzene dimer **1** and *syn-o,o′*-benzene-naphthalene dimer **2**.

of the high exothermicity of the symmetry forbidden [2 + 2] cycloreversion, the cycloreversion of **1** occurs already rapidly at room temperature.[7] The low activation entropy of the reaction and low-level computational studies[8] indicate that the cycloreversion of **1** proceeds via a stepwise pathway with a biradical intermediate. The synthesis and study of the thermal cycloreversion of **2** was also reported.[9]

In this paper, we will address the following questions using experimental and computational methods: (i) is the

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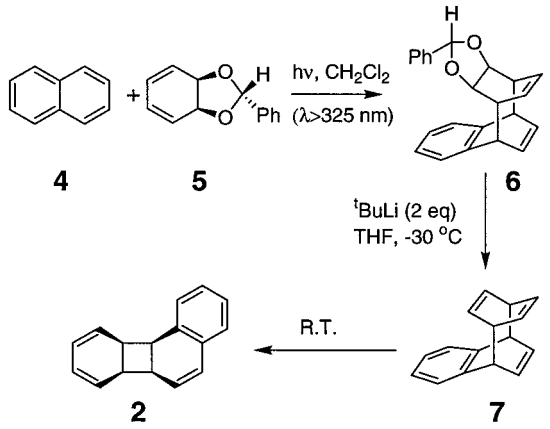


**Figure 2.** Synthesis of **2**.

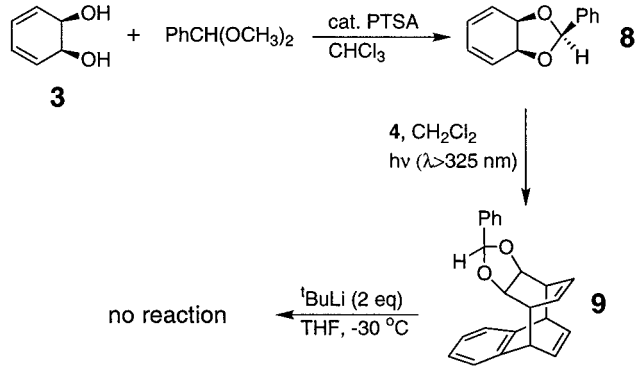


**Figure 3.** Attempted reductive elimination of **9**.

reaction accelerated by electron transfer; (ii) does the reaction proceed via a radical cation chain process or via an electron-transfer sensitized pathway; (iii) does the reaction have an isotope effect and what factors contribute to it, and (iv) what is the effect of the electron transfer on the structure of **1** and **2**. Finally, we will discuss the relevance of these findings for the biologically important cycloreversion of the thymine dimer.

## Results and Discussion

The *anti-o,o′*-dibenzene **1** was synthesized in 13% overall yield from commercially available *cis*-3,5-cyclohexadiene-1,2-diol **3** as described earlier.[7] Compound **2** was obtained following the procedure of Yang and coworkers with minor modifications as outlined in Figure 2. Photocycloaddition of naphthalene **4** and *cis*-3,5-cyclohexadiene-1,2-diol benzaldehyde acetal **5**, followed by reductive deoxygenation[10] of the cycloadduct **6** and facile Cope rearrangement, gave **2** in 10% overall yield.[9] It is noteworthy that **5** cannot be synthesized directly from commercially available **3**. Instead, direct acetalization of **3** gives the epimer **8** as a single diastereomer, which upon photocycloaddition gives **9** (Figure 3). In agreement with recent findings on a related system,[11] **9** does not undergo reductive deoxygenation. This

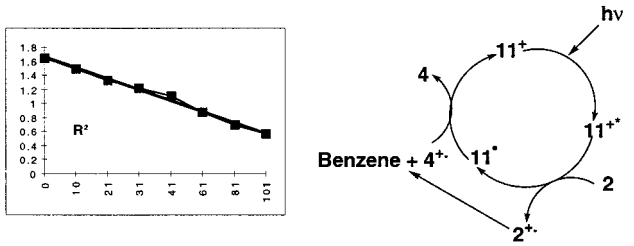


**Figure 4.** Left: plot of log [**2**] vs number of flashes; right: proposed catalytic cycle for the photoinduced electron transfer sensitized [2 + 2] cycloreversion.

diastereospecificity can be explained by considering that, in the course of the reaction, proton abstraction from the acetal carbon occurs concomitant with C−O bond cleavage to give olefin and benzoate anion in one concerted step.[12] Compound **6** may easily attain a geometry with the necessary antiparallel alignment of the C−H bond and C−O bond. The epimer **9** cannot attain such a geometry because of steric repulsion of the $\pi$-systems of the phenyl ring and nearby olefin, and so this isomer remains unreactive.[12] Therefore, **6** was prepared from 1,4-cyclohexadiene as described earlier.[7,9]

