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Mechanistic Insights into the Stepwise Diels–Alder Reaction of 4,6-Dinitrobenzofuroxan

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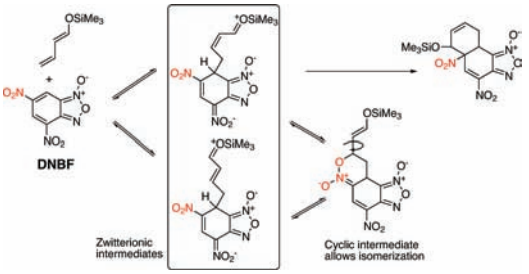
ABSTRACT

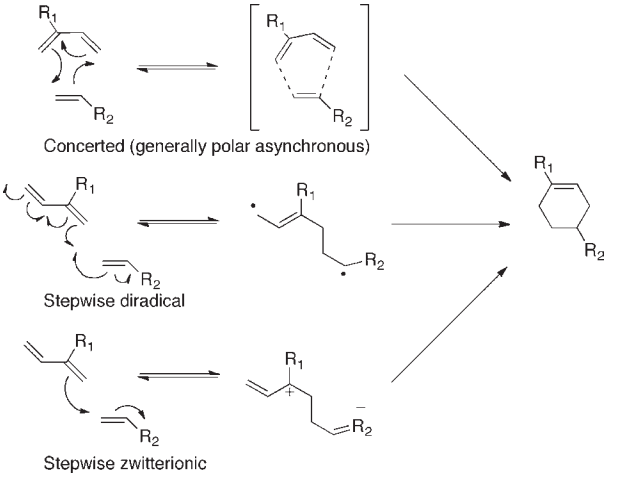


The stepwise Diels–Alder reaction between 1-trimethylsiloxy-1,3-butadiene and 4,6-dinitrobenzofuroxan is explored using state-of-the-art computational methods. The results support a stepwise mechanism via a persistent intermediate, however, not the one previously reported (Lakhdar et al., *Chem. Eur. J.* 2007, *16*, 5681) but a heterocyclic adduct. The novel DFT functional M062X and the SCS-MP2 method were essential to reproduce a reasonable potential energy surface for this challenging system.

The Diels–Alder (DA)[1] reaction has richer chemistry than first meets the eye when one considers the standard textbook drawing of a concerted, pericyclic mechanism. Although the work by Woodward and Hoffmann[2] has been paramount for the understanding of the mechanism, their model is today widely extended into several classes and special cases. Three distinct mechanisms are shown in Scheme 1.

A stepwise, diradical mechanism instead of a concerted one was considered early on, but quantum chemical calculations have discarded this much less favorable alternative,[3] although Domingo et al. very recently suggested a diradical character for nonpolar DA along certain parts of the concerted channel.[4] Many DA reactions use activated reactants to overcome the considerable kinetic barrier. This leads to highly asynchronous transition states (TSs), in which one bond is formed prior to the other along the reaction coordinate. According to one classification,[5a] the vast majority of reactions would fall into the regime of being "polar and asynchronous". While meticulous studies

Scheme 1. Several Representations of the Diels–Alder Reaction



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(2) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
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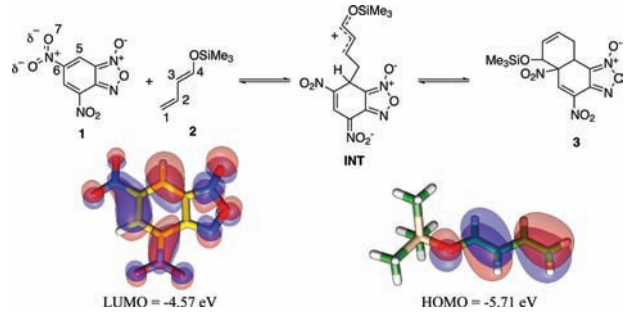
of the reaction pathway of polar DA typically lead to the conclusion that the two bonds are formed during different stages,[5] the reaction is still considered to be concerted. One can also envision a stepwise pathway involving the transfer of an electron pair, leading to a zwitterionic intermediate. A stepwise pathway can be regarded as the extreme case of a polar reaction. This type of mechanism was suggested early on,[6] but only a few computational studies of stepwise DA exist in the literature.[7] It has been argued that the two competing pathways come increasingly close to each other with more activated reactants and that catalysis often promotes even more polar transition structures,[7b,8,9] but until recently, no evidence of stepwise mechanisms yielding persistent intermediates has been presented.

