Reactive molecules

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Predicting Kinetically Unstable C–C Bonds from the Ground-State Properties of a Molecule**

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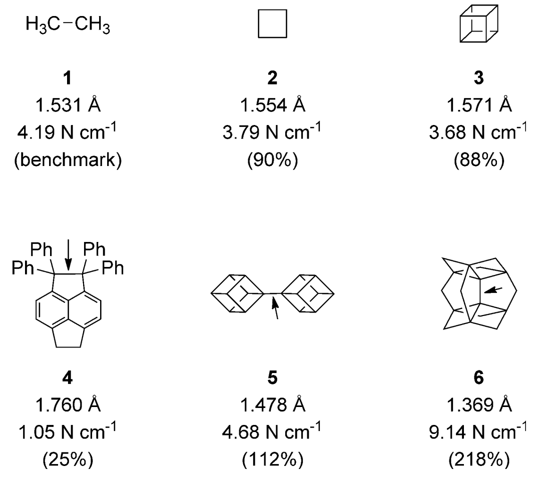
Three prominent scientists have recently called for more realism in the computational prediction of novel molecules.[1–3] A testimony to the reliability of modern computational chemistry methods, their appeal refers to a common problem in the field: Localizing a minimum on a potential energy surface (PES) is a routine task, but does not provide any information about the kinetic stability of the corresponding structure. In order to make predictions about kinetic stability, the transition states of reactive modes have to be localized. Optimization methods towards this aim usually require the geometries of the reactant *and* product molecule or a reasonable guess for the transition state (TS) geometry.[4] Although single-ended algorithms without these limitations have been developed, the a priori determination of transition states from a defined ground state is still difficult and not routinely feasible.[4,5] While chemists with their extensive knowledge of reaction mechanisms can foresee likely reaction paths, this problem becomes ever more daunting with increasing size and complexity of the molecules, and with the possibility of unprecedented reactivity modes in the prediction of conceptually novel molecules. A directed search for transition states starting far off the quadratic TS region is therefore highly desirable. We show herein that the two-dimensional analysis of 1) relaxed force constants and 2) bond lengths of a ground-state geometry can help to identify fragile bonds in a molecule.

What are relaxed force constants? A traditional force constant is defined as the partial second derivative of the energy with respect to a distortion coordinate; these force constants describe the curvature of a rigid PES. This rather artificial setting is not the case for relaxed force constants: they allow the relaxation of all other coordinates during a (infinitesimal) distortion and give a glimpse of the minimum energy path.[6,7] Their unique description of the curvature of a relaxed PES should in principle also reflect the presence of a low-energy TS adjacent to a localized minimum.[8] As such low-energy transition states lead to a flattening of the PES, corresponding distortion coordinates, that is, kinetically labile bonds, would then be characterized by an unusually small relaxed force constant. In order to test this hypothesis, we set out to calculate the relaxed force constants of 71 carbon–carbon single bonds between tetracoordinate carbon atoms. The data set consists of both real and hypothetical molecules from the literature with calculated bond lengths from 1.31 to 1.77 Å. As a reference for labile bonds we included experimentally known fluxional molecules that exhibit low activation barriers for bond-breaking processes.

With density functional theory (DFT) at the B3LYP/6-31G(d) level as our method of choice, the single bonds of 36 molecules were analyzed.[9] In order to get a feeling for general trends we discuss some representative examples from our database (Figure 1); the complete dataset can be found in the Supporting Information. The relaxed force constant of ethane (**1**) has a value of 4.19 $\mathrm{N\,cm^{-1}}$ and shall subsequently serve as the benchmark for C–C single bonds.[8,10–12] Turning to cyclic molecules, we note that the relaxed force constant of cyclobutane (**2**) is 10 % lower than that of **1**.[7,10] The fact that this bond is easier to deform than the ethane bond is readily explained by the concept of ring strain. Four-membered rings are also present in the highly strained cage compound cubane (**3**) and the respective bonds are additionally weakened. An even smaller relaxed force constant is found for the extremely elongated bond in compound **4**;[13] the 0.23 Å elongation compared to the C–C bond in ethane leads to a remarkable 75 % reduction of the relaxed force constant. Moving towards short C–C bonds, we refer to the exocyclic bond of



1
1.531 Å
4.19 $\mathrm{N\,cm^{-1}}$
(benchmark)

2
1.554 Å
3.79 $\mathrm{N\,cm^{-1}}$
(90%)

3
1.571 Å
3.68 $\mathrm{N\,cm^{-1}}$
(88%)

4
1.760 Å
1.05 $\mathrm{N\,cm^{-1}}$
(25%)

5
1.478 Å
4.68 $\mathrm{N\,cm^{-1}}$
(112%)

6
1.369 Å
9.14 $\mathrm{N\,cm^{-1}}$
(218%)

Figure 1. Representative examples of carbon–carbon single bonds and their calculated bond length, relaxed force constant, and relationship to the relaxed force constant of ethane at the B3LYP/6-31G(d) level.

