Beyond strain release: Delocalization-enabled organic reactivity

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The release of strain energy is a fundamental driving force for organic reactions. However, absolute strain energy alone is an insufficient predictor of reactivity, as evidenced by the similar ring strain but disparate reactivity of cyclopropanes and cyclobutanes. In this work, we demonstrate that electronic delocalization is a key factor that operates alongside strain release to boost, or even dominate, reactivity. This delocalization principle extends across a wide range of molecules containing three-membered rings such as epoxides, aziridines and propellanes, and also applies to strain-driven cycloaddition reactions. Our findings lead to a 'rule of thumb' for the accurate prediction of activation barriers in such systems, which can be easily applied to reactions involving many of the strained building blocks commonly encountered in organic synthesis, medicinal chemistry, polymer science and bioconjugation. Given the significance of electronic delocalization in organic chemistry, for example in aromatic π-systems and hyperconjugation, we anticipate that this concept will serve as a versatile tool to understand and predict strain-based organic reactivity.

Introduction

The release of molecular strain has long been harnessed as a powerful driving force in chemical synthesis. A fundamental concept in organic chemistry is 'ring strain',[1,2] which is used to explain the heightened reactivity of three-membered rings due to deviations from ideal bond angles.[3] Consequently, 'strain release' has been widely employed in organic synthesis as a powerful tactic to increase reaction rates, finding applications in total synthesis,[4] polymer science,[5,6] bioconjugation[7,8] bioisosterism;[9,10] it is also an important concept in biosynthesis (Figure 1a).[11] However, despite the common belief that such pent-up strain energy fully explains the reactivity of species such as small rings, cycloalkynes and cyclo-(*E*)-alkenes, even the simplest of these systems presents a paradox: cyclopropanes display markedly heightened ring-opening reactivity compared to cyclobutanes (k_{rel}(cyclopropane) = 10^4–10^7 for intramolecular ring-opening reactions),[12] despite having nearly identical strain energies (27.5 and 26.5 kcal mol^{-1} respectively).[3]

This puzzle has been the subject of extensive theoretical investigations. Stirling et al.[13] proposed that cyclopropane relieves a larger proportion of angle strain (~75%) than cyclobutane (~50%) upon ring-opening, while the groups of Hoz[14] and Houk[15] argued that differences in electronic structure (*i.e.*, bonding) are instead the cause of the reactivity difference. Hoz proposed

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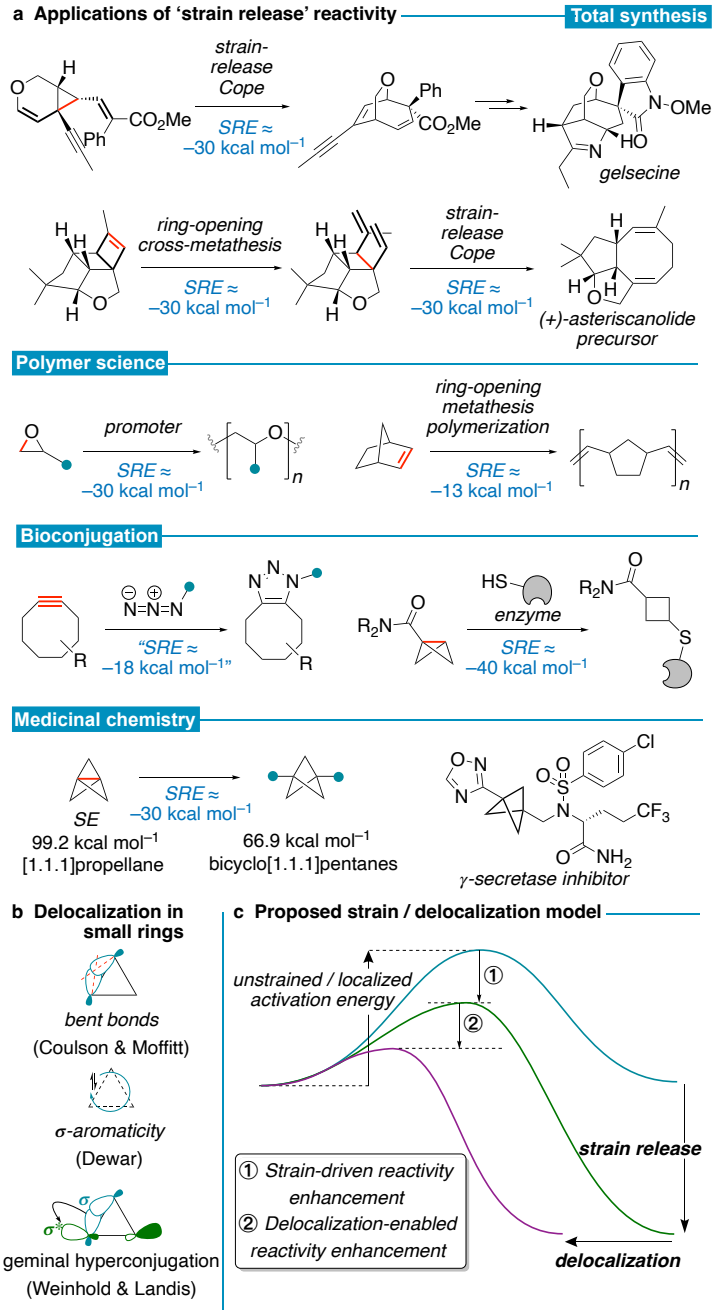

Figure 1. Ring strain in organic chemistry. **a** Examples of strain release driven reactivity, including total synthesis,[25,26] bioconjugation reactions,[7,8] ring-opening polymerization,[27] and bioisostere synthesis.[28] **b** Ground state models for electron delocalization in three-membered rings. **c** This work: Strain release and delocalization combine to enhance reactivity through lower activation barriers and earlier transition states.

that rehybridization induced by bond angle compression enhances the electrophilicity of cyclopropane C–C bonds by lowering the energy of the σ* orbitals. On the other hand, Houk invoked an 'orbital interactions through-bonds' (OITB)[16] argument in which transition state (TS) aromaticity stabilizes ring-opening reactions of cyclopropane, whereas equivalent reactions of cyclobutane are destabilized due to an antiaromatic TS. While these explanations qualitatively

explain the reactivity differences in these systems, a comprehensive predictive model connecting bonding to reactivity has yet to emerge.