Evidence was put forward by Terrier and colleagues,[10] who reported that the highly electrophilic[11] dienophile 4,6-dinitrobenzofuroxan **1** (DNBF) reacts with 1-trimethylsiloxy-1,3-butadiene **2** to form the cycloadduct **3**, in a pathway that forms the zwitterionic intermediate INT in acetonitrile (ACN) at low temperatures (Scheme 2).

Scheme 2. Reactants **1** and **2**, Putative Intermediate **INT**, and Product **3**[a]



[a] The interacting diene HOMO and dienophile LUMO are also shown as calculated at the B3LYP/6-31+G(d) level.

The intermediate was detected using NMR and UV−vis spectroscopy (no intermediates were detected in less polar solvents) and was very recently followed up by a study of a similar reaction by the same group.[12] In this study, we have investigated the mechanism leading to a detectable intermediate and asked what mechanistic and energetic aspects made the intermediate persistent enough.

We have therefore probed the potential energy surface of the reaction between **1** and **2** using density functional theory and the Møller−Plesset perturbation theory. Several pathways are analyzed in an attempt to elucidate the energetic difference between the stepwise mechanism and the standard concerted one. The calculations support the experimental finding of a two-step mechanism but imply the existence of a bicyclic, nonionic intermediate, as opposed to the zwitterion reported by Lakhdar et al.[10] We show that the bicyclic intermediate is ∼5 kcal/mol more stable than the previously reported one. This study shines more light on the ambient nature of stepwise DA reactions and shows that not even species such as **1** may be sufficient to generate detectable zwitterions.

In order to fully evaluate the possible reaction pathways, several TSs and intermediates were optimized at the B3LYP/6-31+G(d)[13] level of theory. To simulate solvation, all optimizations were done using the cPCM model.[14] The resulting geometries are shown on a potential energy diagram in Figure 1, with standard free energies calculated using the M062X[15] and SCS-MP2[16] methods with the 6-311++(2d,2p) basis set and SMD-PCM[17] solvation model for ACN and toluene. B3LYP thermodynamic corrections scaled to −40 °C are included.

We note that the B3LYP energies predict an endergonic overall reaction and low stabilities of the intermediates with respect to the reactants, both results in stark contrast to experimental observations.[10] The B3LYP barriers are also much higher than feasible for the experimental conditions (22−26 kcal/mol) (see Table S1 in Supporting Information). B3LYP overestimation of reaction energies and barriers is a known issue for this type of reaction, whereas M062X and SCS-MP2 energies are much more accurate.[18] It is comforting that the two methods lead to a similar picture of the reaction, considering they have different theoretical foundations. In the following discussion we will refer to the M062X results in ACN unless otherwise noted.

Several pathways for the formation of the first C−C bond were identified, passing over the transition states **TS1t*a***, **TS1t*b***, and **TS1c**, respectively. **TS1c** resembles the

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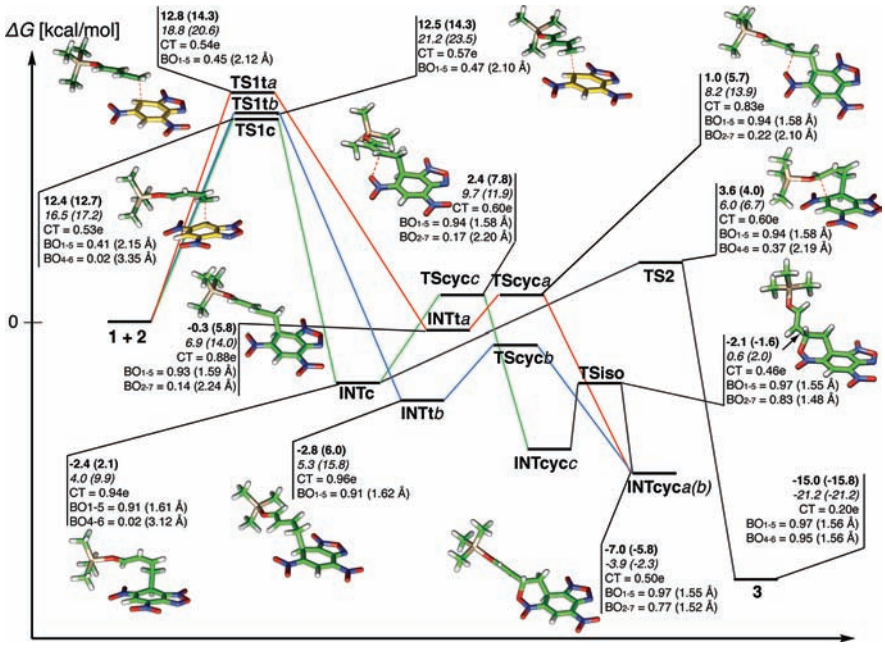

