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Enforced Ring-Opening

Force-Transformed Free-Energy Surfaces and Trajectory-Shooting Simulations Reveal the Mechano-Stereochemistry of Cyclopropane Ring-Opening Reactions**

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Thanks to a wealth of novel experimental techniques which culminated in a series of recent milestone experiments, it is now well established that external mechanical forces can be applied to specific covalent bonds within molecular systems.[1,2] The use of external forces by means of atomic force microscopy (AFM) setups,[3–10] sonochemical experiments,[11–19] or molecular force probes[20,21] constitutes a fundamentally different avenue to initiate, accelerate, and control chemical reactions, thus opening the doors to the emerging field of molecular nanomechanics or covalent mechanochemistry (CMC).[1,2] Given the currently growing interest in the design and preparation of novel "mechanophores" (force-sensitive chemical entities that undergo a chemical reaction as a result of applying mechanical forces), there is an effort to improve the understanding of how the external forces can affect and modify the reactivity of such systems. Gathering information on the possibilities offered by the use of forces in the realm of reactivity is not only extremely valuable for a fundamental understanding of chemical reactions under external mechanical forces, but also has the potential to dramatically influence both synthetic chemistry[16] and materials science.[2,22,23] Cyclobutene-based mechanophores have received a lot of attention[12,13,17,20,24–30] whereas cyclopropane systems, such as *gem*-dihalogencyclopropane derivatives,[10,15,19] are under-researched in the realm of CMC. The force-induced electrocyclic ring-opening of these compound classes has furnished striking results. Indeed, the mechanochemical activation of *cis* benzocyclobutenes has been shown to promote a thermally forbidden disrotatory ring-opening process.[13] The application of a transient tensile force on *gem*-difluorocyclopropanes, has been shown to lead to an unexpected isomerization of *trans* species into their less stable *cis* isomers via a mechanochemical trapping of a diradical transition state.[19] Even more enigmatic are *gem*-dichlorocyclopropane (*g*DCC) systems,[15] which feature a counterintuitive lack of selectivity in the mechanically assisted ring-opening reactions of *cis* versus *trans* isomers: whereas it would be expected that the external forces would promote the ring-opening of cis *g*DCC more efficiently (owing to a better coupling between the mechanical coordinate and the reaction coordinate), the experimental observations indicate that both isomers undergo force-induced ring-opening processes with approximately the same probability.

Herein we scrutinize the mechanochemical reactivity and force-induced stereochemistry of *g*DCCs based on ab-initio simulations. These simulations draw on the conceptual framework provided by force-transformed potential-energy surfaces (FT-PES).[25] In this case, the static "0 K perspective"[25] provided by analyzing the topology[27] of the FT-PES is rigorously generalized to finite temperatures, thereby including thermal, entropic, and dynamical effects by virtue of ab-initio molecular-dynamics (AIMD)[31] techniques. The resulting novel formalism, see Supporting Information, which builds upon the metadynamics technique[32,33] performed in the presence of a constant external force, enables us to compute force-transformed free-energy surfaces (FT-FES) in a thermodynamically well-defined way, thereby providing the proper framework for exploring CMC also at finite temperatures. We note that another rigorous finite-temperature technique complementary to ours has been recently introduced to compute rates.[34] Our thermodynamic approach is supplemented by ab-initio trajectory-shooting simulations operating on the FT-PESs to dissect genuinely dynamical effects on branching ratios as a function of force. Based on these methods we have unveiled the mechanisms of force-induced ring-openings of *cis* versus *trans* *g*DCCs, which rationalizes puzzling experimental findings.[15] Even more importantly, we have discovered an unprecedented complex mechano-stereochemical behavior, whereby the ring-opening of *trans* isomers of 2,3-disubstituted *g*DCCs can lead to two different diastereomers, with the probabilities of obtaining them having an intricate dependence on the force exerted on the system.