We thus questioned whether the electronic structure and distinct reactivity of cyclopropane, and other strained systems, could be understood through the models commonly used to describe their ground state bonding.[17] The Coulson-Moffitt 'bent bonds' description,[18] Walsh's ($p+sp^2$) rehybridization model,[19,20] Dewar's σ-aromaticity proposal,[21] and Weinhold and Landis' geminal hyperconjugation model[22] all suggest that the valence electrons of cyclopropane are not confined to individual C–C σ bonds. Instead, these electrons delocalize in an analogous manner to an aromatic π system, in contrast to the typical localized C–C σ bonds found in cyclobutane. This is illustrated by the higher dipole moment of chlorocyclobutane (2.20 D) compared to chlorocyclopropane (1.76 D), the latter being similar to that of chlorobenzene (1.60 D).[23,24] While the importance of delocalization on the thermodynamic stability of systems containing conjugated π bonds (including aromatic rings) is universally accepted, its effect on bonding and reactivity in σ frameworks, particularly in non-classically delocalized systems such as cyclopropane, has yet to be established.

In this work, we present a quantitative model to understand the interplay between delocalization, strain energy and reactivity (Figure 1c). We propose that enhanced electronic delocalization within three-membered rings results in earlier, lower energy TSs, an effect that is distinct from barrier lowering due to strain release alone. This model not only accounts for the relative reactivity of cyclopropane and cyclobutane, but extends to *all* molecules containing one or more three-membered rings, including heterocycles and polycyclic structures. We demonstrate that in many cases, delocalization is the primary factor that governs reactivity, for example in ring-opening reactions of bicyclo[1.1.0]butanes, [1.1.1]propellane, and epoxides.[29][30] We show that this principle can be generalized in a simple 'rule-of-thumb' in which each three-membered ring fused to the breaking bond lowers the activation barrier by ~10 kcal mol^{-1}, corresponding to a ~10^7 fold rate enhancement at 298 K. This model can also be applied to 'strain-promoted' azide-cycloalkyne (3+2) cycloadditions, which are commonly used as a bioconjugation strategy.[7] Collectively, this framework unites the influence of strain-driven and delocalization-enabled reactivity, and offers quantitative predictions of reaction barriers.

Results and Discussion

Model construction

Our investigations began by establishing a linear free energy relationship (LFER) that connects strain release to reactivity. This LFER is a variant of the Marcus model (eq 1),[31,32] where breaking and forming bonds are represented as a pair of parabolas with the intersection defining the position of the TS on the reaction coordinate.

$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{int} + \frac{1}{2}\Delta E_r + \frac{\Delta E_r^2}{16\Delta E^{\ddagger}_{int}} \quad (1)$$

Here, ΔE_r is the reaction driving force, and $\Delta E^{\ddagger}_{int}$ is the intrinsic activation barrier when $\Delta E_r = 0$. As ΔE_r becomes more negative, an earlier TS and lower energy barrier is expected, in line with Hammond's postulate – as depicted by the vertical movement of the product parabola relative to the reactant (Figure 2a).[33] Truncating eq 1 at first order and introducing a proportionality constant, α, recovers the Bell-Evans-Polanyi (BEP) principle (eq 2),[34,35] in which the activation barrier ($\Delta E^{\ddagger}$) is assumed to vary linearly with the reaction driving force (ΔE_r) between two reactions.

$$\Delta E^{\ddagger} = \alpha \Delta E_r \tag{2}$$

For similar reactions with an equal driving force, the difference in $\Delta E^{\ddagger}$ is simply the difference in $\Delta E^{\ddagger}_{int}$, leading to horizontal 'motion' of the product parabola, such that for an earlier TS a lower activation energy is expected (Figure 2b). In the context of small ring reactivity, we propose that electron delocalization within three-membered rings reduces this intrinsic activation barrier by increasing the polarizability of the ground state electron density, compared with four-membered ring analogues. Hait and Head-Gordon recently demonstrated that the polarizability of the electron density is maximized at or near a transition state due to electron delocalization accompanying partial bond cleavage and formation.[36] Qualitatively, the relationship between this delocalization and reactivity can therefore be understood by considering how delocalization evolves during a bond breaking/making process: Attaining a delocalized electron arrangement at the TS will be facilitated if this bond is already partially delocalized in the ground state, resulting in an earlier, lower-energy TS.

Combining this insight with eq 1 produces a variant of the Marcus model that accounts for variations in both the reaction driving force (through ΔE_r) and the intrinsic activation barrier (through $\Delta E^{\ddagger}_{int}$) on the activation energy (eq 3 and Figure 2c, see SI for full derivation).[37] For simplicity, the curvature of the breaking bond parabola is assumed to remain constant, following previous work.[32] To account for the dependence of $\Delta E^{\ddagger}_{int}$ across a range of similar systems, we introduce a calculated parameter, χ, that captures the physical origin of this variation – in this case proposed to be electron delocalization. The sensitivity constants α and β can be determined using multiple linear regression (MLR).

$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{int}(0) + \alpha \Delta E_r + \beta \chi \tag{3}$$

To quantify the extent of electron delocalization and its effect on reactivity, we employed both an orbital-based and a density-based approach. Firstly, we calculated the occupation number (N_{occ}) of the natural bond orbital (NBO) corresponding to the breaking bond, where deviation from a full occupation of 2 (denoted 2–N_{occ}) describes the degree of bond delocalization (*i.e.*, $\chi = 2 - N_{occ}$).[38] For example, electron donation from a (breaking) C–C σ bond into a geminal σ^* orbital in

cyclopropane increases the value of χ, capturing the hyperconjugation (delocalization) effect proposed by Weinhold and Landis (Figure 1b). We also computed the $\chi = D_\sigma/D_\sigma^0$ ratio used to calculate the electron localization function (ELF = $(1 + \chi^2)^{-1}$), which measures the excess kinetic energy density due to Pauli repulsions (D_σ) relative to the uniform electron gas, D_σ^0.[39] ELF values close to 1 correspond to highly localized electrons, while values closer to 0 indicate complete delocalization. The close agreement between these parameters suggests that the effect of delocalization on reactivity, described by the term χ, is correctly captured. In summary, we therefore expect a decrease in $\Delta E^{\ddagger}$ either through an increase in driving force ($\alpha > 0$, as predicted by the BEP principle), and/or an increase in bond delocalization ($\beta < 0$).