Figure 1. Free energy diagram showing possible channels for **1** and **2** reacting to form **3**. The energies are given as ΔG at 233.15 K (diagram not drawn to scale). M062X/6-311++G(2d,2p)//B3LYP/6-31+G(d) energies are given in boldface for acetonitrile (ACN), and corresponding SCS-MP2 energies are given in italics. Energies in toluene (TOL) are in parentheses. M062X Charge transfer (CT) and relevant bond orders (BOs) in ACN along with distances are also provided. Atom numbering refers to Scheme 2. Lower case letters refer to *cis* (c), *trans* (t), or cyclic (cyc) conformation. Line colors are used to depict pathways following the initial TS: red (**TS1t*a***), blue (**TS1t*b***), and green (**TS1c**).

TS of a typical concerted cycloaddition. The Wiberg bond order[19] (BO) of the incipient C1−C5 bond is nearly the same in all TSs. The C4−C6 BO of **TS1c** is virtually zero, indicating a stepwise or at least highly asynchronous pathway for the *cis* conformation. An IRC calculation[20] started from **TS1c** resulted in the intermediate **INTc**, confirming that the high asynchronicity of **TS1c** actually tips the concerted reaction over to a stepwise pathway. The amount of charge transfer (CT) is close to 0.5 e in the TSs, which translates to an extremely polar reaction in the language of Domingo and Sáez.[5a] In **INTc** and **INTt*a***/**INTt*b*** almost a full electron has been transferred as expected for a zwitterionic intermediate.

TS1t*a* and **TS1t*b*** lie 0.4 and 0.1 kcal/mol above **TS1c**, respectively. There is a larger difference between **INTt*a*** and **INTt*b***, the latter slightly more stable than **INTc**. However, a *trans* intermediate such as the one reported by Lakhdar et al.[10] can readily collapse to the bicyclic dihydrooxazine oxide **INTcyc**. This type of [2 + 4] heteroadduct has been observed for the reaction between **1** and cyclopentadiene.[10,11] We found **TScyc*a*** as a result of a QST[21] calculation, using **INTt*a*** and **INTcyc*a*** as starting guesses. Corresponding TSs between **INTt*b***, **INTc**, and their respective cyclic intermediates were subsequently found, and they have comparable barriers, as seen in Figure 1 and Table 1. The **TScyc** have small barriers in ACN and seemingly nonexistent barriers in TOL (relative **INTt**). It thus seems that polar media create local minima on the PES for the zwitterionic species, wheras **TS1t** leads directly to **INTcyc** in nonpolar media.

Table 1. Additional Species on the Potential Energy Surface

species	ΔG^a M062X	ΔG^a SCS-MP2	CT	BO_{1-5} [b,c]	BO_{2-7} [b]
TScyc*b*	−0.8 (4.9)	6.8 (13.6)	0.81 e	0.95	0.18
INTcyc*b*	−7.1 (−5.4)	−3.4 (−1.3)	0.52 e	0.97	0.74
INTcyc*c*	−6.0 (−4.9)	−2.8 (−1.2)	0.49 e	0.97	0.77

[a] ACN energies in kcal/mol, corrected to 233.15 K. TOL energies are shown in parentheses. [b] Enumeration from Scheme 2. [c] C_1-C_5 bond lengths for the tabulated species are as follows (in Å): 1.57, 1.55, and 1.57.

Attempts to find a heterocyclic, concerted pathway have led to **TS1**-like species. We have seen some indications that there exists a bifurcation on the PES from certain conformations of **TS1**, leading to either **INTt**/**INTc** or the heteroadduct **INTcyc**.[22] However, this will have little influence on the kinetics, since the **TScyc** are low in energy and the equilibria between **INTt**/**INTc** and the **INTcyc** are rapid.

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The cycloaddition can be completed only via **INTc**; the reaction must pass through **TS2**, in which the first bond is somewhat weakened to allow for a more relaxed geometry. The low barrier implies that the first bond formation (**TS1c**) is the rate-determining step. A Claisen-type sigmatropic shift from **INTcyc*c*** to form **3** is in principle also possible but has a calculated barrier of > 30 kcal/mol.

