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Intramolecular Cycloaddition

Thermal Cycloaddition Facilitated by Orthogonal π–π Organization through Conformational Transfer in a Swivel-Cruciform Oligo(phenylenevinylene)**

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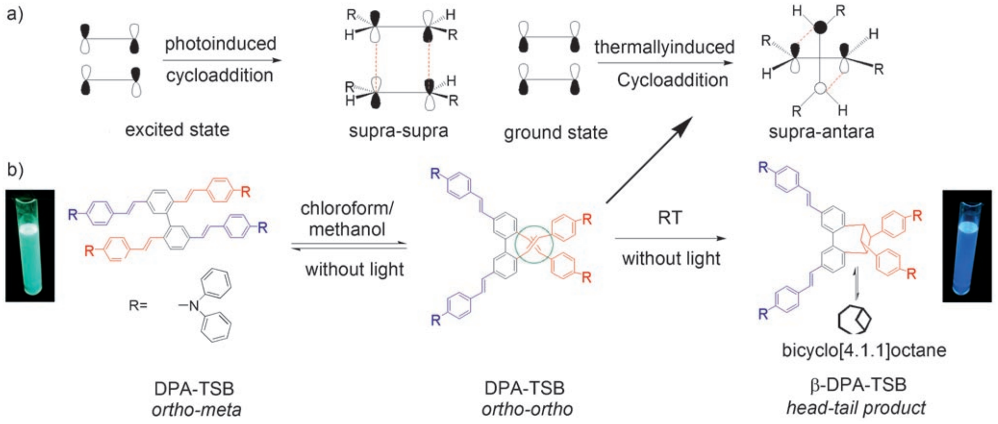
The [2+2] cycloaddition of olefins has been the object of extensive theoretical[1] and experimental studies.[2] It is the most versatile and efficient method for synthesizing four-membered-ring skeletons and has been applied widely in natural products synthesis. Generally, these reactions occur according to the Woodward–Hoffmann rules[1a–e] and can be activated either thermally (supra–antara reaction process) or photochemically (supra–supra reaction process; Scheme 1 a).[3] Bringing two π bonds into close proximity with the correct orientation is a key step in the promotion of [2+2] cycloaddition reactions in a regio- and stereoselective manner with a high rate.[4] For photoinduced [2+2] cycloaddition, the olefinic units must be aligned in a parallel manner at a close distance from one another.[2f,5] Extensive efforts have been made to promote this reaction. For example, microcavities in zeolites[6] or cyclodextrins,[7] rotaxane interaction,[2f] the photoirradiation of stilbene crystals,[8] and silyl-chain tethers[9] have been employed to accelerate the photodimerization. However, although diverse methods are available for the photocycloaddition, hardly any effective methods have been developed for the preorganization of two normal olefins in an orthogonal arrangement as required for a thermal concerted [2+2] cycloaddition. Only a few special examples exist of substrate types, such as cumulative π-bonded systems and a few highly constrained cyclic olefins,[10] that are able to undergo a concerted thermal cycloaddition as a result of their special electronic structure. In the case of stilbene, to our knowledge, no concerted thermal cycloaddition has been described, for the requisite orthogonality is not readily accessible as a result of steric hindrance and angle strain.[1a]



Scheme 1. a) Schematic representation of cycloaddition reactions according to the Woodward–Hoffmann rules. b) Chemical structures of DPA-TSB and its proposed intramolecular-cycloaddition product β-DPA-TSB. Digital photos are shown of dilute solutions of DPA-TSB and β-DPA-TSB under irradiation with UV light.

Herein we report an intramolecular [2+2] cycloaddition at room temperature in the swivel-cruciform molecule 2,5,2′,5′-tetra(4′-*N*,*N*-diphenylaminostyryl)biphenyl (DPA-TSB) with a central biphenyl motif (Scheme 1 b).[11] The central biphenyl tether is responsible for the nonlinear assemblage and relatively free rotation of the molecule. These characteristics result in a swivel-cruciform conformation and the conformational multiformity of DPA-TSB. Conformational transfer of the biphenyl core can place the *ortho*-substituted double bonds in DPA-TSB in the orientation required for thermal [2+2] cycloaddition (an orthogonal arrangement of π orbitals at a short distance) and give the intramolecular cycloaddition product under very mild conditions.

