Supporting Information:

Understanding Covalent Mechanochemistry

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I. COMPUTATIONAL DETAILS

The calculations have been performed using the TURBOMOLE program package\textsuperscript{1} within the framework of density functional theory (DFT)\textsuperscript{2}. These DFT calculations have been carried out using the B3LYP hybrid functional\textsuperscript{3} together with Ahlrichs’ economical SVP basis set\textsuperscript{4} within the spin–unrestricted (polarized) Kohn–Sham formalism. All techniques to perform the reported mechanochemical calculations, such as computing the force–transformed EFEI potential energy surfaces (PES), optimizing molecular structures at isotensional conditions, or mapping force–transformed Intrinsic Reaction Coordinates (IRC), have been implemented in TURBOMOLE or interfaced with it.

In the absence of applying any external force, $F_0 = 0$, the particular electronic structure method chosen yields activation energies of 42.9 and 49.9 kcal/mol for the conrotatory and disrotatory processes, respectively, corresponding to electrocyclic ring–opening reactions of the cis reactant (see Fig. 1 herein for all structures involved in the study). As usual, these activation energies are simply defined as the difference in the Born–Oppenheimer (BO) potential energy, $V_{\text{BO}}$, between the transition state (TS) structures and the reactant structures, i.e. $E^\ddagger = V_{\text{BO}}(x^{\text{TS}}) - V_{\text{BO}}(x^{R})$. The difference in activation energies for both processes agrees very well with the theoretical work by Sakai\textsuperscript{5} on the electrocyclic ring–opening reaction of benzocyclobutene. The CAS–MP2 calculations reported by Sakai are 44.0 and 52.1 kcal/mol for the activation energies of the conrotatory and disrotatory processes, respectively. On the other hand, the experimental activation energy for the conrotatory ring–opening of cis 1,2–dimethylbenzocyclobutene is 36.9 kcal/mol\textsuperscript{6,7}. Both Sakai’s computed values and Roth’s experimental data allow us to safely conclude that our computational methodology yields reliable results at a low computational cost. At this point, we have to stress that the EFEI approach we have introduced can be easily generalized to be used in combination with any other electronic structure method where gradients are available, including high–level wavefunction–based methods that include both electron correlation and multireference character for taking properly bond breaking into account.

With regards to the EFEI calculations where the external force is explicitly included the force has always been applied along the line connecting the carbon atoms of the two methyl groups of the molecule as depicted in Fig. 2 herein, and no part of the molecule has been
II. CONSTRUCTION OF FORCE–TRANSFORMED POTENTIAL ENERGY SURFACES

In general, the PES depicted in Figs. 2(c) to 2(f) of the main text have been constructed from the swarm of the trajectories followed by every IRC in the two-dimensional space spanned by the C₃–C₄ distance and the polar angle φ (see Fig. 2 herein). In particular,
The external force that is explicitly included in the presented EFEI calculations is always applied, in particular at each step of structure optimizations, along the distance that connects the C\(_1\) and C\(_2\) carbon atoms as depicted in this scheme. The coordinate \(\phi\) is the angle between the average of the C\(_1\)–C\(_3\) and C\(_2\)–C\(_4\) vectors and the normal to the average plane spanned by the four carbon atoms that constitute the cyclobutene ring of the reactant.

The surface depicted in Fig. 2(c) of the main text, i.e. the PES at zero force in this two-dimensional subspace, has been constructed from following the IRCs obtained at different values of the external force, but using the Born–Oppenheimer potential energy, \(V_{\text{BO}}\), instead of the force–transformed EFEI energy, \(V_{\text{EFEI}}\), as a function of the C\(_3\)–C\(_4\) distance and the polar angle \(\phi\). This procedure allows one to sample conveniently the PES around the IRC. At finite forces, the surfaces depicted in Fig. 2(d), Fig. 2(e), and Fig. 2(f) of the main text have been obtained by adding the mechanical energy associated with the external force (i.e. \(F_0q(x) = F_0q\), where \(q\) is the distance between the C\(_1\) and C\(_2\) atoms to which the applied force of magnitude \(F_0\) is collinear) to the Born–Oppenheimer energies, \(V_{\text{BO}}\), thus yielding the EFEI energies, \(V_{\text{EFEI}}\), as a function of the C\(_3\)–C\(_4\) distance and \(\phi\). The yellow curves show the IRC at the corresponding external force \(F_0\), whereas the curves depicted in black and red in each surface correspond to the IRC at zero force and the IRC at the maximum force before the C\(_3\)–C\(_4\) bond breaks, respectively. The latter two trajectories define the region where no extrapolations are required to get the energy value whereas the energies shown outside this area have been obtained approximately by extrapolation.
III. MODELS TO DESCRIBE THE DEPENDENCE OF THE ACTIVATION ENERGY ON THE APPLIED FORCE