The C_2-C_3 bond in **INTt** and **INTc** is only $\sim$1.37 Å, which is marginally longer than a C−C double bond. Since the rotational barrier around a C−C double bond is exceedingly high, around 60 kcal/mol, it can be anticipated that the isomerization transition state lies much higher than **TS1t**. However, isomerization between **INTt** and **INTc** can be mediated by the **INTcyc** state, as the C_2-C_3 bond is prolonged to 1.48 Å. It should allow more feasible rotation, which is confirmed by the affordable **TSiso** shown in Figure 1. Hence **TS2** can be reached through all initial pathways via rotamers of **INTcyc**.

The inability to detect an intermediate in toluene is explained by the increased energy difference between **TS1c** and **TS1t** with lower solvent polarity and the fact that the **TScyc** barrier becomes higher than TS2. It is not surprising that the barrier of the *trans* pathway is more sensitive to the solvent polarity, considering that the appearing negative and positive charges are more exposed to the solvent in **TS1t** than in **TS1c**. At the M062X level, **TS1c** is lower by 1.7 kcal/mol, which corresponds to a factor 400 difference in reaction rate at −40 °C. The even larger energy difference, 3.4 kcal/mol, at the SCS-MP2 level corresponds to a staggering 1500 difference in rate. Thus, both methods indicate that the *cis* pathway is strongly dominating in toluene and that only trace amounts of **INTcyc** are likely to be formed.

Comparing SCS-MP2 to M062X, the relative energy differences are fairly conserved, with some discrepancies. There is, for example, a larger difference between **TS1c** and **TS1t*a***/**TS1t*b*** and also lower stability of **INTc** toward **TS2**. In fact, in TOL there is no second barrier with SCS-MP2, which suggests a concerted, classic DA reaction. The **INTt*a*→TScyc*a*** barrier remains unchanged at 1.3 kcal/mol. Curiously, **TS1t*b*** is the highest observed SCS-MP2 barrier, and the subsequent **INTt*b*** is less stable than **INTc**. Overall, M062X seem more reliable since SCS-MP2 overestimates the energies of all **TS1** and **INT** species, given the slow rates emerging from the barriers.

Our computational results lead to the conclusion that **INTcyc** is the only intermediate with sufficient stability toward **TS2** and that this likely is the one detected by Lakhdar et al. Although the computational results indicate that the classic *cis* pathway is also nonconcerted, at least in acetonitrile, neither **INTc** nor **INTt** seem sufficiently long-lived with respect to **INTcyc**. At −40 °C, the estimated rates of forming **3** from **INTcyc(*a*,*b*)** and **INTc** are $\sim 6 \times 10^2$/s and 1×10^7/s, respectively.

Lakhdar et al. propose that they have detected an **INTt**-like intermediate, but we have found this difficult to understand from the PES.[23] Additional support for the **INTcyc** structure was found by comparing the C_1-C_5 bond against chemically similar fragments in the Cambridge Structural Database.[24] The search yielded more hits and better correlation for the $\sim$1.55 Å distance of the cyclic intermediates versus $\sim$1.60 Å of the acyclic ones. (See the Supporting Information for further details). Moreover, in the closely related system studied in ref 12, the authors find computational evidence of analogous heterocyclic intermediates. These do not, however, provide additional stabilization toward the second barrier, which is a reasonable explanation for why no intermediate was experimentally detected.[12b]

We have thus shown that the stepwise DA pathway of **1** + **2** is more complicated than on first glance. First, the *cis* pathway is the dominating channel for forming the Diels−Alder product, but the *trans* pathway has only a slightly higher activation barrier in acetonitrile. The most stable intermediate is **INTcyc**, which can mediate *cis*/*trans* isomerization of the diene moiety. This is the only intermediate with an appreciable stability toward reactants and **TS2** and is from theoretical considerations most likely the intermediate that has been detected. As the literature is abundant with DA reactions between activated species,[25] it is possible that some of these proceed with a stepwise pathway, albeit only with transient intermediates. This notion should be important to bear in mind when designing new catalysts in order to maximize the catalytic efficiency and stereoselectivity.

We can further conclude that commonly used methods such as B3LYP and MP2 are not sufficiently accurate for characterizing the potential energy surfaces of this type of cycloaddition reaction. As our calculations show, the intermediates of this reaction would be overlooked if one considered only the B3LYP PES.

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Note Added after ASAP Publication. On November 29, 2011 this paper was published containing an error. The name of 4,6-dinitrobenzofuran was corrected throughout and it reposted December 5, 2011.

Supporting Information Available. Computational methods, additional figures, structural comparisons to the CSD,[24] comparisons with the system reported in ref 12, B3LYP free energies and molecular coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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