The [2+2] cycloaddition was found to occur during the slow recrystallization of DPA-TSB[11c]. A solution of DPA-TSB (≈2 mg mL^{-1}) in chloroform was sealed carefully under a saturated methanol atmosphere and protected from light. After a slow evaporation process, the solid product was

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precipitated at room temperature. The precipitated solid (named hereafter β-DPA-TSB) was a single compound and required no further purification. It displayed completely different properties to those of DPA-TSB, for example, blue fluorescence instead of the green fluorescence of the initial compound (Scheme 1), as a reflection of the remarkable structural changes that had taken place.

The MALDI-TOF mass spectrum of β-DPA-TSB showed the compound to have the same molecular weight as DPA-TSB and thus indicated that an intramolecular rather than an intermolecular reaction had occurred. The ^{1}H NMR spectra of β-DPA-TSB and DPA-TSB are shown in Figure 1 for comparison. The signals for the hydrogen atoms of DPA-TSB are all located in the aromatic region, in good agreement with its structure, whereas resonances at $\delta = 4.25$ and 3.95 ppm, which are characteristic of methine hydrogen atoms in a cyclobutane structure, are observed for β-DPA-TSB.[4,9a,12] Furthermore, the appearance of only one set of cyclobutane signals in the ^{1}H NMR spectrum suggests that only one product with a cyclobutane ring was formed. The resolved ^{13}C NMR spectrum for β-DPA-TSB further confirms the proposed cyclobutane structure: Two signals at $\delta = 53.8$ and 36.9 ppm[13] can be assigned to the sp^3-hybridized junction carbon atoms. Further evidence for the cyclobutane structure is provided by the appearance in the IR spectrum of new bands due to a methine stretching vibration and a cyclobutane-ring-deformation vibration at 2970 and 667 cm^{-1}, respectively,[14] as well as by the intensity decrease of the *trans*-vinylene vibrational band at 964 cm^{-1}.[15] The results of all structural analyses testify the chemical structure and configuration of β-DPA-TSB as shown in Scheme 1. The decrease in the π conjugation through the formation of the four-membered-ring structure in β-DPA-TSB accounts for the blue shift observed in the electronic spectrum.

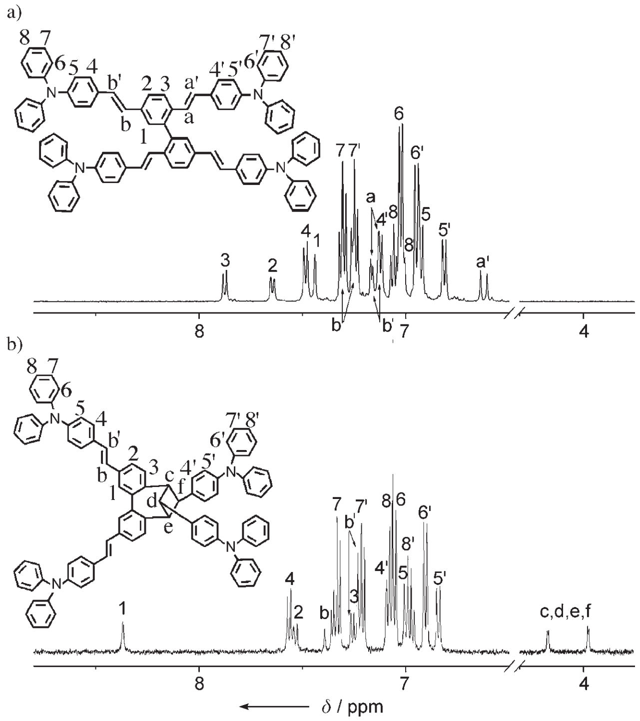


Figure 1. ^{1}H NMR spectra of a) DPA-TSB and b) β-DPA-TSB in [D$_6$]DMSO at room temperature.

