Delocalisation-enabled organic reactivity

Alistair J. Sterling,[1] Russell C. Smith,[2] Edward A. Anderson[3,*] & Fernanda Duarte[3,*]

The release of strain energy is a fundamental driving force for organic reactions. However, strain release alone is an insufficient predictor of reactivity, as seen in the equivalent strain energies but disparate reactivity of cyclopropane and cyclobutane. Here we show that bond delocalisation is a key factor that operates alongside strain release to boost and even dominate reactivity, significantly lowering the energy required for bond-breaking in cyclopropanes and cycloalkynes. Thermodynamic and delocalisation parameters explain the relative reaction rates of molecules containing these functional groups, leading to a 'rule-of-thumb' that accurately predicts activation barriers. These principles are demonstrated in the context of the reactions of strained building blocks commonly encountered in organic synthesis, medicinal chemistry, polymer science and bioconjugation. By introducing delocalisation as a means to control reactivity profiles, these findings will transform the use of strain as a design concept in synthesis.

The release of strain energy has long been harnessed as a fundamental driving force in chemical synthesis. For example, 'ring strain' – one of the basic tenets of undergraduate chemistry[1] – imparts heightened reactivity in three- and four-membered rings due to deviations from ideal bond angles.[2] Accordingly, 'strain release' is often deployed in organic synthesis as a powerful tactic to increase reaction rates (Fig. 1a), with applications in total synthesis,[3] polymer science,[4,5] bioconjugation[6,7] and bioisosterism;[8] it is also an important concept in biosynthesis.[9] However, despite the prevailing dogma that pent-up strain energy explains the reactivity of small rings and medium-ring alkynes and alkenes, even the simplest of these systems presents a paradox: although cyclopropanes display markedly heightened ring-opening reactivity over cyclobutanes (k_{rel} = 10^4 – 10^7 for intramolecular ring-opening reactions),[10] the two molecules possess nearly identical strain energies (27.5 and 26.5 kcal mol^{-1} respectively).[2] This puzzle has been the subject of decades of theoretical investigation: Stirling *et al.*[11] proposed that a larger proportion of angle strain is relieved in cyclopropane (~75%) than cyclobutane (~50%) upon ring-opening, while the groups of Hoz[12] and Houk[13] argued that differences in electronic structure (*i.e.*, bonding) are instead the cause of the reactivity difference. Hoz proposed that the rehybridisation induced by bond angle compression enhances the electrophilicity of cyclopropane C–C bonds by lowering the energy of the σ* orbitals, while Houk invoked an 'orbital interactions through-bonds' (OITB)[14] argument in which transition state (TS)

[1] Physical and Theoretical Chemistry Laboratory, South Parks Road, Oxford, OX1 3QZ, UK
[2] Abbvie Drug Discovery Science & Technology (DDST), 1 North Waukegan Road, North Chicago, IL 60064, USA
[3] Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK.
E-mail: edward.anderson@chem.ox.ac.uk, fernanda.duartegonzalez@chem.ox.ac.uk

aromaticity stabilises ring-opening reactions of cyclopropane, whereas equivalent reactions of cyclobutane are destabilised through an antiaromatic TS. While offering qualitative explanations for the observed reactivity differences in these specific systems, a general predictive model that connects bonding differences to reactivity in any organic molecule is yet to emerge.