In this section we present a detailed explanation of the approximate phenomenological models that can be used to rationalize the force–dependence of the activation energy of non–covalent reactions, i.e. in the limit of sufficiently small forces, as analyzed in Fig. 1 of the main text.

The earliest phenomenological model to describe the increased rate of bond dissociation under external force $F_0$ was proposed by Bell\textsuperscript{8} for estimating the associated decrease of lifetime, $\tau = \tau_0 \exp[E^\dagger_{\text{Bell}}(F_0)/k_BT]$, for rather weak non–covalent bonds associated to electrostatic, van der Waals or hydrogen bonding interactions to describe cell adhesion. Bell’s model assumes a small reduction of the barrier of the probed process by the applied force without considering any structural change, neither for the reactant nor for the transition state configuration. Thus, Bell’s model assumes that the underlying Born–Oppenheimer energy landscape of the reaction does not change when applying the force. All features of this energy landscape are represented by one single parameter, $\Delta q_{\text{BO}}$, which is the difference between the value of the mechanical (generalized) coordinate $q$ at the transition state structure $q_{\text{BO}}(x_{\text{TS}}(F_0 = 0))$ and at the reactant minimum structure $q_{\text{BO}}(x_{\text{R}}(F_0 = 0))$ on the Born–Oppenheimer surface $V_{\text{BO}}(x)$ in the absence of force, i.e. $\Delta q_{\text{BO}}$ is the “distance to the TS” coming from the reactants along $q$. Thus, the force-dependence of the activation energy in Bell’s model is simply given by $E^\dagger_{\text{Bell}}(F_0) \approx E^\dagger_{\text{BO}}(F_0 = 0) - F_0 \Delta q_{\text{BO}}(F_0 = 0)$, where $E^\dagger_{\text{BO}}(F_0 = 0)$ is the activation energy of the reaction at zero force, $F_0$ is the applied external force, and $\Delta q_{\text{BO}}(F_0 = 0) = q_{\text{BO}}(x_{\text{TS}}(F_0 = 0)) - q_{\text{BO}}(x_{\text{R}}(F_0 = 0))$ is, in our particular case, the change of the C$_1$–C$_2$ distance (see Fig. 2 herein) in going from the reactant to the TS structure at $F_0 = 0$; note that $\Delta q_{\text{BO}}(F_0 = 0)$ is identical to Bell’s parameter\textsuperscript{8} $\gamma$ in Eq. (16) of Ref. 8.