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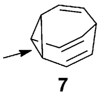
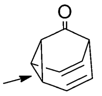
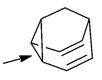
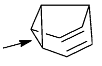
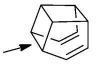
cubylcubane (**5**), which is shortened due to an increased s-orbital contribution.[14] Consequently, its relaxed force constant is 12% higher than that of ethane. Carbon–carbon bonds can be further compressed by geometric constraints as demonstrated in the hypothetical molecule **6**.[15] Compression by 0.17 Å compared to the C–C bond in ethane more than doubles the relaxed force constant and places it close to the value of 9.92 $\mathrm{N\,cm^{-1}}$ for the double bond in ethylene.[8,10,12] It should be emphasized that such comparisons would not be straightforward with traditional force constants, as these are usually related to delocalized normal modes, or, if defined for a specific bond, depend heavily on the internal coordinate system, making them difficult to compare.[6,7]

We now turn to the main point of our study: If relaxed force constants are able to sense low-energy transition states, they will be unusually small for kinetically labile bonds. As a test case we chose degenerate Cope rearrangements in fluxional molecules as prototypical processes with low barriers for C–C bond breaking. Representative molecules for these rearrangements are shown in Table 1 and we begin our analysis with bullvalene (**7**). First envisioned by Doering and Roth, its activation enthalpy for bond breaking was experimentally determined to 13.3 $\mathrm{kcal\,mol^{-1}}$.[16] Calculations at the B3LYP/6-31G(d) level—despite the well-documented shortcomings of this computational method[17]—gave a reliable value of 12.5 $\mathrm{kcal\,mol^{-1}}$ and also work reliably for other molecules in Table 1.[18] Interestingly, the calculated bond length in **7** is only marginally longer than that in ethane, but the relaxed force constant is almost 30% smaller—a clear indication of an unusually soft bond-stretch potential in conjunction with a low-lying transition state. The increasing strain along the series barbaralone (**8**), barbaralane (**9**), and semibullvalene (**10**) leads to increasing bond elongation and decreasing activation enthalpies. This is consistently reflected by the relaxed force constants. For semibullvalenes in particular, the activation enthalpy of various derivatives has recently been correlated with other properties of the ground state, for example, the coupling constant ^1J.[19] The activation enthalpy of hypostrophene (**11**), on the other hand, was calculated to be 21.9 $\mathrm{kcal\,mol^{-1}}$, which is considerably higher than that of any other compound in Table 1.[20,21] Most importantly, hypostrophene (**11**) features a slightly longer C–C bond than semibullvalene (**10**) but its relaxed force constant is substantially higher than that of **10**. The almost fivefold increase in activation enthalpy on going from **10** to **11** is markedly reflected by the relaxed force constant.

Table 1: Fluxional molecules and their calculated bond length r_{eq}, relaxed force constant k_{rel} (including the relationship to k_{rel} of ethane), and activation enthalpy $\Delta H^{\neq}_{298}$ at the B3LYP/6-31G(d) level.[18,21]

Molecule	r_{eq} [Å]	k_{rel} [$\mathrm{N\,cm^{-1}}$]	$\Delta H^{\neq}$ [$\mathrm{kcal\,mol^{-1}}$]
 **7**	1.536	2.98 (71%)	12.5[18]
 **8**	1.556	2.54 (61%)	8.8[22]
 **9**	1.588	2.09 (50%)	6.4[18]
 **10**	1.610	1.78 (42%)	4.5[18]
 **11**	1.620	2.53 (60%)	21.9[21]

The striking sensitivity of relaxed force constants to low-lying transition states is also demonstrated in Figure 2, where our data set of 71 relaxed force constants is plotted against the respective bond lengths.[23] The most popular description of the relationship between traditional force constants and bond lengths is based on Badger's rule.[24–26] A fit to Badger's rule and to an exponential function are shown in Figure 2; parameters are given in the Supporting Information. Both formulae generally underestimate the relaxed force constant of bonds that are shorter than 1.58 Å, while overestimating the relaxed force constant of longer bonds. We note, however, that the presented data set is heavily biased towards unusual and highly strained molecules. The main outcome of this two-dimensional plot is nevertheless obvious: the data points of the fluxional molecules **7**–**10** are markedly lower than what Badger's rule would suggest.[27] It is thus possible to identify kinetically labile bonds through a simple two-dimensional analysis of bond lengths and relaxed force constants. The limits of the approach are demonstrated by hypostrophene (**11**), which features the highest activation enthalpy of the fluxional molecules considered (21.9 $\mathrm{kcal\,mol^{-1}}$). Its data point is in line with Badger's rule and we therefore estimate that strong deviations can only be observed for labile bonds with an activation enthalpy $\Delta H^{\neq} < 15\ \mathrm{kcal\,mol^{-1}}$. In this context, we wish to reemphasize the importance of a two-dimensional description of the problem: returning to Table 1,