Cycloreversion of **1** and **2** was achieved by using 0.2 equiv of tris(4-bromophenyl)-aminium salt **10** for thermal electron transfer or catalytic amounts of tris(4-methoxyphenyl) pyrilium cation $\mathbf{11}^+$ as the tetrafluoroborate salt and visible light ($\lambda$ > 320 nm) for the photoinduced electron transfer. For the thermally induced electron transfer, the reaction was completed in less than 1 min after addition of **10**. Since the half-life of **1** at 60 °C is 33 min[7c] and that of **2** at 40 °C is ∼24 h,[9,13] the estimated rate acceleration by electron transfer is at least $10^5$ times over the thermal background reaction. Preliminary results from matrix isolation spectroscopy of $\mathbf{1}^{\bullet+}$ in a Freon matrix indicate that the activation barrier for cycloreversion is smaller than 5 kcal/mol.[14]

After establishing that electron transfer can efficiently catalyze the [2 + 2] cycloreversion of **1** and **2**, we investigated the mechanism of the reaction. Two catalytic cycles are conceivable for the electron transfer step: (i) a radical cation chain reaction in which the product radical cation oxidizes the reactant, thus acting as the chain carrying species and (ii) an electron transfer sensitized mechanism as shown in Figure 4 right, where the reduced form of the sensitizer is reoxidized by the product radical cation. To gain insight into the catalytic cycle of the cycloreversion, a solution of **1** in the presence of 0.02 equiv of $\mathbf{11}^+$ was exposed to defined amounts of light by repeated flashes from a photoflash and monitored by NMR. The plot of the logarithm of reactant concentration vs the number of light flashes is shown in Figure 4 left. The observed linear relationship is most easily explained by an electron transfer sensitized reaction with the catalytic cycle shown in Figure 4 right.[15]

Finally, we studied the deuterium isotope effect of the cycloreversion. In principle, the observed isotope effect ($IE_{obs}$) of an electron transfer induced reaction can be due

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(15) The alternative interpretation of the linear relationship is that the chain length is independent of the reactant concentration, which is highly unlikely.

to an equilibrium or kinetic isotope effect in the electron transfer step or a kinetic or equilibrium isotope effect in the chemical step. In previous studies of electron transfer induced reactions, the isotope effects on the electron transfer were considered to be small and $IE_{obs}$ is assumed to represent the kinetic isotope effect of the reaction.[16]

Our model systems **1** and **2** are suitable to test these assumptions. The highly exothermic cycloreversion is irreversible and consequently has no equilibrium isotope effect in the chemical step. For the same reason, the reaction should have an extremely early transition state. Therefore, a kinetic isotope effect on the chemical step of unity or a very small normal isotope effect due to the $sp^3$ to $sp^2$ rehybridization would be expected. With an excited state oxidation potential of 1.98 V vs NHE for $\mathbf{11}^+$,[17] the difference in redox potentials between $\mathbf{11}^+$ and **2** is more than 400 mV. The electron transfer step should be diffusion controlled, and therefore should not have a kinetic isotope effect. Consequently, the observed isotope effect for these systems should correspond to the isotope effect of forward and back electron transfer, i.e., the isotope effect on the pseudoequilibrium between **2** and $\mathbf{2}^{\bullet+}$.

We prepared the isotopically labeled naphthalene-benzene dimer $\mathbf{2}-d_8$ starting from predeuterated naphthalene $\mathbf{4}-d_8$ as outlined in Figure 2 and subjected it to intermolecular competition experiments at low (~10%) conversion using PET conditions with 0.02 equiv of $\mathbf{11}^+$ as sensitizer. Interestingly, an *inverse* isotope effect, $k_{H8}/k_{D8}$, of 0.91 ± 0.02 was observed. This indicates that the $IE_{obs}$ is indeed due to the electron transfer and not the chemical step. To confirm these findings, we also calculated the isotope effect of the equilibria of **1** and $\mathbf{1}^{\bullet+}$, as well as of **2** and $\mathbf{2}^{\bullet+}$, using the B3LYP/6-31G* method.[18] Selected results of these calculations are shown in Figure 5.

Upon electron transfer, the $C_{2h}$ symmetry of **1** is lowered to $C_2$ in $\mathbf{1}^{\bullet+}$ by substantial elongation by 0.12 Å of one of the bonds in the four membered ring. These changes are in agreement with a stepwise pathway corresponding to the biradicaloid mechanism of neutral benzene dimers where the bonds are broken sequentially. The cycloreversion of **1** and **2** can therefore be seen as a higher analogue of the electron transfer catalyzed cycloreversions of tricyclo[2.2.0.0]octa-2,6-diene[13] and 5,8-methano-4,5,8,9-tetrahydroindene,[19] where the singly linked intermediates have been detected spectroscopically. Other changes in the bond lengths in the four-membered ring of **1** and **2** are only 0.03−0.05 Å where

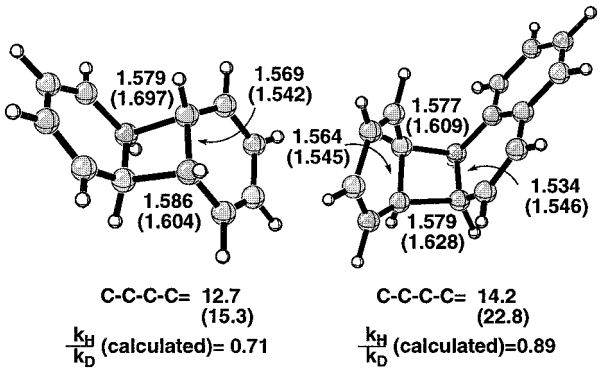


**Figure 5.** Calculated structures (B3LYP/6-31G*) of **1** (left) and **2** (right). Plain text: results for **1**/**2**; parentheses: results for $\mathbf{1}^{\bullet+}/\mathbf{2}^{\bullet+}$.