A more advanced model to describe the force–dependence of the activation energy of non–covalent reactions is the so–called “tilted potential energy surface” model\textsuperscript{9,10}. The improved assumption that this model makes concerning the underlying PES of the reaction is that the force–dependence of the activation energy can be estimated based on the IRC of the reaction at zero force. How is this model applied in our particular case? Let us consider the energy profile of the ring–opening reaction of cis 1,2–dimethylbenzocyclobutene at zero force
as depicted in the lowest panel of Fig. 3 herein (black line). This energy profile is plotted against the mechanical reaction coordinate, \( q \), it being the coordinate along which the force will be applied later on, i.e. the \( C_1-C_2 \) distance. Thus, it is the standard Fukui reaction energy profile obtained by monitoring the \( V_{BO} \) energies and the \( C_1-C_2 \) distances along the IRC followed by the reaction in the absence of force. The tilted PES model (green lines) postulates that the energy profile of the reaction carried out under a tensile force \( F_0 \) can be simply obtained by adding the term \(-F_0q_{BO}\) to the energy profile at zero force; in our case \( q_{BO} \) is the \( C_1-C_2 \) distance on the Born–Oppenheimer PES \( V_{BO}(x) \) along which the force of magnitude \( F_0 \) is applied collinearly to the atoms \( C_1 \) and \( C_2 \). The main consequence of this idea is that this model takes into account, though in a non self–consistent way, the structural changes that the external forces cause in the reactant and TS configurations (marked by green circles). According to this model, qualitatively the reactant and TS configurations are predicted to shift to longer and shorter \( C_1-C_2 \) distances, respectively. In particular, if an external force \( F_0 \) is exerted on the system, the reactant will shift to longer \( C_1-C_2 \) distances along the energy profile up to the point where internal and external forces cancel, \( F + F_0 = 0 \), i.e. where the internal force \( F \) equals \(-F_0\) and thus where the derivative of the curve is equal to \(+F_0\). In contrast, the TS will move to shorter \( C_1-C_2 \) distances until the derivative of the curve equals \(+F_0\). This procedure allows one to determine \( q \) at the reactant and TS configurations knowing the IRC at zero force. Hence, given the value of the applied external force, \( F_0 \), and given the energy profile at zero force, the tilted PES model allows one to predict the values of the mechanical coordinates \( q_{BO}(x^{TS}(F_0)) \) and \( q_{BO}(x^{R}(F_0)) \) for the TS and reactant configurations and the associated Born–Oppenheimer energies, \( V_{BO} \), at these stationary points, i.e. \( V_{BO}(x^{TS}(F_0)) \) and \( V_{BO}(x^{R}(F_0)) \). The force-dependence of the activation energy predicted by the tiled PES model is thus given by \( E_{\text{t–PES}}^a(F_0) \approx [V_{BO}(x^{TS}(F_0)) - V_{BO}(x^{R}(F_0))] - F_0[q_{BO}(x^{TS}(F_0)) - q_{BO}(x^{R}(F_0))]. \) But it is of capital importance to understand that this model assumes that any structural changes take place along the IRC at zero force and thus does not take into account the force–induced distortion of the underlying PES as such.

In Fig. 3 herein, the energy profiles predicted by the tilted PES (green) and Bell’s (blue) models are compared at different external forces to the EFEI energy profiles (red). The EFEI energy profiles are exact since they are based on the correct force–transformed PES, \( V_{EFEI}(x,F_0) \), and, consequently, they take self–consistently into account the non–linear dis-
ortion of the reactant and TS configurations due to the applied force, at variance with both Bell’s model and the tilted PES model. Thus, the exact force dependence of the activation energy is simply obtained from \( E_{\text{exact}}^\dagger(F_0) = [V_{\text{EFEI}}(x_{\text{TS}}, F_0) - V_{\text{EFEI}}(x_{\text{R}}, F_0)] \), which generalizes nicely Eyring’s formula \( E_{\text{exact}}^\dagger(F_0 = 0) = E_{\text{exact}}^\dagger = [V_{\text{BO}}(x_{\text{TS}}) - V_{\text{BO}}(x_{\text{R}})] \) valid at zero external force, when using the properly force–transformed EFEI potential evaluated at the TS and reactant configurations. The exact EFEI profiles at a given force have been obtained by monitoring the \( V_{\text{EFEI}} \) energies and the \( \text{C}_1–\text{C}_2 \) distances along the IRC followed by the reaction on the EFEI PES for that force. On the other hand, it should be noted that, in fact, there is no profile defined in Bell’s model as no assumption is made regarding the underlying profile of a reaction. Therefore, for Bell’s model we have just plotted two points in each panel of Fig. 3 herein corresponding to the energies at the reactant and TS configurations (blue squares) without connecting them by straight lines.