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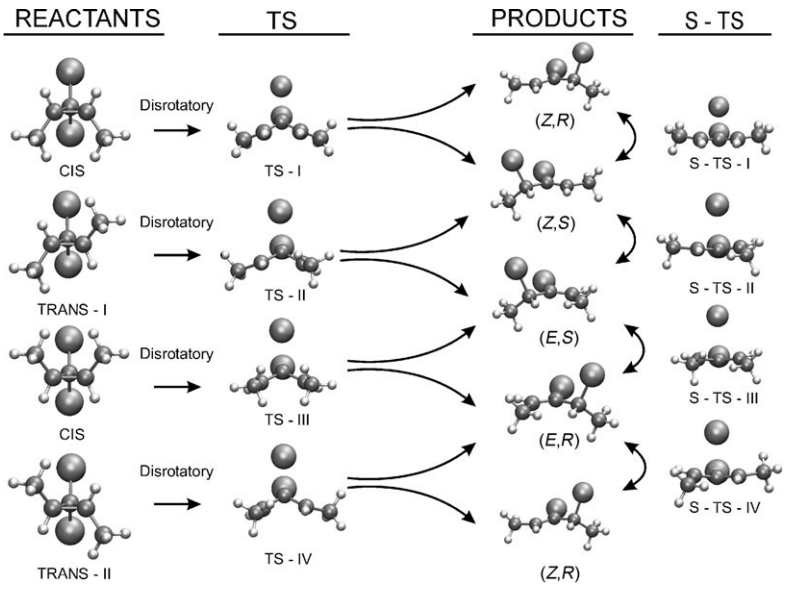

Figure 1. The species involved, that is, all the reactants (*cis*; *trans*-I and *trans*-II being enantiomers), transition states (TS-I to TS-IV; S-TS-I to S-TS-IV), and products (*Z*,*R*; *Z*,*S*; *E*,*S*; *E*,*R*). The arrows connecting the reactants with the products through the corresponding TSs represent the reaction paths obtained from IRC mapping and ab-initio trajectory shooting starting from the TSs (see text). The second set of TSs (S-TS) belongs to interconversion reactions between selected products as indicated. For simplicity all the structures correspond to the stationary points at zero force, the *Z*,*R* product is reproduced twice for clarity, and the Cl atoms are shown as large spheres.

The model system chosen to explore the mechanochemistry of *g*DCCs is 1,1-dichloro-2,3-dimethylcyclopropane: its *cis* and *trans* isomers and the four possible distinct reaction products of the corresponding ring-opening processes are depicted in Figure 1, which serves as our roadmap, together with the transition states (TSs). Let us set the stage by analyzing the thermal reactions of *g*DCCs at zero force, $F_0 = 0$. Our simulations[35] (both at 0 K and at 300 K) reveal that the ring-opening of these molecules to yield the corresponding 2,3-dichloroalkenes proceeds by a concerted disrotatory mechanism, whereby the breaking of the C–C bond takes place in concert with the C–Cl bond cleavage and the subsequent Cl migration; note that a similar mechanism has been obtained[36] for *gem*-dibromocyclopropanes. This result is relevant as both one-step and two-step mechanisms were reported for the ring-opening of *g*DCCs.[37–41] For *cis* *g*DCC there are two possible pathways as indicated in Figure 1: the "outward pathway" which passes through TS-I and the "inward pathway" via TS-III with activation energies $\Delta E^{\ddagger}$ of 30.0 and 35.0 kcal mol^{-1}, respectively, at 0 K. Hence the thermal ring-opening of *cis* *g*DCC occurs by a "disrotatory outward mechanism", whose BO-PES (BO: Born–Oppenheimer) features a TS of C_s symmetry (TS-I) and a bifurcation point along the intrinsic reaction coordinate (IRC) after passing through the TS. By virtue of this topological feature, the migrating Cl atom can move either to the C atom on the right side (thus yielding the *Z*,*R*-alkene) or to the left (leading to *Z*,*S*-alkene, see Figure 1). Given the topology of the underlying PES, the ring-opening of *cis* *g*DCC is expected to yield the two enantiomeric alkenes with equal probability.

The disrotatory ring-opening of *trans* *g*DCC at zero force, in its turn, implies either the TS-II or the TS-IV according to Figure 1, with neither of these two TSs is symmetric. An IRC calculation starting from TS-II shows that this TS connects *trans* *g*DCC with the *E*,*S*-alkene. Nevertheless, the information gathered by means of such static calculations is clearly insufficient. Indeed, the results obtained from trajectory shooting initiated from TS-II bring to light the surprising fact that the ring-opening of *trans* *g*DCC can also yield the corresponding *Z*,*S*-alkene in the absence of external forces! The specific calculated probabilities of obtaining the *E*,*S*- and the *Z*,*S*-alkenes starting from *trans* *g*DCC and passing through TS-II are 0.76 and 0.24, respectively. The branching ratio of obtaining *E*,*R*- versus *Z*,*R*-alkenes via TS-IV are identical because of symmetry.