DPA-TSB can transform spontaneously and in a highly stereospecific manner into β-DPA-TSB at room temperature (25 °C) in the dark. It is surprising that such a [2+2] cycloaddition can occur under such mild conditions. A slight increase in the temperature can improve dramatically the reactivity of DPA-TSB in this process (see Supporting Information). On the basis of the product structure and the reaction conditions, the reaction is most likely a thermal [2+2] cycloaddition.[16] Generally, the occurrence of a thermal [2+2] cycloaddition requires very special conditions, typically a close and orthogonal stacking of the two double bonds. High electron density at the reacting positions is also favorable for reaction efficiency.[17] The special structural features of DPA-TSB satisfy these requirements.

The first requirement is satisfied by the conformational multiformity of such swivel-cruciform molecules. The two substituted styrene moieties at *ortho* positions of the biphenyl core of DPA-TSB show [2+2] cycloaddition activity in the configuration described as *ortho–ortho* in Scheme 1. The total energy of DPA-TSB was calculated by using density functional theory (DFT) at the B3LYP/6-31G level as implemented in Gaussian 03 for different conformations with fixed dihedral angles. The energy was plotted against the dihedral angle of the biphenyl unit from 30 to 150° (Figure 2). In the profile there are two minima, for dihedral angles of 64.3 and 116.6°; the energy of the latter conformation is slightly higher by 2 meV.[18] The structures of the corresponding conformers are shown in Figure 2. The quantum-chemical simulations indicate that in its most stable conformation, DPA-TSB is a cruciform and centrally symmetrical molecule in which there is a 64.3° dihedral angle between one *meta*-positioned arm and one *ortho*-positioned arm. This conformation is also the predominant conformation of DPA-TSB in the ground state in solution, as confirmed by ^{1}H NMR spectroscopy.[19] In this conformation, all the double bonds are too far away from one another to react. Upon rotation about the biphenyl bond, a series of conformations located around the two minima within a wide range of approximately 60 to 120° are close in energy.

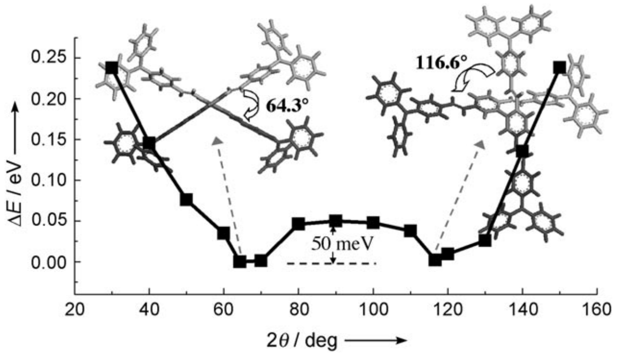
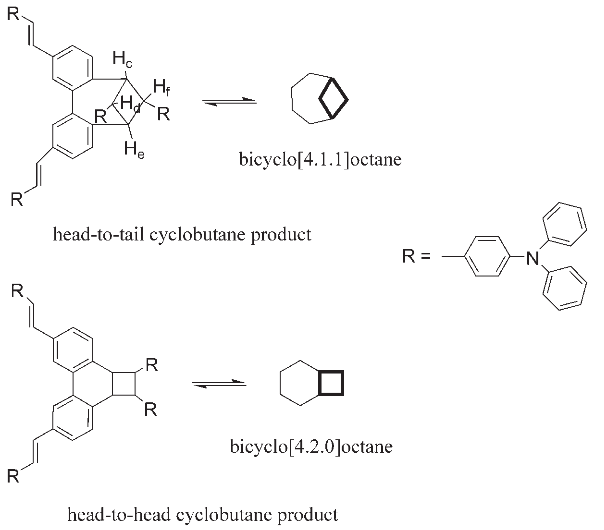


Figure 2. Calculated energy profile of DPA-TSB for rotation about the biphenyl bond, and the two conformations of the lowest-energy states.

The highest-energy conformation within this series has a dihedral angle of 90° and results in an energy barrier between the two most stable conformations. However, this energy barrier is only approximately 50 meV: slightly higher than the thermal energy kT at room temperature (25 meV). Therefore, theoretically, mild conditions can trigger free rotation about the aryl–aryl bond in DPA-TSB to give a series of different conformations. Moreover, in the second stable conformation with a dihedral angle of 116.6°, the two *ortho*-positioned arms are found to come closer to one another and overlap in the form of a cross. The π orbitals of the corresponding double bonds are arrayed spontaneously in an orthogonal orientation compatible with the Woodward–Hoffmann rules for a concerted thermal cycloaddition. The experimental observation that the reaction proceeds under very mild conditions can be justified by these theoretical results.

