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Comment on T. Stauch, A. Drew, “Stiff-stilbene photoswitch ruptures bonds not by pulling but by local heating”, *Phys. Chem. Chem. Phys*. 2016, 18, 15848.

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In 2009 we reported[1] a series of macrocycles combining either *E* or *Z* isomer of stiff stilbene with trans-dialkylcyclobutene (Fig. 1a). Relative to the *Z* macrocycles, the *E* analogs are strained, with the smaller macrocycles relatively more strained than the larger ones. Careful kinetic measurements revealed the activation enthalpy of isomerization of dialkylcyclobutene moiety (blue, Fig. 1a) to E,E-butadiene (reaction 1) in every *E* macrocycle, $\Delta H_E^{\ddagger}$, to be lower than in the corresponding *Z* analog, $\Delta H_Z^{\ddagger}$.

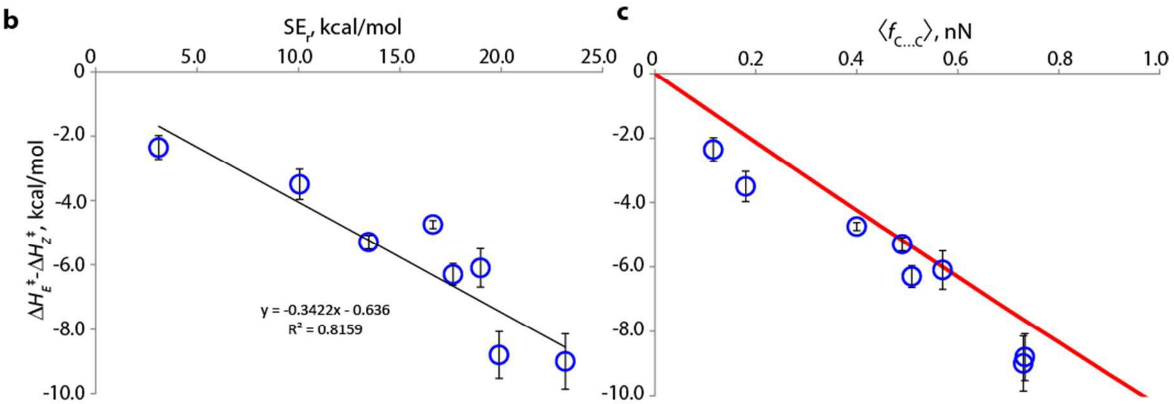

Figure 1. Summary of the reactivity of dialkylcyclobutene (blue) connected to *E* or *Z* stiff stilbene: (a) the chemical structures of the macrocycles and a qualitative energy diagram for isomerization of cyclobutene to butadiene; (b-c) the differences of measured enthalpies of activation of cyclobutene isomerization in *E* and *Z* isomers of the same macrocycle, $\Delta H^{\ddagger}_E$- $\Delta H^{\ddagger}_Z$ correlates well with both the strain enthalpy of *E*-r relative to *Z*-r, SE$_r$ (b) and the restoring

force of the C…C coordinate (red arrows in (a)) in *E*-r, $\langle \boldsymbol{f}_{C\ldots C} \rangle$(c). The red line is the calculated barrier lowering of *trans*-dimethylcyclobutene isomerization with force applied across the C atoms of the methyl groups. The data is from refs. 1, 2.

Like many other strained organic molecules studied by chemists over the years,[3-6] the difference is attributable to partial relief of strain in the respective transition state of the *E* isomers (*E*-ts). This rationalization is supported, for example, by a good correlation between the measured barrier lowering and the calculated strain energy of *E*-r relative to *Z*-r, SE_r (Fig. 1b). What sets these macrocycles apart from hundreds of other known strained organic molecules is that the measured barrier lowering in *E* macrocycles, $\Delta H_E^{\ddagger}$- $\Delta H_Z^{\ddagger}$, correlates remarkably well (Fig. 1c) with the restoring force of the $C \cdots C$ coordinate defined by red arrows in Fig. 1a. This restoring force quantifies kinetically significant strain imposed on cyclobutene by the macrocycle and represents a coarse-grained description of all molecular degrees of freedom of the macrocycles other than 36 of the dimethylenecyclobutene core (blue in Fig. 1a). Unlike strain energy, restoring force describes strain-induced changes in chemical reactivity irrespectively of the molecular nature of the coarse-grained degrees of freedom, which is particularly valuable in discussing reactions in stretched polymers, where explicit description of all molecular coordinates is untenable.[7-10] Consequently, stiff stilbene macrocycles of the architectures shown in Fig. 1, containing cyclobutene or other reactive moieties,[11-15] link small strained molecules to polymer mechanochemistry.[16] For example, we previously demonstrated[11] that kinetics of gem-dibromocyclopropane isomerization incorporated in stiff stilbene macrocycles predicts accurately the mechanochemical behavior of poly(dibromocyclopropanes) observed by single-molecule force spectroscopy.[17]