The activation energy $\Delta E^{\ddagger}$ for the ring-opening of *trans* *g*DCC is 2.9 kcal mol^{-1} higher than for the "outward ring-opening" of *cis* *g*DCC. The computed activation free energies, $\Delta A^{\ddagger}$, at 300 K (26.5 and 22.2 kcal mol^{-1} for *trans* *g*DCC and *cis* *g*DCC, respectively) confirm this trend, which is consistent with the experimental observation that *cis* *g*DCC reacts around 20-times faster than its *trans* isomer.[42]

Another aspect of our exploration of the reactivity of *g*DCCs at zero force concerns the possibility of interconversion between the reaction products. Indeed, the produced dichloroalkenes could isomerize by means of a migration of one Cl atom from one C atom to the other, through the set of S-TSs depicted in Figure 1. The activation energies of these processes are in the range of 31.4 to 41.9 kcal mol^{-1} with respect to the products (see Supporting Information).

After the analyses of the thermochemical mechanisms of *g*DCCs we now dissect the mechanochemical behavior of these molecules with the help of Figure 2. Our first target is to identify which subset of the reaction pathways considered plays an important role in their mechanochemistry. The activation energy of the "outward ring-opening" of the *cis* reactant decreases as F_0 increases, whereas the force-dependence for the "inward pathway" exhibits a surprising behavior since its $\Delta E^{\ddagger}(F_0)$ increases with F_0 in the low-force regime. Consequently, the activation energy for the "outward mechanism" stays lower not only in the thermochemical limit at $F_0 = 0$ nN, but also in the whole force range, the difference in $\Delta E^{\ddagger}(F_0)$ values reaching a maximum value of 22.2 kcal mol^{-1} at 0.8 nN. The "inward mechanism" will therefore no longer be considered in what follows. Similar arguments can be used to exclude the isomerizations between the reaction products as relevant reaction steps. Given the fact that their activation energies are essentially force-independent (see Figure 2) and that their corresponding $\Delta E^{\ddagger}(F_0)$ values are as high as approximately 30 kcal mol^{-1} throughout, it can be safely concluded that the stereochemistry of the reaction products

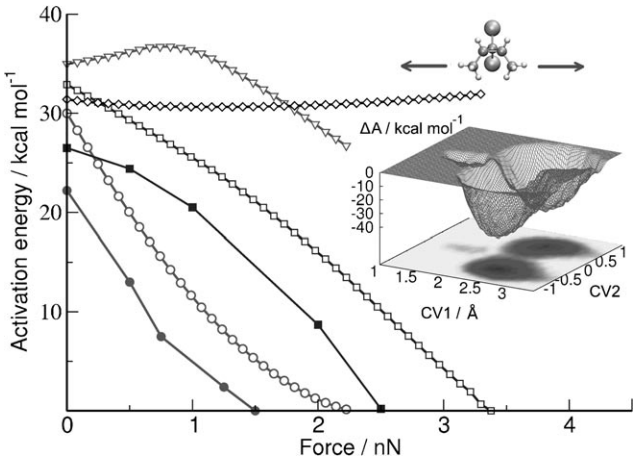

Figure 2. Force-dependence of activation energies $\Delta E^{\ddagger}(F_0)$ (open symbols) and free energies $\Delta A^{\ddagger}(F_0)$ at 300 K (filled symbols) of the disrotatory ring-opening of *cis* (circles for the "outward" pathway; triangles for "inward" pathway) and *trans* (squares) 1,1-dichloro-2,3-dimethylocyclopropanes. The force-dependence of $\Delta E^{\ddagger}(F_0)$ for the interconversion between *Z*,*R* and *Z*,*S* products is also depicted (diamonds). The stretching force is applied to the C atoms of the two terminal methyl groups as indicated in the upper inset. Main inset: Force-transformed free-energy landscape for ring-opening of the *cis* reactant at a constant external force of $F_0 = |\mathbf{F}_0| = 1.25$ nN (see Supporting Information for other FT-FESs). These FT-FESs have been obtained in a reaction subspace spanned by two collective variables: CV1 is the C···C distance associated with the bond that yields upon the ring-opening process. CV2 is the difference $CN_1 - CN_2$ of the coordination numbers (CN) of both chlorine atoms with respect to the left (CN_1) or right (CN_2) carbon atom in the cyclopropane ring (see Supporting Information for details).

of the ring-opening of *g*DCCs is exclusively determined by the primary ring-opening processes themselves.