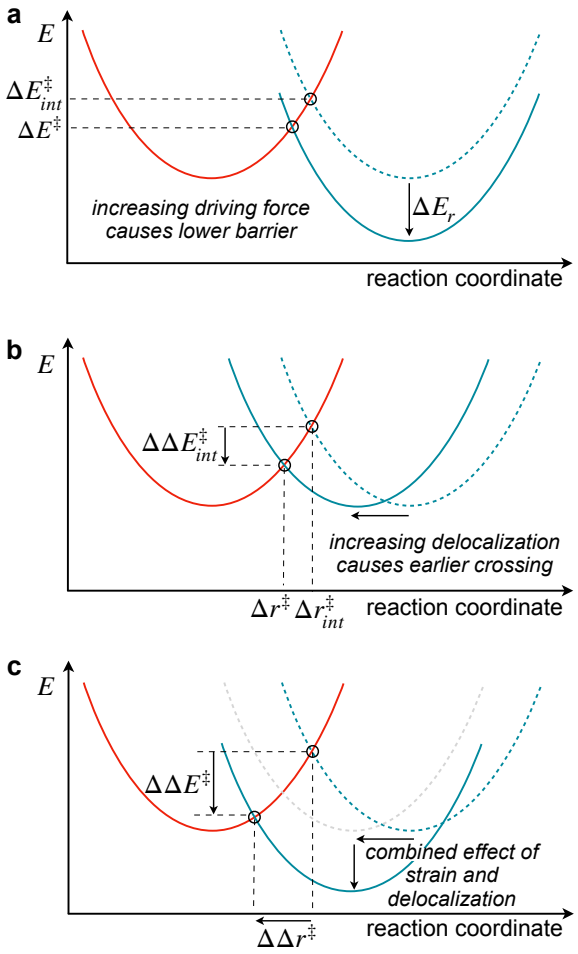

Figure 2. Linear free energy relationships connecting strain release and reactivity. **a** According to Marcus theory, an increase in reaction driving force (ΔE_r) causes an earlier curve crossing, lowering the transition state energy ($\Delta E^{\ddagger}$) relative to the intrinsic activation barrier ($\Delta E^{\ddagger}_{int}$). **b** Increasing bond delocalization decreases $\Delta E^{\ddagger}_{int}$, causing a lower energy, earlier curve crossing. **c** Increasing the reaction driving force and bond delocalization combine to enhance reactivity.

Polycyclic hydrocarbon ring opening

To explore the importance of delocalization on the reactivity of small rings, activation and reaction enthalpies ($\Delta H^{‡}$ and ΔH_r) were calculated for the addition of methyl radical to a test set of 12 acyclic, monocyclic, and fused polycyclic hydrocarbons with ring sizes varying from three to five (Figure 3a). Applying the BEP principle (eq 2) to this set revealed that, as anticipated, ΔH_r alone is an inaccurate predictor of reactivity (Figure 3b), with a poor correlation (R^2 = 0.51) and a root mean squared error (RMSE) of 10.1 kcal mol^{-1}. Particularly notable is the >30 kcal mol^{-1} span of activation enthalpies for [1.1.1]propellane (**H**), cyclopropane (**B**) and cyclobutane (**C**) ($\Delta H^{‡}$ = 5.0, 26.4 and 36.1 kcal mol^{-1}, respectively) despite their similar reaction enthalpies (ΔH_r = –28.2, –28.4 and –26.8 kcal mol^{-1}).[40] However, incorporation of bond delocalization ($\chi = 2–N_{occ}$) into the model (i.e. eq 3) resulted in an excellent correlation between predicted and calculated activation enthalpies (Figure 3c, R^2 = 0.97) and low RMSE (2.5 kcal mol^{-1}). The negative value of the 'delocalization coefficient' β (–192 kcal mol^{-1} e^{-1}) reflects the decrease in the intrinsic barrier with increasing delocalization. Inclusion of the $2–N_{occ}$ parameter alongside ΔH_r^2 leads to near-identical results (Figure S2). Employing density-based delocalization parameters was similarly successful in predicting activation barriers (R^2 = 0.94, RMSE = 3.3 kcal mol^{-1}, Figure S3), independently validating the interpretation that the localized NBO descriptor effectively captures the electron delocalization effect. Notably, descriptors based on canonical orbital properties (*e.g.*, HOMO-LUMO gap) gave unphysical results (SI Figures S4–6), such as negative intrinsic activation barriers. These results not only confirm that our model improves the originally poor correlation obtained by the BEP principle, but also provides a physically-grounded explanation of the connection between χ and electron delocalization, as illustrated by these orbital and density analyses.

To directly compare the impact of delocalization on activation barriers, we examined changes in barrier ($\Delta\Delta H^{‡}$) for the test set relative to bicyclo[2.2.0]hexane (**G**, Figure 3d), which exhibits a moderate strain release value (–52.5 kcal mol^{-1}) but has a small $2–N_{occ}$ value (0.045 *e*). Among the test set, *delocalization, not strain release emerged as the primary cause of reactivity difference for seven of the twelve members relative to* ***G*** (denoted by asterisks). In four cases (**D**, **F**, **H** and **J**) the overall favorable $\Delta\Delta H^{‡}$ arises from a large delocalization contribution, which overcomes the unfavorable change in strain energy relative to **G**. It is especially notable that for the classic 'strain release' reagents bicyclo[1.1.0]butane (**D**) and [1.1.1]propellane (**H**), ring strain *increases* the reaction barriers by 3.4 and 7.6 kcal mol^{-1} respectively; the barrier-lowering delocalization effects of –15.4 and –23.5 kcal mol^{-1} are therefore not only essential, but are the fundamental basis of their 'spring-loaded' behavior. The nature of the delocalization effect was further probed by plotting the electron density difference (EDD) between the total TS electron density, and the densities of each distorted fragment at the TS, for a series of C–C bond cleavage reactions (Figure 4). For the reaction of methyl radical with ethane, the EDD plot involves the expected removal of electron density from the breaking C–C bond (red lobes), and accumulation in the forming C–C bond (blue