In ref. [18] Stauch and Dreuw claim that the observed lowering of the activation enthalpy of cyclobutene isomerization in *E* macrocycles relative to their *Z* analogs cannot be attributed to the partial relaxation of strained *E* macrocycle in the transition state of cyclobutene ring-opening (e.g., “the mechanical work transmitted from stiff-stilbene to cyclobutene is much too low to account for the observed facilitation of the ring opening” and “little evidence exists that the photoswitch pulls indeed ‘‘strong enough’’ to break the covalent bond in cyclobutene.”). Instead, they rationalize our observations as resulting from “local heating”, which seems to refer to the so-called “hot ground state” reactivity in which a highly vibrationally excited chromophore in the ground electronic state overcomes an activation barrier before dissipating the energy of the absorbed photon into the environment by intermolecular vibrational energy transfer (VER).[19] These claims reflect misunderstanding of how activation enthalpies in Fig. 1b-c were measured, how fast solutes thermalize and how molecular strain, whether in a small molecule or a stretched polymer, lowers the activation energies of chemical reactions. All these points have been addressed repeatedly in the literature but the appearance of claims like those in ref. [18] suggests that they need repeating.

1. Irradiating solutions of *Z***3**-*Z***8** at room temperature produced photostationary mixtures containing only *Z*-r and *E*-r macrocycles without any traces of the products *E*-p or *Z*-p. The activation parameters of cyclobutene isomerization in these macrocycles were measured by heating individual isomers in the dark. This immediately rules out any contribution of photon absorption to the acceleration of cyclobutene isomerization in **3**-**8**.[1]
2. The reactivity of *Z* macrocycles **1**-**2** is more complex. No new species was observed upon irradiating solution of *Z***1**-*Z***2** at temperatures <30 °C. At ≥45 °C, depletion of *Z*-r was accompanied by the appearance of *E*-p and *Z*-p macrocycles at a rate whose temperature and photon-flux dependence was consistent with highly strained *E*-r macrocycles thermally relaxing to *Z*-r analogs in preference to *E*-p products ($\Delta H^{\ddagger}_{E \rightarrow Z}$ = 16.5±0.8 and $\Delta H_E^{\ddagger}$=21.3±0.7 kcal/mol).[20] These barriers, which agreed well with computations,[1, 20] are too high to be traversed before the

E-r macrocycles fully thermalize. The cooling dynamics of aromatic solutes, including stilbene, has been studied extensively.[19, 21] Less information is available on stiff stilbene, but its cooling dynamics seems to resemble that of stilbene.[22] Sension et al.[23] found that in hexadecane at 300 K absorption of a 312 nm photon by *Z*-stilbene produced the *E* isomer in 1 ps with the vibrational temperature of 725±100 K, which subsequently thermalized with the rate constant of 0.07±0.01 ps^{-1}. In other words, in 1 ps stilbene lost approximately 65% of the absorbed photon energy. Since intramolecular vibrational redistribution is faster than 1 ps,[24] standard RRKM theory[25] allows one to estimate that at 45 °C an *E*-r macrocycle **1**-**2** with 25 kcal/mol excess energy (35% of 375 nm photon) traverses a 20 kcal/mol barrier with the rate constant of <0.1 ms^{-1}, or 6 orders of magnitude slower than the cooling rate constant measured by Sension et al. To illustrate this difference: in the time it took macrocycle *E*-r**1** or *E*-r**2** to cool from 700 K to 600 K (3.5±0.7 ps) only 1 molecule in ~10^7 could have converted to *E*-p and the ratios became increasingly unfavorable for cyclobutene isomerization as the cooling proceeded. Since *E*-r of **1**-**2** is >20 kcal/mol higher in energy than the *Z* analogs, the most plausible excess vibrational energy in *E*-r 1 ps after photon absorption is ~10 kcal/mol, making hot ground state reactivity even more fantastical than the estimates above suggest. This conclusion agrees well with the previous conclusion that hot ground state reactivity contributes negligibly to isomerization of dimethylcyclobutene (a molecule 1/5th the size of macrocycles **1**-**3**) irradiated at 230 nm.[26]