As CMC experiments are typically carried out around room temperature, it is essential to examine the corresponding reaction free energies. The data in Figure 2 show that the force-dependence of $\Delta A^{\ddagger}$ and $\Delta E^{\ddagger}$ follows a similar general trend. However, the values of $\Delta A^{\ddagger}(F_0)$ are lower by about 6–7 kcal mol^{-1} over the whole range of forces, which results in a dramatic rate acceleration owing to finite temperature and entropy effects not accounted for by $\Delta E^{\ddagger}(F_0)$. More importantly, the mechanochemically barrierless regime is reached for forces which are about 1 nN smaller at 300 K than those predicted at 0 K. The inset of Figure 2 clearly illustrates that the *cis* reactant basin in the FT-FES at $F_0 = 1.25$ nN is very shallow and close to vanishing. On the other hand, the qualitatively different shapes of the energy curves associated with the *cis* and *trans* reactants reflect that the external forces enhance the ring-opening of *cis* *g*DCCs more efficiently. In fact, the difference in $\Delta E^{\ddagger}$ between the two processes increases with the force until reaching a maximum value of 15.9 kcal mol^{-1} at $F_0 = 1.48$ nN. The more efficient mechanochemical activation of *cis* *g*DCCs also manifests itself in the corresponding rupture forces (that is, the minimum force required for *g*DCCs isomerize to the corresponding dichloroalkenes in a barrierless process). The rupture forces at 0 K for the *cis* and *trans* reactants are 2.3 nN and 3.4 nN, respectively, and decrease significantly to 1.5 nN and 2.5 nN at 300 K.

Given the predicted selectivity with which the external force favors the ring-opening of *cis* *g*DCCs over the *trans* isomers, the *cis* *g*DCCs would be expected to react much faster under stress conditions than the *trans* isomers. Quite surprisingly, though, the sonochemical experiments on *g*DCCs[15] revealed that both isomers undergo ring-opening with nearly equivalent probabilities. The most plausible suggestion for resolving such an apparent contradiction is to speculate[15] that in the sonochemical experiments forces the generated were large enough to reach the barrierless regime. Actually, according to our free energy data in Figure 2, forces on the order of 2 nN would be sufficient to induce purely mechanical ring-opening of both *cis* and *trans* isomers at 300 K, thus precluding any sort of mechanochemical selectivity. Note that while our simulations mimic truly "monochromatic" isotensional experiments at well-specified forces, there is an unknown but certainly broad "force spectrum" generated by sonication, which would lead to a weighted superposition of reaction products within the respective force window of Figure 2.

The most striking feature found in our investigations, is the force-dependent selectivity of the ring-opening of *trans* reactants to yield either the *Z*- or the *E*-diastereomer of the corresponding dichloroalkene. Recall that the probabilities of obtaining the *Z*,*S*- and *E*,*S*-alkenes upon thermochemical ring-opening of *trans* reactant are 0.24 and 0.76, respectively, at zero force. Most surprisingly, this branching ratio changes dramatically and non-monotonically as a function of F_0 (Figure 3). The probability at each force has been obtained by means of extensive ab-initio trajectory shootings on the corresponding FT-PES initiated from the stationary points associated with TS-II (see Figure 1) as optimized at each force (see Supporting Information). The simulations yield three critical forces, 0.7 nN, 1.9 nN, and 2.2 nN, where the branching

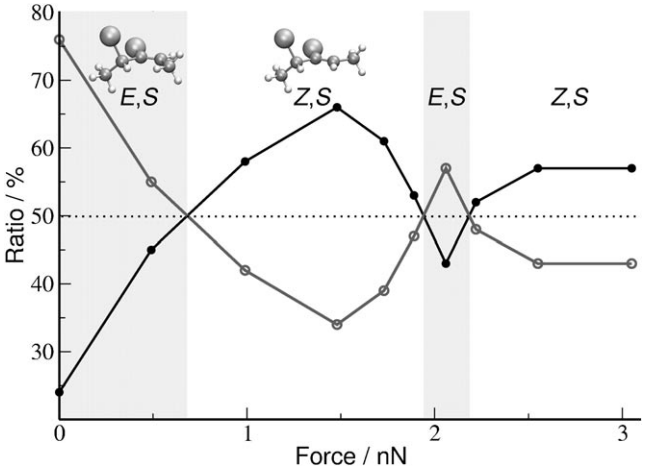

Figure 3. Force-dependence of the probability of obtaining the *E*,*S*-products (○) and *Z*,*S*-products (●) upon ring-opening of *trans* reactants, computed from dynamic trajectory-shooting simulations. The range of forces with shaded and white backgrounds correspond to the forces at which the majority product of the ring-opening process is the *E*,*S*-alkene or the *Z*,*S*-alkene, respectively.