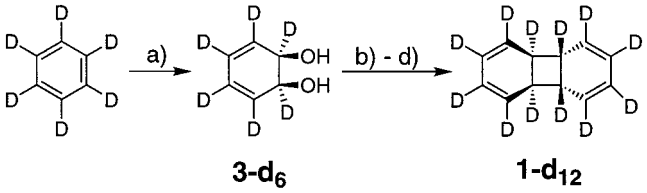


**Figure 6.** Synthesis of $\mathbf{1}-d_{12}$: (a) *E. coli* JM109(pDTG601) fermentation; (b) *hν*, thioxanthone, methanol; (c) *N*,*N*-dimethylformamid dimethyl acetal, 55 °C; (d) triflic anhydride, methylene chloride, *N*,*N*-diisopropylamine, 0 °C.

the bonds connecting the aromatic systems are lengthened and the bonds within the six-membered rings are shortened. There is a large change in the puckering angle of the cyclobutane upon electron transfer. It was pointed out by Aida et al. that although the puckering potentials in the cyclobutane radical cation are relatively soft, the changes in orbital alignment are important for the cycloreversion reaction.[20] The calculated isotope effect of 0.89 for the electron transfer in **2** is in excellent agreement with the experimental value, demonstrating that the observed isotope effect is indeed due to the equilibrium isotope effect of electron transfer.

The isotope effect in the electron transfer catalyzed [2 + 2] cycloreversion of **1** was also studied experimentally. Perdeuterated **1** was synthesized as outlined in Figure 6 by oxidation of perdeuteriobenzene in a whole cell fermentation with a recombinant strain of *Escherichia coli* which was engineered to overproduce *Pseudomonas putida* toluene dioxygenase as described by Gibson and co-workers.[21] Alternatively, the known *cis*-diol derived from bromobenzene-$d_5$ and obtained in higher yield[22] could be reduced by tributyltin deuteride to give $\mathbf{3}-d_6$. Photocycloaddition and reductive deoxygenation as described earlier[7] then gave $\mathbf{1}-d_{12}$.

Because $\mathbf{1}-d_{12}$ does not contain any hydrogens, the intermolecular competition experiment relies on the separate recording of $^1H$ and $^2H$ NMR spectra, which are then related to each other by an internal standard, 4-$d_3$-methylpyridine, which gives signals in both spectra. Although the integration of the $^2H$ spectrum was not accurate enough to yield reliable quantitative informa-

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tion, the observed strong inverse isotope effect is qualitatively in agreement with the theoretical value for $k_{H12}/k_{D12}$ of 0.71 computed at the B3LYP/6-31G* level of theory.

## Summary and Outlook

In this paper, we presented experimental and theoretical results for the electron transfer induced [2 + 2] cycloreversion of benzene dimers. The cycloreversion of these compounds, which are symmetry forbidden for the neutral ground-state molecules, is accelerated through thermal electron transfer by a factor of at least $10^5$. It was shown that the PET catalysis of the cycloreversion of **1** occurs through an electron transfer sensitized mechanism in which the product radical cation reoxidizes the pyrylium radical. The observed secondary isotope effect of $k_{H8}/k_{D8} = 0.91 \pm 0.02$ for the PET induced cycloreversion of **2** is due to the equilibrium isotope effect in the electron transfer step. The results of B3LYP/6-31G* calculations are in excellent agreement with the experimental results. These findings are particularly of interest because of the apparent disagreement between theory and experiment for the electron transfer catalyzed repair of the thymine dimer in UV light damaged DNA. Although the observed isotope effects have been interpreted as indicative of a concerted mechanism, ab initio calculations from our own group[23] and semiempirical studies from others[24] both predicted a stepwise mechanism. Our results indicate that the observed isotope effect might be a composite of several isotope effects. The assumption of negligible isotope effect of the electron transfer step may not be correct, and isotope effect studies for the elucidation of reaction mechanisms of electron transfer induced reaction have to be used with caution because of the complexity of the various contributing factors.

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**Supporting Information Available:** Energies, zero point energies, reduced partition functions and Cartesian coordinates of all computed structures (11 pages) as well as experimental details and $^1H$ and $^2H$ NMR spectra for the determination of the isotope effects on the electron-transfer catalyzed cycloreversion of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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