We questioned whether the electronic structure and distinct reactivity of cyclopropane, and related molecules, can be connected to the models commonly used to describe its bonding. The Coulson-Moffitt 'bent bonds' description,[15] Dewar's σ-aromaticity proposal,[16] and Weinhold and Landis' geminal hyperconjugation model[17] all indicate greater electronic delocalisation of the C–C bonds in the ground state, such that the bonding electron pair is partially delocalised around the three-membered ring (Fig. 1b), in contrast to the 'ordinary' localised C–C σ bonds of cyclobutane. In this work, we generalise this delocalisation principle to link bonding, strain energy and reactivity (Fig. 1c). We propose that enhanced delocalisation of the electrons from breaking bonds within three-membered rings results in earlier, lower energy transition states, an effect that complements and is distinct from barrier lowering due to strain release alone. Our model explains not only the relative reactivity of cyclopropane and cyclobutane, but that of *any* molecule containing one or more three-membered rings, including heterocycles and polycyclic structures. In many cases, delocalisation dominates reactivity; for example, we show that the 'spring-loaded' behaviour of highly-strained bicyclo[1.1.0]butanes and [1.1.1]propellane derives entirely from their ability to benefit from bond delocalisation.[18] Similarly, C–O delocalisation in epoxides explains their far greater propensity to undergo ring-opening than oxetanes, the latter of which can even be employed as chemically inert bioisosteres for carbonyl groups.[19] We found that these individual examples can be generalised in a simple 'rule-of-thumb' in which activation barriers decrease by ~10 kcal mol^{-1} per three-membered ring fused to the breaking bond, which corresponds to a ~10^7 fold rate enhancement at 298 K. We further show that the cumulative effects of strain release and bond delocalisation can be applied to the 'strain-promoted' azide-cyclooctyne (3+2) cycloaddition, commonly used as a bioconjugation strategy.[6] Collectively, this unifying framework provides a quantitative prediction of strain-driven and delocalisation-enabled reactivity.