ratio is 1:1 and, thus, at which the majority reaction product switches. In the range of 0–0.7 nN the main ring-opening product is the *E*,*S*-alkene; between 0.7–1.9 nN the *Z*,*S*-alkene is preferentially obtained; in the short force interval of 1.9–2.2 nN the *E*,*S*-isomer is again expected as the majority product; and finally for $F_0 > 2.2$ nN the reaction produces the *Z*,*S*-alkene as the majority product. This intricate switching behavior implies that a ratio of about 50:50 is expected to be observed only close to these critical forces, in particular around 2 nN. Furthermore, in the limit of large forces the probabilities of obtaining the *Z*,*S*- versus the *E*,*S*-products are about 60:40, which is the opposite to the situation encountered at zero force. To our knowledge, this is the first time that such an intricate mechanochemical behavior of a reaction resulting from intrinsically dynamic effects that determine its stereochemistry is reported. Not only does this discovery call for new experiments, but it also increases the potential of mechano-stereochemistry.

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[1] M. K. Beyer, H. Clausen-Schaumann, *Chem. Rev.* **2005**, *105*, 2921 – 2948.
[2] M. M. Caruso, D. A. Davis, Q. Shen, S. A. Odom, N. R. Sottos, S. R. White, J. S. Moore, *Chem. Rev.* **2009**, *109*, 5755 – 5798.
[3] M. Grandbois, M. Beyer, M. Rief, H. Clausen-Schaumann, H. E. Gaub, *Science* **1999**, *283*, 1727 – 1730.
[4] A. S. Duwez, S. Cuenot, C. Jérôme, S. Gabriel, R. Jérôme, S. Rapino, F. Zerbetto, *Nat. Nanotechnol.* **2006**, *1*, 122 – 125.
[5] F. R. Kersey, W. C. Yount, S. L. Craig, *J. Am. Chem. Soc.* **2006**, *128*, 3886 – 3887.
[6] S. W. Schmidt, M. K. Beyer, H. Clausen-Schaumann, *J. Am. Chem. Soc.* **2008**, *130*, 3664 – 3668.
[7] A. P. Wiita, R. Perez-Jimenez, K. A. Walther, F. Gräter, B. J. Berne, A. Holmgren, J. M. Sanchez-Ruiz, J. M. Fernandez, *Nature* **2007**, *450*, 124 – 127.
[8] S. R. Koti Ainavarapu, A. P. Wiita, L. Dougan, E. Uggerud, J. M. Fernandez, *J. Am. Chem. Soc.* **2008**, *130*, 6479 – 6487.
[9] S. Garcia-Manyes, J. Liang, R. Szoszkiewicz, T. L. Kuo, J. M. Fernandez, *Nat. Chem.* **2009**, *1*, 236 – 242.
[10] D. Wu, J. M. Lenhardt, A. L. Black, B. B. Akhremitchev, S. L. Craig, *J. Am. Chem. Soc.* **2010**, *132*, 15936 – 15938.
[11] G. Cravotto, P. Cintas, *Angew. Chem.* **2007**, *119*, 5573 – 5575; *Angew. Chem. Int. Ed.* **2007**, *46*, 5476 – 5478.
[12] S. L. Potisek, D. A. Davis, N. R. Sottos, S. R. White, J. S. Moore, *J. Am. Chem. Soc.* **2007**, *129*, 13808 – 13809.
[13] C. R. Hickenboth, J. S. Moore, S. R. White, N. R. Sottos, J. Baudry, S. R. Wilson, *Nature* **2007**, *446*, 423 – 427.
[14] S. Karthikeyan, S. L. Potisek, A. Piermattei, R. P. Sijbesma, *J. Am. Chem. Soc.* **2008**, *130*, 14968 – 14969.
[15] J. M. Lenhardt, A. L. Black, S. L. Craig, *J. Am. Chem. Soc.* **2009**, *131*, 10818 – 10819.
[16] A. Piermattei, S. Karthikeyan, R. P. Sijbesma, *Nat. Chem.* **2009**, *1*, 133 – 137.
[17] M. J. Kryger, M. T. Ong, S. A. Odom, N. R. Sottos, S. R. White, T. J. Martinez, J. S. Moore, *J. Am. Chem. Soc.* **2010**, *132*, 4558 – 4559.