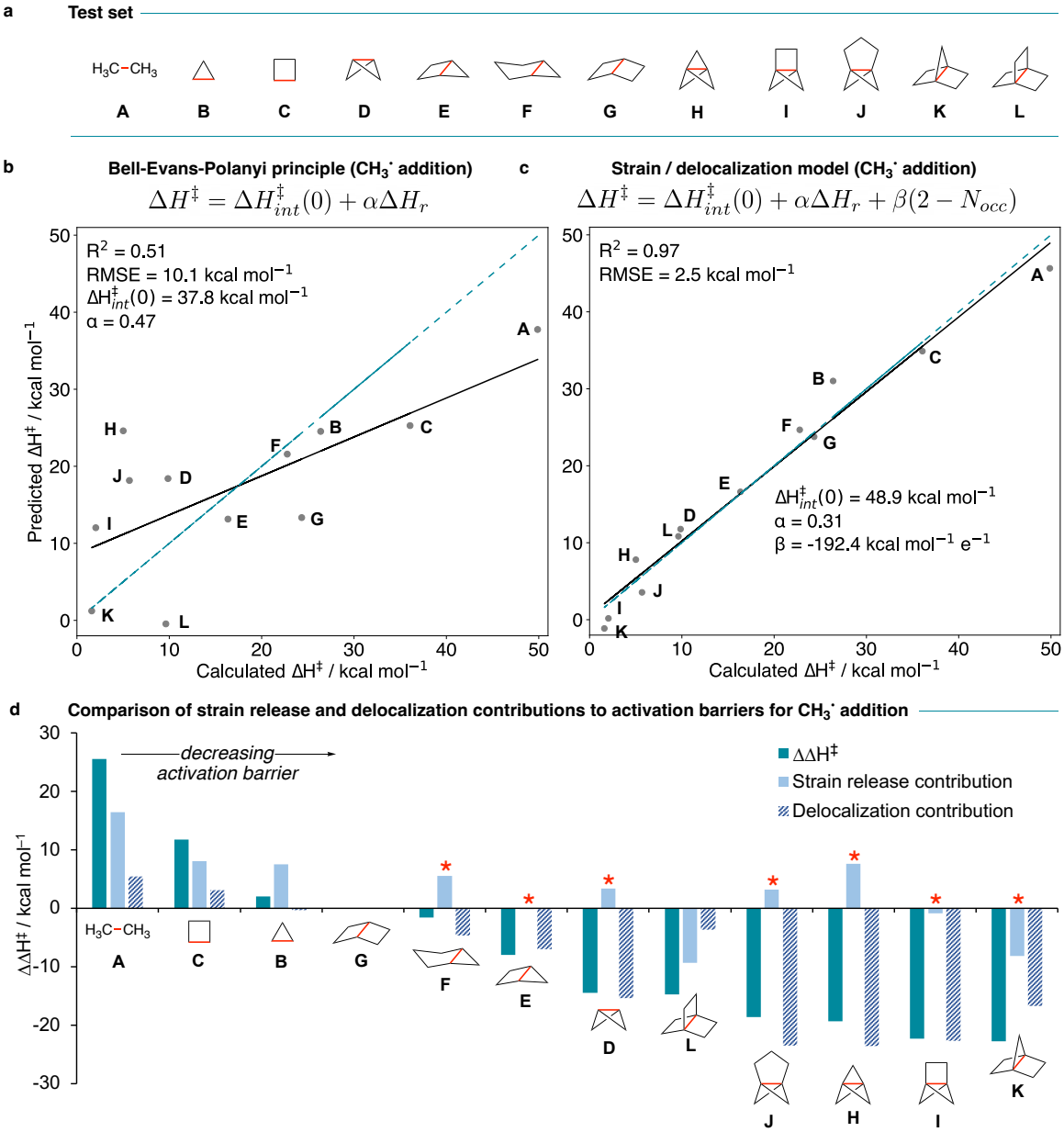

Figure 3. Delocalization dominates trends in 'strain release' ring-opening reactions. **a** Test set of acyclic, monocyclic, and fused polycyclic hydrocarbons. **b** Bell-Evans-Polanyi (BEP) plot (predicted vs calculated $\Delta H^{\ddagger}$, kcal mol^{-1}) for the addition of methyl radical to the red bonds of the molecules in the test set. The blue dashed line denotes perfect correlation. **c** Prediction of $\Delta H^{\ddagger}$ from ΔH_r and $2–N_{occ}$ (eq 3). **d** Breakdown of strain and delocalization ($2–N_{occ}$) contributions to $\Delta\Delta H^{\ddagger}$(kcal mol^{-1}) for the addition of methyl radical to the test set, relative to bicyclo[2.2.0]hexane (**G**). Asterisks indicate cases where delocalization dominates over strain release.

lobes). Similar behavior is observed with cyclobutane, with a node between the bridging methylenes indicating a lack of through-bond communication. However, for cyclopropane, a build-up of electron density on the bridging methylene indicates stabilizing delocalization. [1.1.1]Propellane shows an equivalent effect, where delocalization now extends across all three bridging methylene groups and the bridgehead carbon atoms.[29]

It is interesting to note that while the interbridgehead bond in [1.1.1]propellane can be described as a charge-shift bond,[41] the origins of its *reactivity* are thus no different to those of the covalent bonds of, for instance, cyclopropane; it is simply the combination of the strain release driving force and the ability to delocalize electrons over an additional two methylene groups that explains the reactivity differences.

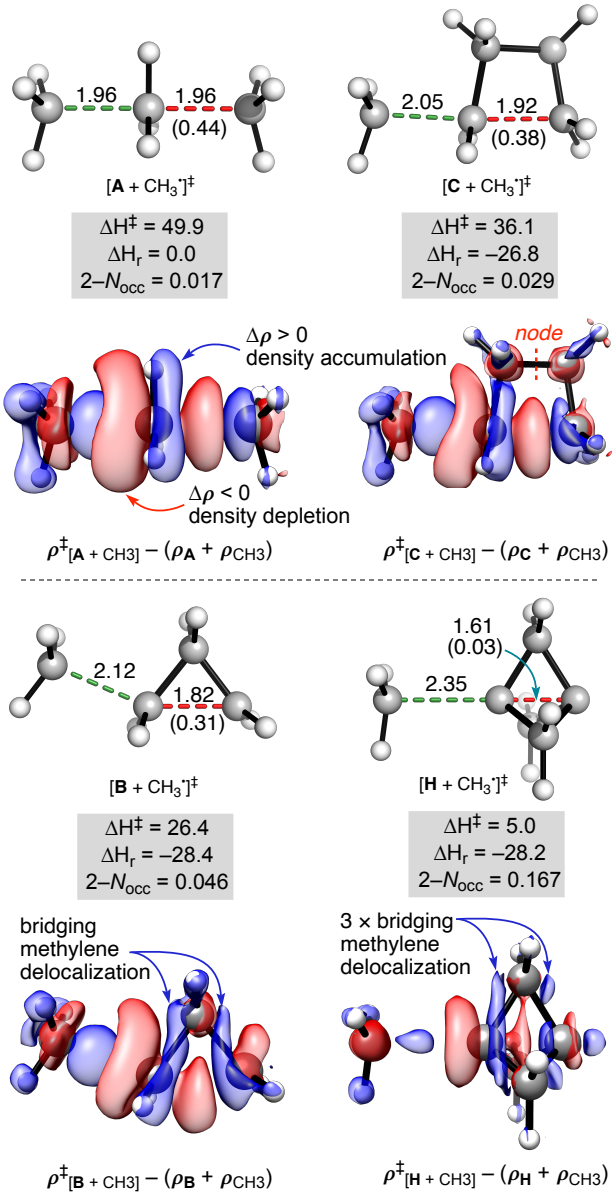

Figure 4: Selected TS geometries (distances in Å), enthalpies (kcal mol^{-1}), 2–N_{occ} values (e), and electron density difference plots (isovalue of 0.015 e Å^{-3}) for the addition of methyl radical to ethane, cyclobutane, cyclopropane and [1.1.1]propellane. Difference between TS and equilibrium bond lengths ($\Delta r^{‡}$) are shown in parentheses.