The lowest panel of Fig. 3 herein depicts the reference energy profile in the absence of external forces (black line) along the mechanical coordinate \( q \), the \( \text{C}_1–\text{C}_2 \) distance, on which the energies at the reactant and TS configurations, i.e. \( V_{\text{BO}}(x_{\text{R}}(F_0 = 0)) \) and \( V_{\text{BO}}(x_{\text{TS}}(F_0 = 0)) \), respectively, are marked by diamonds. In addition, the corresponding difference of the TS and reactant state along \( q \), i.e. \( \Delta q_{\text{BO}}(F_0 = 0) = q_{\text{BO}}(x_{\text{TS}}(F_0 = 0)) - q_{\text{BO}}(x_{\text{R}}(F_0 = 0)) \), is marked by a horizontal dashed line. Increasing the force to \( F_0 = 0.41 \) nN shows that at such moderate forces the tilted PES profile (green) matches almost perfectly the exact EFEI profile (red). In addition, the changes of the \( \text{C}_1–\text{C}_2 \) distance \( \Delta q(F_0 > 0) \) in going from the reactant to the TS configuration, marked by dashed horizontal (green and red) lines, agrees very closely. Since this force is still too small to produce important structural rearrangements, even the reactant and TS configurations of Bell’s model are close (in terms of both the \( \text{C}_1–\text{C}_2 \) distance and the corresponding energies) to the corresponding EFEI results (cf. blue dashed line versus red dashed line and blue squares versus red triangles, respectively). At a force of \( F_0 = 1.64 \) nN, however, Bell’s model already deviates significantly from the EFEI results. At this force, important structural rearrangements, which are not accounted for in Bell’s model, take place as shown when comparing to the exact EFEI results. The tilted PES model, on the other hand, is still a reasonable approximation in this range of forces. Finally, at a force of \( F_0 = 3.05 \) nN, just before the covalent \( \text{C}_3–\text{C}_4 \) bond breaks at \( 3.09 \pm 0.04 \) nN, the tilted PES model and certainly Bell’s model both fail. At this force, Bell’s model even predicts a negative activation energy, which might not be surprising given
FIG. 3: Lower panel: energy profile of the disrotatory ring–opening reaction of cis 1,2–dimethylbenzocyclobutene as a function of the mechanical coordinate $q$, i.e. the $C_1–C_2$ distance, in the absence of external forces. This profile corresponds to the IRC followed by the reaction on the Born–Oppenheimer PES, $V_{BO}(x)$. The diamonds on top of the curve define where the reactant and TS configurations are located in this zero force limit. The horizontal dashed line measures the distance $\Delta q_{BO}$ between the TS and reactant configurations along $q$ at $F_0 = 0$ and constitutes the reference to which the various force–transformed distances $\Delta q(F_0 > 0)$ depicted in the upper panels by color–coded horizontal dashed lines should be compared. Upper panels: energy profiles of the same reaction at the different forces indicated as predicted by Bell’s model (blue squares) and the tilted PES model (green lines) together with the exact EFEI profiles (red lines). The green circles and the red triangles on top of the lines indicate the position of the reactants and TS at the different forces for the tilted PES model and for the EFEI profiles, respectively. The horizontal dashed lines measure the distance between the TS and the reactant as predicted by Bell’s model (blue, squares), by the tilted PES model (green, circles), and by the EFEI approach (red, triangles). Note that there is no energy profile associated with Bell’s model as it does not consider the energy landscape of the reaction, see text.

the fact that this model is a purely linear model (as nicely shown by Fig. 1 in the main text). As for the tilted PES model, it can be seen that it predicts still a noticeable reaction
barrier at this force, whereas the EFEI profile clearly shows that the reaction barrier has essentially vanished due to applying a force of this magnitude, thus allowing for a barrierless mechanochemical process.

In conclusion, Fig. 3 clearly demonstrates that the tilted PES model is able to capture part of the nonlinear behavior of the force–dependence of the activation energy and thus improves upon Bell’s model. Nevertheless, the tilted PES model obviously fails before reaching the realm of covalent mechanochemistry, i.e. the force regime of several nano–Newtons (see also Fig. 1 in the main text).