[18] K. M. Wiggins, T. W. Hudnall, Q. Shen, M. J. Kryger, J. S. Moore, C. W. Bielawski, *J. Am. Chem. Soc.* **2010**, *132*, 3256 – 3257.
[19] J. M. Lenhardt, M. T. Ong, R. Choet, R. E. Christian, T. J. Martinez, S. L. Craig, *Science* **2010**, *329*, 1057 – 1060.
[20] Q. Z. Yang, Z. Huang, T. J. Kucharski, D. Khvostichenko, J. Chen, R. Boulatov, *Nat. Nanotechnol.* **2009**, *4*, 302 – 306.
[21] Z. Huang, Q. Z. Yang, D. Khvostichenko, T. J. Kucharski, J. Chen, R. Boulatov, *J. Am. Chem. Soc.* **2009**, *131*, 1407 – 1409.
[22] D. A. Davis, A. Hamilton, J. Yang, L. D. Cremar, D. V. Gough, S. L. Potisek, M. T. Ong, P. V. Braun, T. J. Martinez, S. R. White, J. S. Moore, N. R. Sottos, *Nature* **2009**, *459*, 68 – 72.
[23] J. M. Lenhardt, S. L. Craig, *Nat. Nanotechnol.* **2009**, *4*, 284 – 285.
[24] M. T. Ong, J. Leiding, H. Tao, A. M. Virshup, T. J. Martinez, *J. Am. Chem. Soc.* **2009**, *131*, 6377 – 6379.
[25] J. Ribas-Arino, M. Shiga, D. Marx, *Angew. Chem.* **2009**, *121*, 4254 – 4257; *Angew. Chem. Int. Ed.* **2009**, *48*, 4190 – 4193.
[26] J. Ribas-Arino, M. Shiga, D. Marx, *Chem. Eur. J.* **2009**, *15*, 13331 – 13335.
[27] J. Ribas-Arino, M. Shiga, D. Marx, *J. Am. Chem. Soc.* **2010**, *132*, 10609 – 10614.
[28] P. Dopieralski, P. Anjukandi, M. Rückert, M. Shiga, J. Ribas-Arino, D. Marx, *J. Mater. Chem.* **2011**, *21*, 8309 – 8316.
[29] G. S. Kochhar, A. Bailey, N. J. Mosey, *Angew. Chem.* **2010**, *122*, 7614 – 7617; *Angew. Chem. Int. Ed.* **2010**, *49*, 7452 – 7455.
[30] J. Friedrichs, M. Lüßmann, I. Frank, *ChemPhysChem* **2010**, *11*, 3339 – 3342.
[31] D. Marx, J. Hutter, *Ab Initio Molecular Dynamics: Basic Theory and Advanced Methods*, Cambridge University Press, Cambridge, **2009**.
[32] A. Laio, M. Parrinello, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 12562 – 12566.
[33] M. Iannuzzi, A. Laio, M. Parrinello, *Phys. Rev. Lett.* **2003**, *90*, 238302.
[34] W. Li, F. Gräter, *J. Am. Chem. Soc.* **2010**, *132*, 16790 – 16795.
[35] All ab-initio molecular-dynamics, metadynamics, and trajectory-shooting simulations were performed on the FT-PES using our in-house version of CPMD, the BLYP density functional, and a plane-wave basis set together with norm-conserving pseudopotentials. All static calculations were performed using Turbomole, the BLYP density functional, and the TZVP basis set. A detailed account of these methods, including an assessment of BLYP for this purpose, and the computational details together with the pertinent references are compiled in the Supporting Information.
[36] O. N. Faza, C. S. Lopez, R. Alvarez, A. R. de Lera, *J. Org. Chem.* **2004**, *69*, 9002 – 9010.
[37] E. Bergman, *J. Org. Chem.* **1963**, *28*, 2210 – 2215.
[38] R. C. D. Selms, C. M. Combs, *J. Org. Chem.* **1963**, *28*, 2206 – 2210.
[39] H. Tanida, K. Tori, K. Kitahonoki, *J. Am. Chem. Soc.* **1967**, *89*, 3212 – 3224.
[40] R. Fields, R. N. Haszeldine, R. N. Peter, *J. Chem. Soc. C* **1969**, *1*, 165 – 172.
[41] A. P. Marchand, D. Xiang, S. G. Bott, *Tetrahedron* **1996**, *52*, 825 – 832.
[42] W. E. Parham, K. S. Yong, *J. Org. Chem.* **1970**, *35*, 683 – 685.