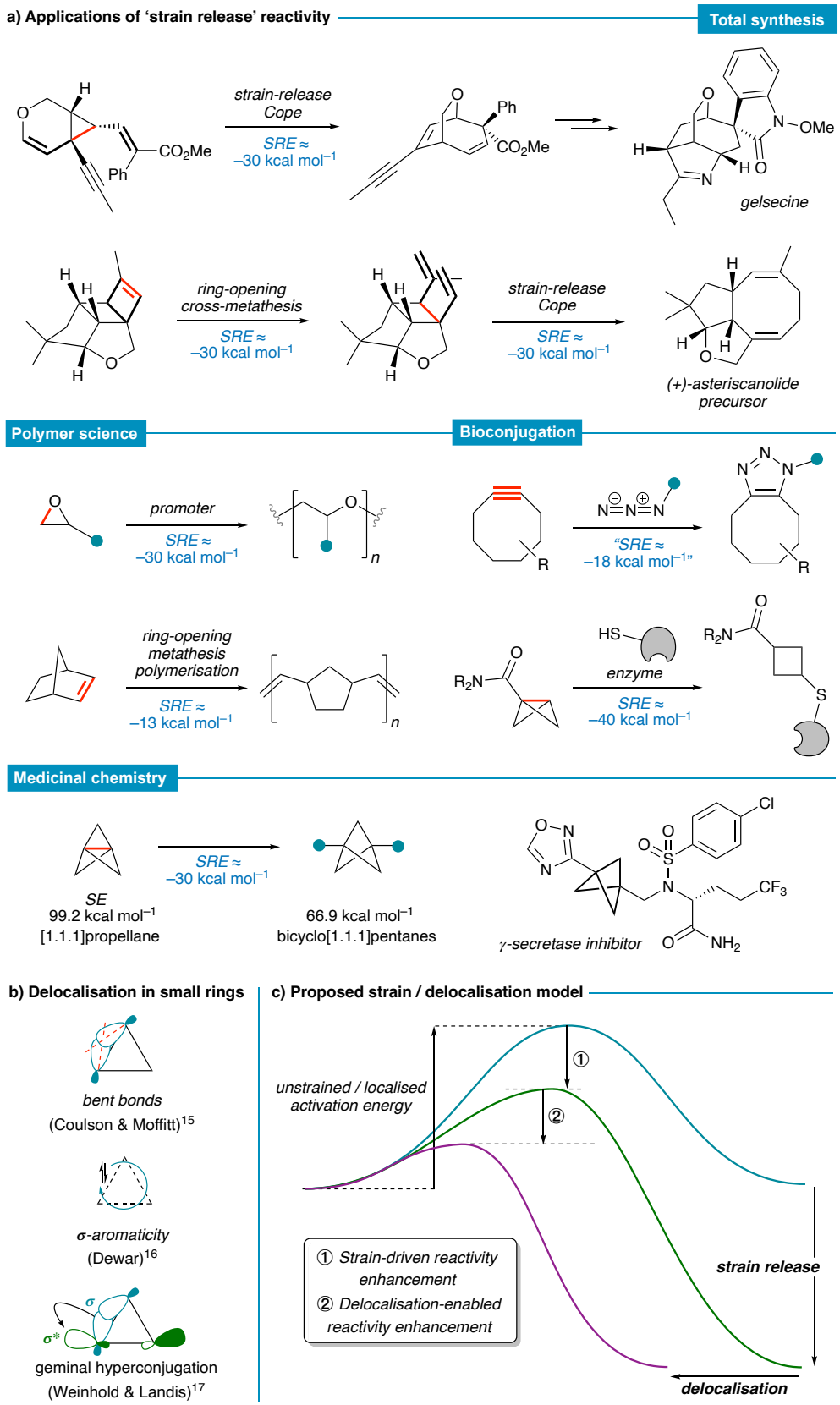

Fig. 1: Role of strain in organic synthesis. a Examples of strain release in organic chemistry including total synthesis,[20,21] bioconjugation reactions,[6,7] ring-opening polymerisation,[22] and bioisostere synthesis.[23] **b** Delocalisation in three-membered rings. **c** This work: Strain release and delocalisation combine to enhance reactivity through lower activation barriers and earlier transition states.

Strain is traditionally proposed to modulate reactivity by relating the reaction driving force E_r to its activation barrier E_a. An early example is the Bell-Evans-Polanyi (BEP) principle (Eq. 1, Fig. 2a),[24,25] in which the difference in activation barrier for two similar reactions (ΔE_a) is proportional to the difference in driving force (ΔE_r). Marcus theory (Eq. 2, Fig. 2b) includes a quadratic correction, defining $E_{a,int}$ as the activation barrier in the absence of a driving force.[26,27]

$$\Delta E_a = \alpha \Delta E_r \tag{1}$$

$$E_a = E_{a,int} + \frac{1}{2}\Delta E_r + \frac{\Delta E_r^2}{16 E_{a,int}} \tag{2}$$

In the context of strain release reactivity, both theories predict that an increase in 'strain release energy' (SRE) will lead to a lower activation barrier; however, the similar strain energies of cyclopropane and cyclobutane would then erroneously imply similar reaction profiles. This inability to correctly predict relative reactivities arises from the assumption that the breaking C–C bonds are equivalent, despite the increased bond delocalisation in cyclopropane (*vide supra*); the breaking of a more delocalised bond will have a lower intrinsic activation barrier since the redistribution / unpairing of the bonding electrons incurs a lower energetic penalty (Fig. 2c). Activation barriers for a series of similar substrates should therefore depend on both strain release (through differences in E_r) *and* delocalisation (through differences in $E_{a,int}$).