3. Stauch and Dreuw argument about stiff stilbene not being "'strong enough' to break the covalent bond in cyclobutene" is meaningless without referencing the timescale. For example, at 300 K the half-life of *E*-dimethylcyclobutene with respect to isomerization to *E*,*E*-hexadiene is ~134 years without any force at all. A tensile force of 800 pN acting on the C atoms of the methyl groups reduces this half-life to 1 h and a force of 1.3 nN reduces it to 1 s.[2] The stretching force of 700 pN, which Stauch and Dreuw acknowledge[18] *E* stiff stilbene can apply on cyclobutene, is enough to reduce the half-life of *E*-dialkylcyclobutene 10^5-fold at 300 K. This acceleration was observed experimentally.[1, 20] In other words, stiff stilbene is plenty "strong" to measurably accelerate cyclobutene isomerization.
4. Stauch and Drew further argue[18] that the cyclobutene core in *E* macrocycles is not strained enough to become more reactive. Partitioning of strain energy among various internal coordinates of a strained reactant is irrelevant in determining whether strain relief contributes to acceleration of its reactions,[6] only that the strain is (partially) relieved in the rate-determining transition state. For example, most if not all models of mechanochemical kinetics assume that the strain energy of the reactive moiety changes negligible between the reactant and the rate-determining transition state, compared to the energy released by relaxation of "non-reactive" molecular coordinates (i.e., molecular coordinates outside the reactive site) over the same part of the reaction path. The energy released by such (partial) relaxation is approximately a product of the elongation of the molecule along the pulling axis and the stretching force, and is often referred to as "mechanochemical work".[8-10] In *E* macrocycles, the molecular basis of this "work" is partial relaxation of strained *E* stiff stilbene, which is obvious from an increase in the stiff stilbene torsion in the transition state of cyclobutene isomerization (Fig. 2) and the linkers connecting it to the cyclobutene moiety.
5. Finally, contrary to the authors' claim, isomerization of cyclobutene to butadiene studied by us in refs. 1-2 and illustrated in Fig. 1 of ref. [18] is not [2+2] cycloreversion, which produces an alkyne and an olefin,[26] but electrocyclic isomerization.[3] Few if any genuine examples of thermal [2+2] cycloreversions exist,[3] because they require very high activation barriers (e.g., thermal dissociation of cyclobutane into ethylene has the activation energy of >60 kcal/mol[27] and probably proceeds by a radical mechanism) whereas electrocyclic reactions have moderate

barriers (e.g., 31.0±0.5 kcal/mol for *trans*-dimethylcyclobutene[1]) and proceed by a concerted mechanism.

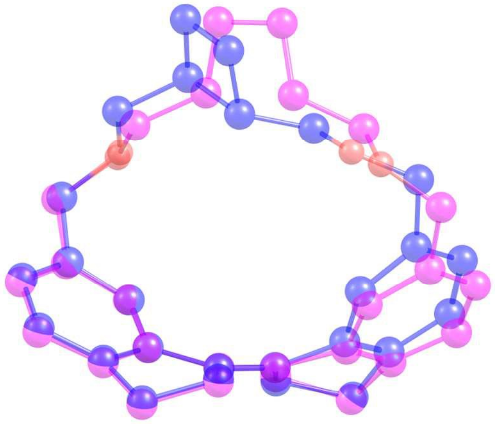

Figure 2. An overlay of the minimum-energy conformers of *E*-r (blue) and *E*-ts (magenta) of macrocycle **1** demonstrating that the formation of *E*-ts is accompanied by an increase in the torsion of stiff stilbene towards its strain-free value of 180°, thus partially releasing strain energy of molecular degrees of freedom outside the cyclobutene moiety. The structures are at the O3LYP/6-311G(2d,p) level of the DFT in the gas phase.

In summary, hot ground state reactivity in solution is very rare; among solutes of the size of macrocycles **1**-**8** it is unprecedented. Careful measurements and computations are consistent with the acceleration of cyclobutene isomerization in the *E* macrocycles reflecting strain relief primarily of *E* stiff stilbene and potentially the linkers, made possible by the elongation of the exocyclic C···C distance of the dialkylcyclobutene moiety in *E*-ts (Fig. 1a). The energy gain of this partial relaxation of the corresponding molecular degrees of freedom is approximated well as the product of the restoring force of the C···C coordinate (red arrows, Fig. 1a) and the difference in its length between the reactant and transition state (Fig. 1c). This product, often referred to as mechanochemical work, is widely used in mechanochemical kinetics to estimate lowering of activation barrier in stretched polymers. Consequently, molecular architectures exemplified by macrocycles **1**-**8** establish a connection between small-molecule reactivity and polymer mechanochemistry.

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