Structure-reactivity relationship

We next investigated whether the *number* of three-membered rings fused to the breaking bond alone (n_3) could be used as a metric for delocalization (eq 4).

$$\Delta H^{\ddagger} = \Delta H^{\ddagger}_{int}(0) + \alpha \Delta H_r + \beta n_3 \tag{4}$$

Substituting n_3 for 2–N_{occ} in eq 3 leads to a remarkably accurate prediction of reactivity (Figure 5a). Specifically, each three-membered ring fused to the breaking C–C bond reduces the intrinsic activation energy by ~10 kcal mol^{-1}, corresponding to a ~10^7-fold increase in the rate constant at 298 K. As noted above, this simple model effectively captures the greater reactivity of cyclopropane over cyclobutane, and also the contrasting reactivities of [1.1.1]propellane and cyclopropane; the increased reactivity of the former can be attributed to a greater number of three-membered rings fused to the breaking bond (n_3 = 3). Varying the number of three-membered rings fused to a breaking bond therefore offers a simple way to modulate the reactivity of the system – for example, switching the behavior of a molecule from a highly-reactive bioconjugation warhead (*e.g.*, bicyclo[1.1.0]butanes similar to **D**)[8,9,42] to an inert lipid tail group (e.g. bicyclo[2.2.0]hexane 'ladderanes' based on **G**).[43]

We recently applied this concept to develop the radical ring-opening reactivity of [3.1.1]propellane (**J**).[44] Compared with [1.1.1]propellane, [3.1.1]propellane sacrifices bond delocalization (n_3 = 3 vs 2, respectively) in exchange for an increased driving force (ΔH_r = –28.2 vs –42.1kcal mol^{-1}, respectively, Figure 5b). The predicted difference in $\Delta H^{\ddagger}$ between these systems for a radical addition is 3.8 kcal mol^{-1}, in good agreement with the calculated value of 1.1 kcal mol^{-1} ($k_{rel,calc}$ ~ 0.2 at 298 K).[44] This result suggests that the antagonistic effect of decreasing delocalization but increasing strain release coincidentally results in similar radical reactivity to [1.1.1]propellane. Pleasingly, [3.1.1]propellane was found to be a viable substrate for numerous radical reactions previously developed for [1.1.1]propellane, including atom transfer radical additions, dual photoredox/Cu catalysis, and chalcogen atom addition reactions.[44]

The delocalization model (eq 4) can also be applied to two-electron processes, such as the nucleophilic addition of amide anions to **D**, **E** and **H**.[42,45] When using NH_2^- as a model nucleophile, an excellent correlation and low error was observed between predicted and calculated activation enthalpies (R^2 = 0.98, RMSE = 2.7 kcal mol^{-1}, Figure 5c). The β coefficient (–10.4 kcal mol^{-1}) is almost identical to the one-electron reaction, which supports the idea that delocalization-modulated reactivity is intrinsic to the bonding pattern found in the small rings. If delocalization effects were absent, the barrier to nucleophilic addition to [1.1.1]propellane would increase by ~30 kcal mol^{-1}, rendering it inert under the reaction conditions. In other words, strain release alone cannot account for the observed reactivity – delocalization again emerges as the primary driver of reactivity. This same principle holds true for bicyclo[1.1.0]butanes (**D**) and bicyclo[2.1.0]pentanes (housanes, **E**), where activation barriers would increase by ~20 and ~10 kcal mol^{-1} respectively in the absence of delocalization. This effect is corroborated by experimental results on the addition of dibenzylamine

across the interbridgehead bonds of bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane sulfones (Figure 5d), where the former affords the cyclobutylamine product at ambient temperature, whereas the latter requires heating to 80 °C to form the equivalent cyclopentane.[45] This reactivity difference directly opposes the behavior that would be expected solely based on strain release energies (*i.e.*, thermodynamics) alone (–40.2 and –48.1 kcal mol^{-1} for bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane, respectively).