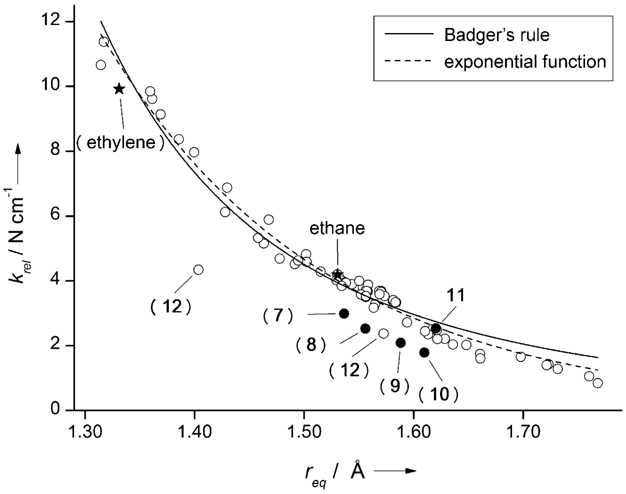
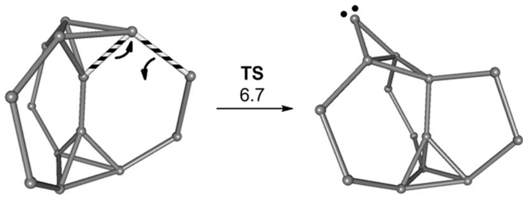


Figure 2. Plot of relaxed force constants k_{rel} against bond lengths r_{eq} (B3LYP/6-31G(d); filled circles belong to fluxional molecules; data points in brackets were not included in the fit).

barbaralone (**8**) and hypostrophene (**11**) show exactly the same relaxed force constants but glaringly different kinetic stabilities. Only when relevant bond length information is included as in Figure 2 can **8** be identified as an outlier and thus as a molecule with a barrier to C–C bond cleavage of less than 15 kcal mol^{-1}.

The fluxional molecules discussed so far served as a successful proof of concept and as a calibration for the presented approach. But interestingly, Figure 2 contains two additional data points that deviate strongly from Badger's rule: one of them at 1.40 Å is more than 3 units too low in its relaxed force constant and the second one at 1.57 Å is perfectly in line with the data points of the fluxional molecules **7**–**10**. Are these two bonds particularly prone to break? Both data points belong to molecule **12** (Figure 3), which was predicted by theory in the search for highly compressed C–C bonds.[28] Inspired by the above observations, we performed a scan along the two bond-stretch coordinates and were indeed able to locate a TS involving both bonds with an activation enthalpy of 6.7 kcal mol^{-1}. Such a low barrier characterizes **12** as a "fleeting" molecule: a minimum on the PES that cannot be isolated under standard laboratory conditions.[1] The TS describes a 1,2-shift to give the rearranged product **13**, in which the two bonds have been broken to generate one new bond and a (singlet) carbene. Compound **13** is an impressive 105.7 kcal mol^{-1} lower in enthalpy than reactant **12**. That a low-valent carbene is energetically favored over a formally correct Lewis structure is a remarkable manifestation of the immense strain in **13**.[29] Most importantly, we dare to assume that such an unusual reactivity mode would be hard to foresee without a well-informed guess: one of the involved bonds is very short (1.404 Å) and would traditionally not be associated with a low barrier towards bond breaking.[30] Once the relevant relaxed force constant information is included, however, the kinetic instability is evident.



12

13

Figure 3. Rearrangement of **12** along the bonds with an unusually small relaxed force constant and calculated relative enthalpies ΔH_{298} in kcal mol^{-1} at the B3LYP/6-31G(d) level. Two of the labile bonds are highlighted; hydrogen atoms are omitted for clarity.

The described examples demonstrate an effective way to predict kinetic instability: Deviations from the empirically established relationship between relaxed force constant and bond length indicate labile bonds within a molecule.[26] The direct identification of the "Achilles heel" of a molecule in combination with efficient and well-established algorithms that localize saddle points on the PES, renders the laborious search for transition states less time-consuming. We thus hope that the presented approach will contribute to more realism in the prediction of novel molecules. As it is based on routinely available properties of the ground state, it is easily applicable to a wide range of compounds and the production of analogous Badger plots for a variety of bonds, also between different elements, should be straightforward.

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