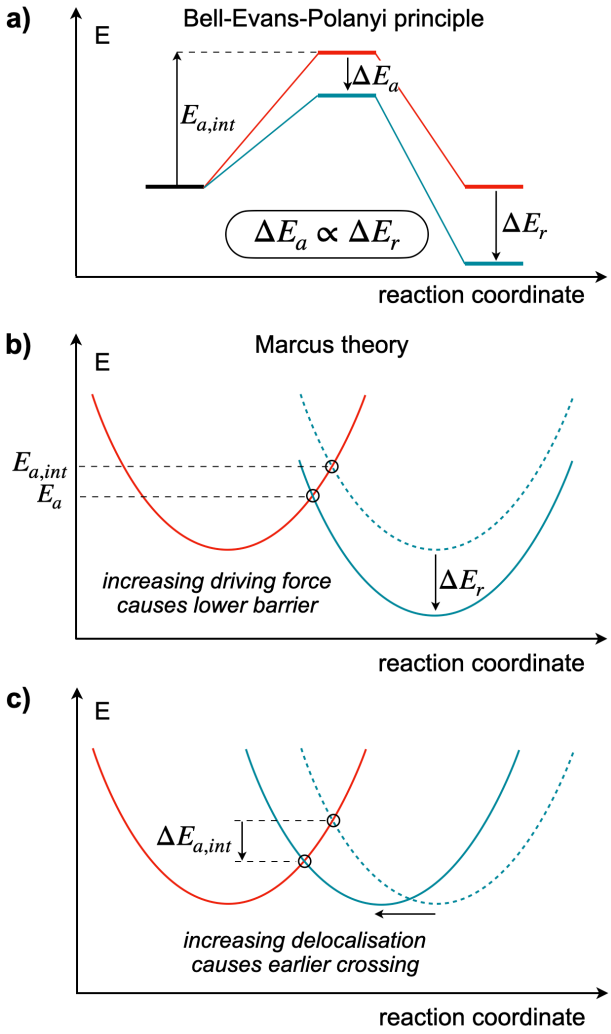

Fig. 2: Linear free energy relationships connect strain release to reactivity. a The Bell-Evans-Polanyi principle: A linear relationship connects differences in the reaction driving force (ΔE_r) and the activation energy (ΔE_a) relative to the intrinsic activation barrier ($E_{a,int}$). **b** Marcus theory: the intersection of parabolas describing the reactants (red) and products (blue) approximates the energy of the TS barrier. An increase in driving force again causes earlier curve crossing through a decrease in E_a. **c** Increasing bond delocalisation also causes earlier curve crossing, decreasing the intrinsic activation barrier by $\Delta E_{a,int}$.

To explore the importance of delocalisation on reactivity, we calculated activation and reaction enthalpies ($\Delta H^{‡}$ and ΔH_r) 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 (Fig. 3a). Application of the BEP principle to this set showed that ΔH_r alone is an inaccurate predictor of reactivity (Fig. 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 in 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) in spite of very similar reaction enthalpies (ΔH_r = –28.2, –28.4 and –26.8 kcal mol^{-1}). A similarly poor correlation was found using Marcus theory (§S1).