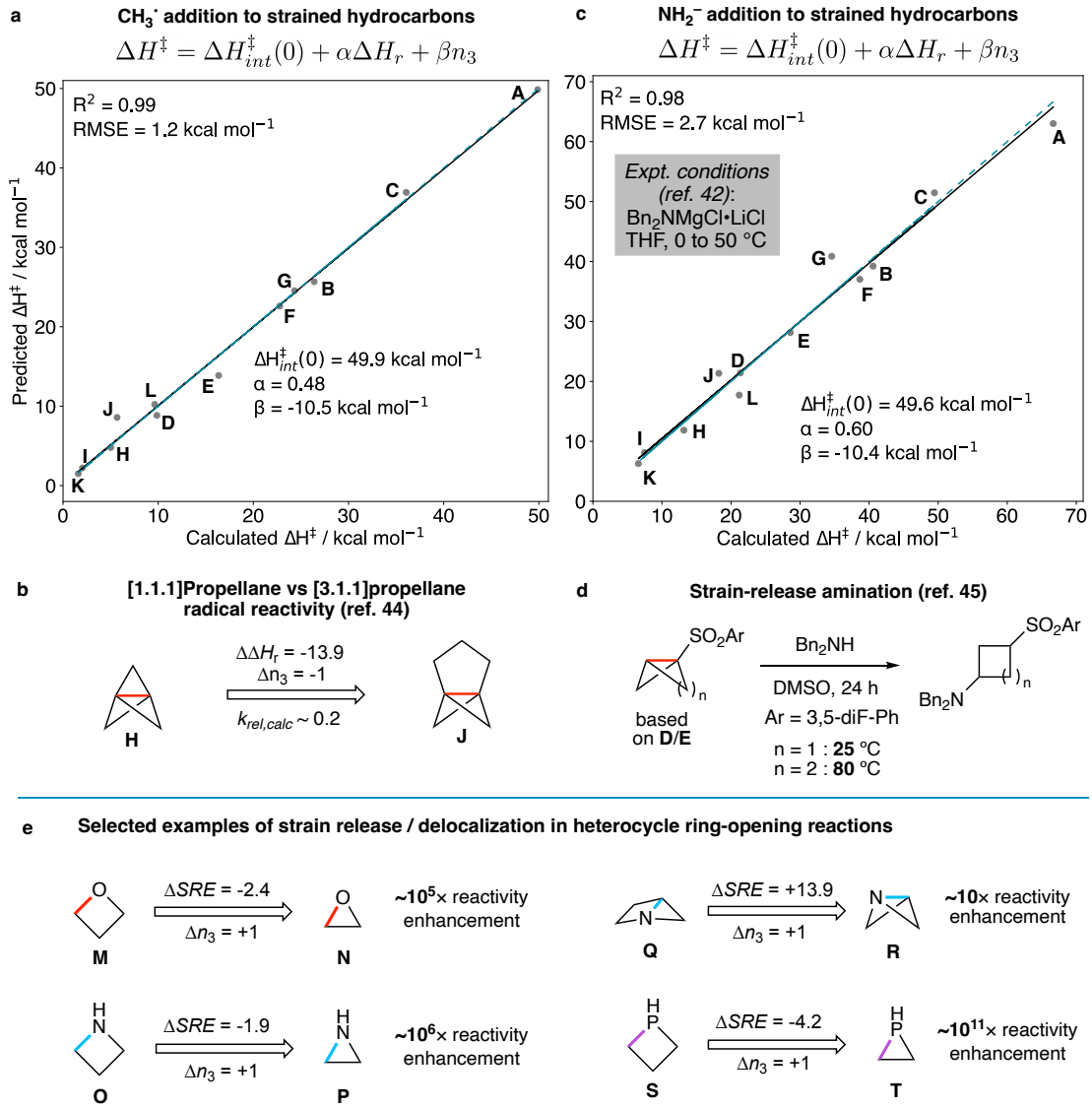

Figure 5: Implications of strain and delocalization on general reactivity. **a** Multiple linear regression plots for the prediction of $\Delta H^{‡}$ from ΔH_r and n_3 for the hydrocarbon test set with $CH_3^{\bullet}$ using eq 6. The blue dashed lines denote perfect correlation. **b** Increasing strain release driving force for [3.1.1]propellane (**J**) vs [1.1.1]propellane (**H**) counteracts the decrease in intrinsic reactivity due to a loss of bond delocalization, resulting in similar reactivity. **c** Increased delocalization lowers the required reaction temperature for the amination of a bicyclo[1.1.0]butane sulfone compared with housane. **d** Selected examples of the importance of strain release and delocalization in the ring-opening reactivity of heterocycles. See the SI (Figures S9–S10) for Marcus E_a values from refs. [46] and [47], and the full dataset of radical and anionic reactivity. All relative reaction rates estimated at 298 K.

Heterocycle ring opening

We next extended the model in eq 4 to radical and anionic ring-opening reactions of heterocyclic systems encompassing a range of bond types (C–C, C–N, C–O, C–P, C–S), previously studied by Hoz and co-workers.[46,47] Notably, three-membered rings are consistently more reactive than their four-membered homologues, owing to pronounced bond delocalization. This trend is exemplified by the significant increase (~10^5) in anionic ring-opening rate for ethylene oxide **N** (n_3 = 1) over oxetane **M** (n_3 = 0) despite only a 2.4 kcal mol^{-1} difference in strain release energies (Figure 5d) – a phenomenon that underscores the utility of epoxides in synthesis and biosynthesis,[11][5] and conversely may explain the success of oxetanes as biostable motifs in drug discovery.[30] Similarly, aziridine **P** undergoes nucleophilic ring opening ~10^6 times faster than azetidine **O**, primarily attributed to delocalization effects in the breaking of its three-membered ring. Remarkably, despite azabicyclo[2.1.0]pentane **Q** (n_3 = 1) releasing almost 14 kcal mol^{-1} more strain energy than azabicyclo[1.1.0]butane **R** (n_3 = 2) upon nucleophilic ring opening, the latter molecule is predicted to be similarly reactive. Interestingly, heterocycles containing third-row heteroatoms (e.g. phosphorus and sulfur) are more sensitive to the number of three-membered rings than their second-row counterparts, resulting in far greater predicted ring-opening reactivity of (unknown) epiphosphine **T** than phosphetane **S** (Figure 5d). This can be understood by considering the higher polarizability of third-row atoms,[48] which facilitates additional electron delocalization at the TS compared with second-row elements.[36]

Rule of thumb for reactivity prediction

The delocalization effects that explain the enhanced reactivity of three-membered rings can be simplified into a 'rule of thumb' for rapidly estimating relative reactivity. This model utilizes tabulated SREs (available for most common substrates in https://github.com/duartegroup/strain-delocalisation, and Figure S11); α is taken as 0.5 and β as –10 kcal mol^{-1} based on the results for radicals and anions obtained above. By approximating eq 4, differences in activation barriers between two substrates ($\Delta\Delta H^{\ddagger}$) can be estimated as follows:

$$\Delta\Delta H^{\ddagger} \approx 0.5\Delta SRE - 10\Delta n_3. \tag{5}$$

where ΔSRE is the difference in strain release energies between a pair of substrates (tabulated in Figure S11), and Δn_3 is the difference in the number of three-membered rings fused to the breaking bonds for this pair of substrates. This model is easily applied to rationalize differences in reactivity for the radical addition reactions of [1.1.1]propellane (**H**), bicyclo[1.1.0]butane (**D**) and bicyclo[2.1.0]pentane (**E**) with $BrCCl_3$ or CCl_4 (Figure 6); While **H** and **D** readily undergo addition of the trichloromethyl radical, **E** does not.[49] Additional competition reactions demonstrate that **H** undergoes significantly more rapid reaction than **D**. SREs alone fails to explain this reactivity pattern, but our rule of thumb (eq 5) correctly predicts the observed trend (Figure 6a). The estimated activation enthalpies for **D** and **E** are 4.0 and 10.1 kcal mol^{-1} higher than **H**, respectively,

in line with calculated values of 3.5 and 10.2 kcal mol^{-1} (Figure 6b). These barriers translate to relative addition rates (k_{rel}) that are ~10^2 and ~10^7 times slower for **D** and **E** than **H** at 298 K – sufficient to entirely suppress reactivity in the case of **E**.

Estimation of the relative reactivity of bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane sulfones offers a further example of application of the model (Figure 5c); eq 5 suggests that the greater strain released in the ring-opening of the bicyclo[2.1.0]pentane should again be offset by the greater delocalization in the (more reactive) bicyclo[1.1.0]butane. The strain release contribution to the TS barrier change, 0.5ΔSRE, is approximately +4 kcal mol^{-1} (half the difference between –40.2 and –48.1), and the delocalization contribution, Δn_3, is approximately –10 kcal mol^{-1} (from the difference of one three-membered ring), leading to a 6 kcal mol^{-1} lower TS barrier for bicyclo[1.1.0]butane than bicyclo[2.1.0]pentane. From the reported reaction conditions,[45] $\Delta\Delta G^{\ddagger}$ can be roughly estimated as 5 kcal mol^{-1} (see Section S6 for further discussion), which is only a 1 kcal mol^{-1} difference from the rule of thumb prediction. In short, the enhanced reactivity of bicyclo[1.1.0]butane can therefore be predicted simply by looking up strain release energies and counting the number of three-membered rings.