The very high electron density of the double bonds in DPA-TSB as a result of the strong electron-donor effect of the diphenylamine substituents satisfies the second requirement for enhanced cycloaddition reactivity. Although the energy barrier to conformational transfer is very low according to simulations in the gas phase by theoretical methods, ^{1}H NMR spectroscopic studies[19] show that, practically, the most stable conformation (with a dihedral angle of 64.3°) is very much the predominant conformation of DPA-TSB in solution at room temperature. Fluctuations in the orientation of the biphenyl core occur mainly around this conformation, and the probability of transfer to the second stable conformation is low. Thus, a high reactivity of the alkenes is required to promote the [2+2] cycloaddition. Earlier studies[1f,10b,20] showed that only activated alkenes with electron-donating or electron-withdrawing substituents are able to undergo [2+2] cycloadditions under mild conditions; otherwise, a high temperature is required. Indeed, the analogue of DPA-TSB without diphenylamine substituents, 2,5,2′,5′-tetrastyrylbiphenyl (TSB),[11a] shows no cycloaddition activity at all.

For a simple thermal [2+2] cycloaddition reaction, a stepwise process via either zwitterionic or biradical intermediates is the commonly accepted mechanism.[1g] However, this reaction is independent of the polarity of the solvents or the addition of a radical initiator (see Supporting Information). DPA-TSB undergoes the [2+2] cycloaddition under very mild conditions and is converted into the product in a highly stereospecific manner without the occurrence of side reactions. On the basis of these characteristics of the reaction, we propose a concerted mechanism. However, a stepwise process can not be fully excluded, and the possibility will be investigated further. According to the geometry of DPA-TSB and the supra–antara combination of the π bonds, β-DPA-TSB should be a head-to-tail cyclobutane product rather than a head-to-head product,[1g] as confirmed by ^{1}H–^{1}H NOESY (nuclear Overhauser enhancement spectroscopy) analysis (see Supporting Information). The four hydrogen atoms on the cyclobutane ring (H_c, H_d, H_e, and H_f) were found to have homogeneous chemical environments, which is consistent with the hypothetical bicyclo[4.1.1]octane structure in the supposed head-to-tail cycloadduct (Scheme 2). Therefore, the configuration of the double bonds in DPA-TSB is conserved in the transformation into β-DPA-TSB.



Scheme 2. Hypothetical molecular structure of the cycloadduct β-DPA-TSB (top), and the structure of an alternative cyclobutane product for comparison (bottom).

In summary, we have described an unprecedented intramolecular [2+2] cycloaddition under very mild conditions. The special framework of DPA-TSB plays important roles in this reaction. The π bonds of the two *ortho*-positioned arms in DPA-TSB can be aligned in an orthogonal manner for an efficient diastereospecific thermal [2+2] cycloaddition. This result will inspire new ideas for methods in organic synthesis, especially in the fields of materials and medicinal science.

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[16] We are not considering a biradical mechanism at present because of the purity of the product and high stereospecificity of the reaction (hardly any side reaction occurred), as well as the mild conditions. The use of a radical initiator failed to trigger the reaction (see Supporting Information)..

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[18] Through theoretical studies, we found that the *meta* substituents in DPA-TSB play an important role in decreasing the energy difference of the two energy minima and stabilizing the second stable conformation.

[19] The predominant conformation adopted by an analogous molecule, 2,5,2′,5′-tetra(4-*tert*-butylphenyl)-1,1-biphenyl, as a result of a strong π–π interaction between the *ortho*-substituted arms is similar to the second stable conformation of DPA-TSB (with a dihedral angle of 116.6°): B. S. Nehls, F. Galbrecht, A. Bilge, D. J. Brauer, C. W. Lehmann, U. Scherf, T. Farrell, *Org. Biomol. Chem.* **2005**, *3*, 3213.

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