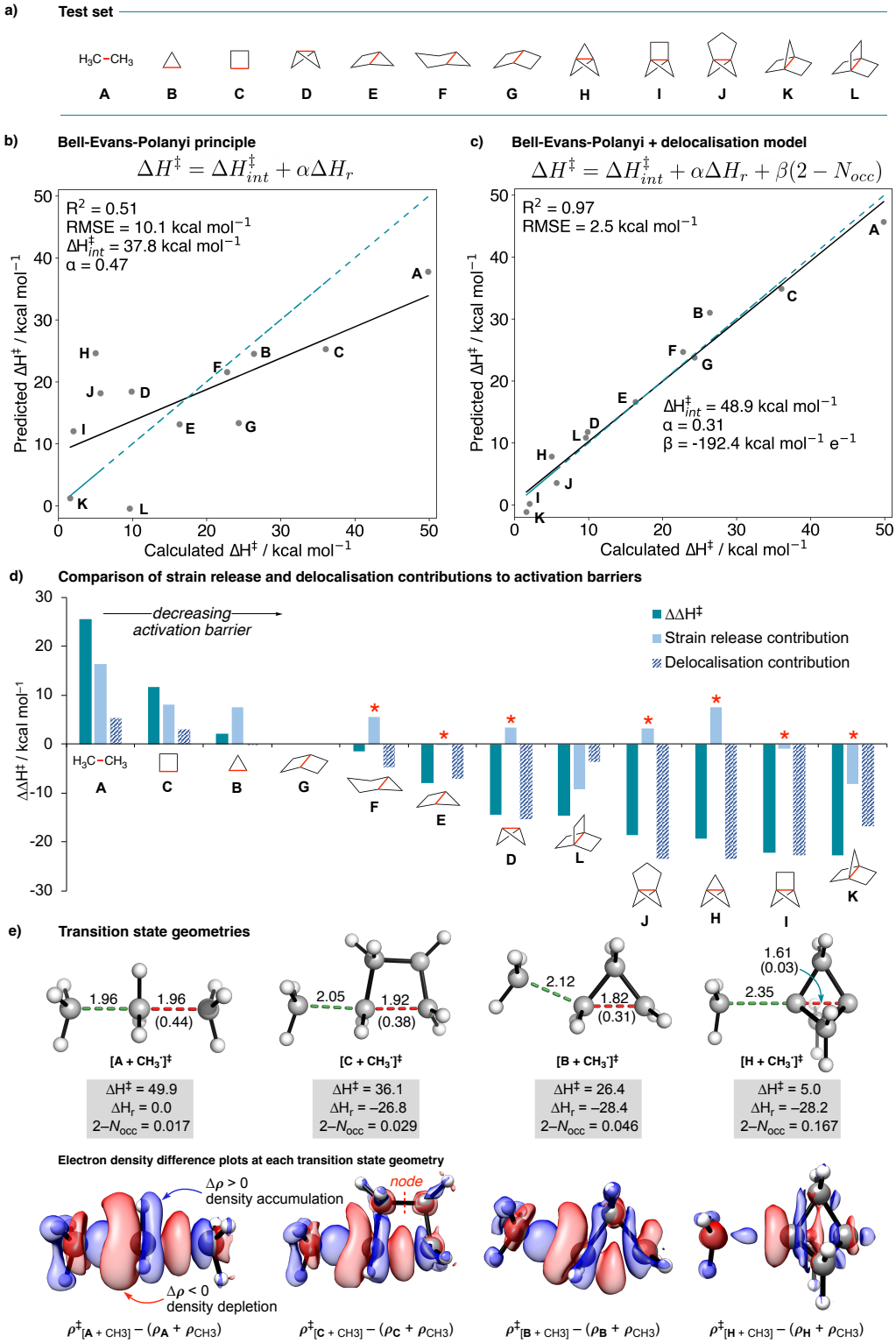

Fig. 3: Delocalisation dominates trends in 'strain release' ring-opening reactions. a Test set of acyclic, monocyclic, and fused polycyclic hydrocarbons. **b** Bell-Evans-Polyani (BEP) plot (ΔH_r vs $\Delta H^{\ddagger}$, kcal mol^{-1}) for the addition of methyl radical to the red bonds of the molecules 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 delocalisation ($2–N_{occ}$) 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 delocalisation dominates over strain release. **e** 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 are shown in parentheses.

To investigate the role of delocalisation on the reactivity of these systems, 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 delocalisation. For example, electron donation from a C–C σ bond into a geminal σ^* orbital in cyclopropane increases the value of 2–N_{occ}, capturing the hyperconjugation (delocalisation) effect proposed by Weinhold and Landis (Fig. 1b). Incorporation of this 2–N_{occ} parameter into the BEP model using multiple linear regression (Eq. 3 and Fig. 3c) resulted in an excellent correlation between predicted and calculated activation enthalpies (R^2 = 0.97) and low RMSE (2.5 kcal mol^{-1}). The negative value of the 'delocalisation parameter' β (–192 kcal mol^{-1} e^{-1}) reflects the decrease in the intrinsic barrier due to delocalisation. Inclusion of the 2–N_{occ} parameter into the Marcus equation leads to near-identical results (§S1).

$$\Delta H^{\ddagger} = \Delta H^{\ddagger}_{int} + \alpha \Delta H_r + \beta(2 - N_{occ}) \quad (3)$$

To directly compare the impact of this delocalisation effect on activation barriers, we examined changes in barrier ($\Delta\Delta H^{\ddagger}$) for the test set relative to bicyclo[2.2.0]hexane (**G**, Fig. 3d), which exhibits a moderate strain release value but a has small value of 2–N_{occ}. In 7 of the 11 substrates, denoted by asterisks, *the primary cause of reactivity differences is delocalisation, not strain release*. In four of these cases, delocalisation even compensates for an increase in activation barrier due to a *decrease* in strain release. Notably, for the classic 'strain release' reagents bicyclo[1.1.0]butane (**D**) and [1.1.1]propellane (**H**), ring strain changes increase the reaction barriers by 3.4 and 7.6 kcal mol^{-1} respectively; the barrier-lowering delocalisation effects of –15.4 and –23.5 kcal mol^{-1} are therefore not only essential, but are the fundamental basis of their spring-loaded behaviour.

The nature of the delocalisation 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 (Fig. 3e). For the reaction of the localised C–C bond in 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 lobes). Cyclobutane is similar, 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 from the breaking C–C bond indicates continued delocalisation which stabilises the system. [1.1.1]Propellane shows an equivalent effect, where delocalisation occurs between the three bridging methylene groups and the bridgehead carbon atoms.[18]