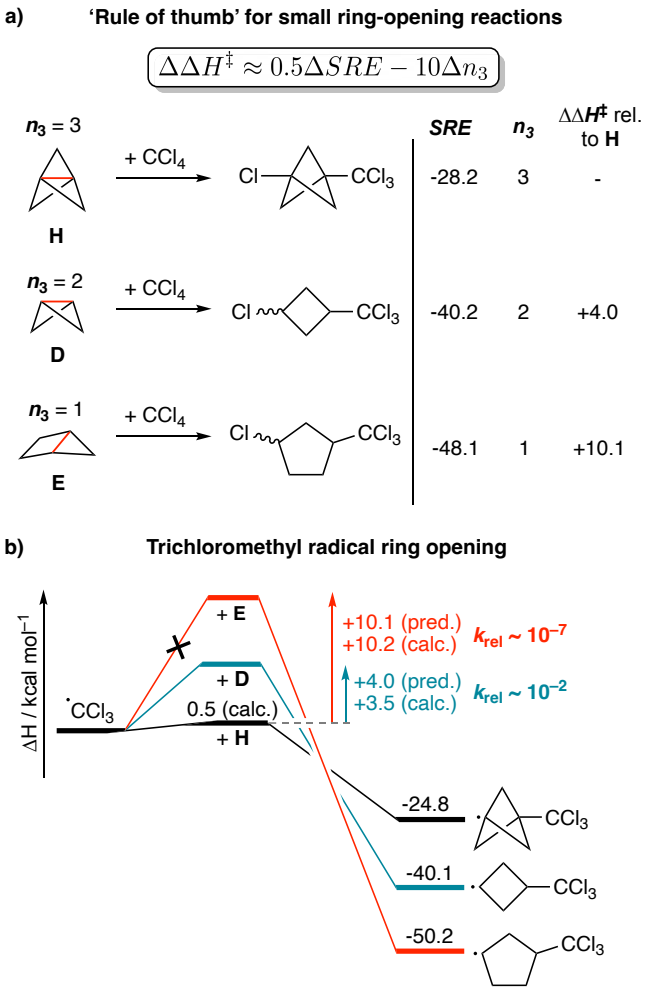

Figure 6: Applications of the rule of thumb. **a.** Predicted relative activation enthalpies ($\Delta\Delta H^{\ddagger}_{pred}$, kcal mol^{-1}) based on SRE and n_3 using eq 5. **b.** Comparison of estimated and calculated ring-opening activation barriers using eq 5.

Extension to cycloaddition reactions

This model can be extended to reactions other than the three-membered ring cleavage in which electronic delocalization can operate simultaneously with strain release. We have compiled a dataset encompassing strain release energies and $2–N_{occ}$ values for various bonds types across commonly-employed strained molecules, including carbocycles, heterocycles, cycloalkynes and cycloalkenes (Figure S11 and https://github.com/duartegroup/strain-delocalisation). For example, the principle that more delocalized bonds are intrinsically more reactive is found to apply to reactions such as strain-releasing 'click' (3+2) azide-alkyne cycloadditions.[50] Strategies to accelerate such reactions have primarily focused on increasing the strain of the alkyne, for example by incorporating the alkyne into a medium-sized ring.[51,52] Significant efforts have been undertaken to understand reactivity patterns in these reactions using the distortion/interaction-activation/strain (DI-AS) model, which has identified both enhanced alkyne distortion and greater inter-fragment interactions as factors that reduce TS barriers.[53,54]A BEP analysis of the cycloaddition between methyl azide and a range of alkynes (Figure 7a) reveals a loose correlation (R^2 = 0.67) between the reaction driving force (ΔH_r) and the activation barrier ($\Delta H^‡$) with a reasonably low RMSE (2.3 kcal mol^{-1}). This result suggests that, in general, strain release does enhance alkyne reactivity, causing faster cycloadditions as the ring size decreases from 10 (**A3**) to 7 (**A10**).

However, as noted by Alabugin and co-workers,[51] an exception to this relationship is dibenzocyclooctyne **A8.** This compound was designed under the premise that an increased number of sp^2 centers within the cyclooctyne ring would enhance its strain, consequently increasing strain-release reactivity. In fact, **A8** is more reactive than its strain release energy alone would suggest: The reaction enthalpy of **A8** is 6 kcal mol^{-1} *less exothermic* than the parent cyclooctyne **A4**, which should in principle *increase* its activation barrier relative to **A4** by around 3 kcal mol^{-1} if strain release alone were to govern reactivity. Upon dissection of the $\Delta\Delta H^‡$ between **A8** and **A4** into strain release and delocalization components (using eq 3), it becomes evident that enhanced delocalization due to greater π-conjugation ($\Delta(2–N_{occ})$ = 0.05 *e*) in **A8** accounts for a 6 kcal mol^{-1} barrier-lowering effect. Consequently, *delocalization counteracts the effect of decreased strain release observed in **A8***, resulting in a net lowering of the activation barrier by 3 kcal mol^{-1} – an approximate 10^3-fold rate acceleration at 298 K compared with **A4**. A similar analysis across a set of cycloalkynes (Figures 7b and 7c) reveals the importance of delocalization on the reactivity of monobenzocyclooctynes (**A5**), and to a smaller extent difluorinated cyclooctyne **A9** and distal benzocyclooctyne **A7**, denoted by red asterisks in Figure 7c. As with the small ring-opening reactions discussed above (Figure 3c), the negative sign of the delocalization coefficient β for this cycloaddition reaction (–114 kcal mol^{-1} e^{-1}) reflects the decrease in the intrinsic barrier due to delocalization. The smaller magnitude of β for the cycloaddition reaction compared with the small-ring opening (–114 vs –192 kcal mol^{-1} e^{-1}, respectively, for $\chi = 2–N_{occ}$) reflects the lower sensitivity of the cycloaddition towards variation in bond delocalization. We suggest that this lower sensitivity

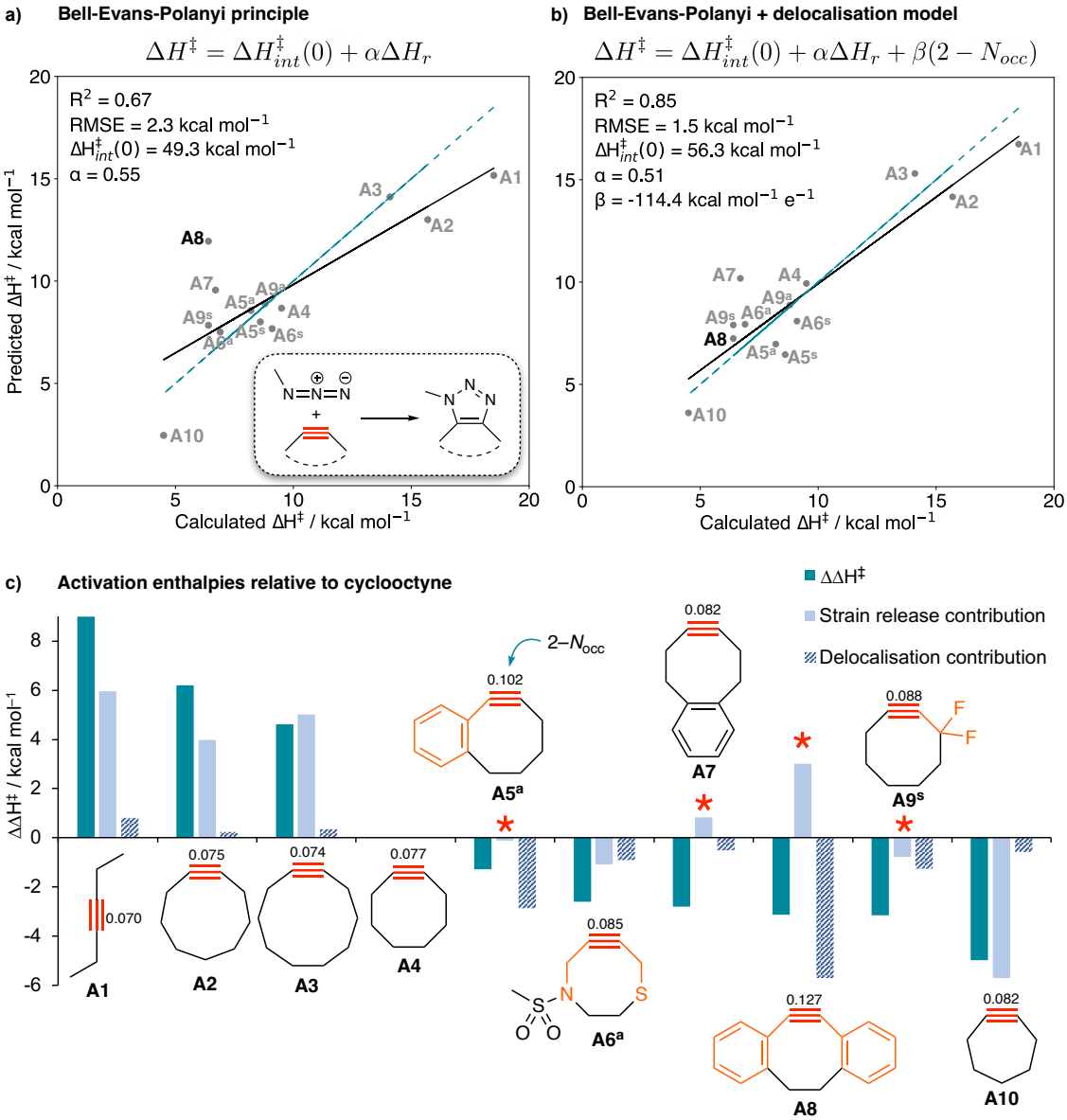

Figure 7: Application to (3+2) azide-alkyne cycloaddition reactions. Delocalization, not strain release, explains the enhanced reactivity of dibenzocyclooctyne over cyclooctyne in (3+2) cycloadditions with methyl azide. **a** Bell-Evans-Polanyi (BEP) plot (predicted vs calculated $\Delta H^{\ddagger}$, kcal mol^{-1}) for the addition of methyl azide to the red bonds of the alkynes in the test set. The blue dashed line denotes perfect correlation. **b** Prediction of $\Delta H^{\ddagger}$ from ΔH_r and $2–N_{occ}$ (eq 3). **c** Breakdown of strain release and delocalization ($2–N_{occ}$) contributions to $\Delta\Delta H^{\ddagger}$ (kcal mol^{-1}) for the addition of methyl azide to the test set, relative to cyclooctyne (**A4**). Asterisks indicate cases where delocalization dominates over strain release, and superscript ^{a} and ^{s} refer to *anti* and *syn* transition states, respectively.

may arise from smaller orbital overlap between the breaking π bond and the hyperconjugating group, such that the effect of this electron delocalization on the transition state is less pronounced.

As with any empirical model, there is an inherent limitation to the accuracy achievable with the 'strain/delocalization' components from which it derives, since other factors, such as dipole effects and non-covalent interactions present at the TS but not in the reactant or product, and explicit variation in bond force constants, are neglected. Such additional factors could be incorporated into

a linear free energy relationship through the inclusion of further descriptors. However, we feel that the overall improvement in barrier height prediction (R^2 = 0.85, RMSE = 1.5 kcal mol^{-1}, Figure 7b) compared with the BEP model (R^2 = 0.67, RMSE = 2.3 kcal mol^{-1}, Figure 7a) illustrates the generality and importance of delocalization on reactivity across a range of organic reactions without recourse to a deeper analysis of multiple factors. It is also instructive to compare the results of conventional DI-AS analysis to the complementary strain/delocalization model introduced here: the more delocalized a breaking bond is, the less such a bond is required to distort to adopt the TS geometry, leading to an earlier TS. Likewise, greater delocalization could facilitate stronger electronic interaction between reactants due to enhanced orbital overlap earlier along the reaction coordinate. One drawback of the DI-AS approach is the necessity for explicit knowledge of the TS geometry and energy; in contrast, the strain/delocalization model introduced in this work enables a quick and quantitative estimation of reactivity using solely ground state properties. This feature is anticipated to be valuable when designing new 'strain-release' driven reactions.

Conclusion

While strain energy is often invoked to rationalize observed reactivity patterns, and is commonly cited as the cause of the heightened reactivity of small carbo- and heterocyclic rings, and cycloalkynes, it is evident that thermodynamic strain-release arguments alone are insufficient to explain the origins of such reactivity. Through analysis of radical and nucleophilic additions to small rings, and azide/cycloalkyne click reactions, bond delocalization is shown to be an equally important factor that works alongside – and in many cases dominates – strain release effects to promote these facile reactions. To aid the integration of these ideas into novel 'strain release' strategies, a simple model has been developed that offers rapid and quantitative reactivity predictions.

Supporting Information

Additional material are included as an electronic PDF containing Supplementary Methods, Supplementary Discussion (Sections S1–S4), Supplementary Figures S1–S16, Supplementary Tables S1–S7, and Supplementary References.[39,46,47,49,55–73]

Data Availability: Cartesian coordinates and energies of all stationary points are openly available at https://github.com/duartegroup/strain-delocalisation.

Code Availability: Code to generate all linear regression data and plots discussed in this paper is openly available at https://github.com/duartegroup/strain-delocalisation.

Methods

QM calculations were run using ORCA (v 4.2.1)[68] at the [DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP] level of theory ($CH_3^\bullet$ reactions) or [SMD(THF)/DLPNO-CCSD(T)/ma-def2-QZVPP (TightPNO)//SMD(THF)/B2PLYP-D3BJ/def2-TZVP (ma-def2-TZVP on N)] level of theory (NH_2^- reactions).[73–77] Strain release energies were obtained at the [DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP] level of theory. Alkyne (3+2) cycloadditions calculated at the B2PLYP-D3BJ/def2-TZVP level. NBO occupation numbers were calculated using the NBO program (v 7.0) based on the relaxed density, and density-based descriptors were calculated with Multiwfn (v 3.6).[62] All data processing was carried out using the *Scikit-learn* package with Python 3.7.[63] Enthalpies were chosen for a direct comparison with strain energies, which are commonly reported instead of Gibbs free energies. Trends in enthalpy and Gibbs free energy were found to be in excellent agreement for all reactions studied here. For further details, see the Supplementary Methods.

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