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

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

Using this parameter in place of ($2 - N_{occ}$) leads to a remarkably accurate predictor of reactivity (Fig. 4a): for each three-membered ring fused to the breaking C–C bond, the intrinsic activation energy is lowered by ~10 kcal mol^{-1}, corresponding to a ~10^7-fold increase in the rate constant at 298 K. This simple model not only captures the greater reactivity of cyclopropane over cyclobutane, but also the contrasting reactivities of [1.1.1]propellane and cyclopropane, where the greatly enhanced reactivity of the former can be attributed entirely to the higher number of three-membered rings fused to the breaking bond (n_3 = 3). Variation of the number of three-membered rings fused to a breaking bond is therefore a simple and predictable way to modulate the reactivity of the system, for example switching the behaviour of a molecule from a highly-reactive bioconjugation warhead (*e.g.*, bicyclo[1.1.0]butanes derived from **D**)[7,28] to an inert lipid tail group (e.g. bicyclo[2.2.0]hexane 'ladderanes' based on **G**).[29]

The delocalisation model in Eq. 4 is also applicable to anionic processes, such as the addition reactions of amide anions to **D**, **E** and **H**.[28,30] Using NH_2^- as a model nucleophile, an excellent correlation (R^2 = 0.98) was observed between predicted and calculated activation enthalpies (Fig. 4b). Notably, the β coefficient of ~–10 kcal mol^{-1} suggests that, if delocalisation effects were removed from [1.1.1]propellane, the barrier to this reaction would increase by ~30 kcal mol^{-1}, rendering it inert under the reaction conditions. In other words, the release of strain energy alone cannot enable the observed reaction: delocalisation once again causes its 'spring-loaded' behaviour. The same is true of bicyclo[1.1.0]butanes (**D**) and bicyclo[2.1.0]pentanes (**E**), where activation barriers would increase by ~20 and ~10 kcal mol^{-1} respectively, in the absence of delocalisation. This effect is corroborated by experimental results on the addition of dibenzylamine to bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane sulfones (Fig. 4c), where the former affords the cyclobutylamine product at ambient temperature, whereas the latter requires heating to 80 °C to form the equivalent cyclopentane.[30] This reactivity difference directly opposes the expected behaviour from SREs alone (–40.2 and –48.1 kcal mol^{-1} for bicyclo[1.1.0]butane and bicyclo[2.1.0]pentane, respectively).

Delocalisation also explains the reactivity difference between three- and four-membered heterocycles. Three-membered rings are always more reactive than their four-membered homologues (Figs. 4d and §S2),[31,32] exemplified by the calculated ~10^5 increase in anionic ring-

opening rate for ethylene oxide over oxetane despite similar SREs (Fig. 4d) – a result that enables the employment of epoxides in biosynthetic cascades,[9] polyether synthesis,[4] and conversely explains the success of oxetanes as biostable motifs in drug discovery.[19] Similarly, aziridine undergoes nucleophilic ring opening ~10^6 times faster than azetidine due to delocalisation effects in the breaking of its three-membered ring. Remarkably, despite azabicyclo[2.1.0]pentane releasing almost 14 kcal mol^{-1} more strain energy than azabicyclo[1.1.0]butane upon nucleophilic ring opening, the latter molecule is ~10 times more reactive – again underlining the effect of an additional three-membered ring on the intrinsic activation barrier.

The delocalisation effects that explain the enhanced reactivity of three-membered rings can be simplified to a 'rule of thumb' that enables rapid estimation of relative reactivity. This model employs the modified BEP approach (Eq. 5) and tabulated SREs that are available for most common substrates (§S3); α is taken as 0.5 and β as –10 kcal mol^{-1} based on the results obtained above. Differences in activation barriers between two substrates ($\Delta\Delta H^{\ddagger}$) can be estimated as follows:

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

This model can be readily applied to rationalise the 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 (Fig. 4d), where **H** and **D** readily undergo addition of the trichloromethyl radical, but **E** does not.[33] Additional competition reactions showed that **H** undergoes significantly more rapid reaction than **D**. SREs are unable to explain this reactivity pattern (Fig. 4e), but the 'rule-of-thumb' correctly predicts the observed trend (Eq. 5); the estimated activation enthalpies are 4.0 and 10.1 kcal mol^{-1} higher for **D** and **E** respectively than **H**, compared to calculated values of 3.5 and 10.2 kcal mol^{-1} (Fig. 4e and §S4). These barriers imply relative addition rates (k_{rel}) that are ~10^2 and ~10^7 times slower for **D** and **E** than **H** at 298 K – enough to shut down reactivity entirely in the latter case.

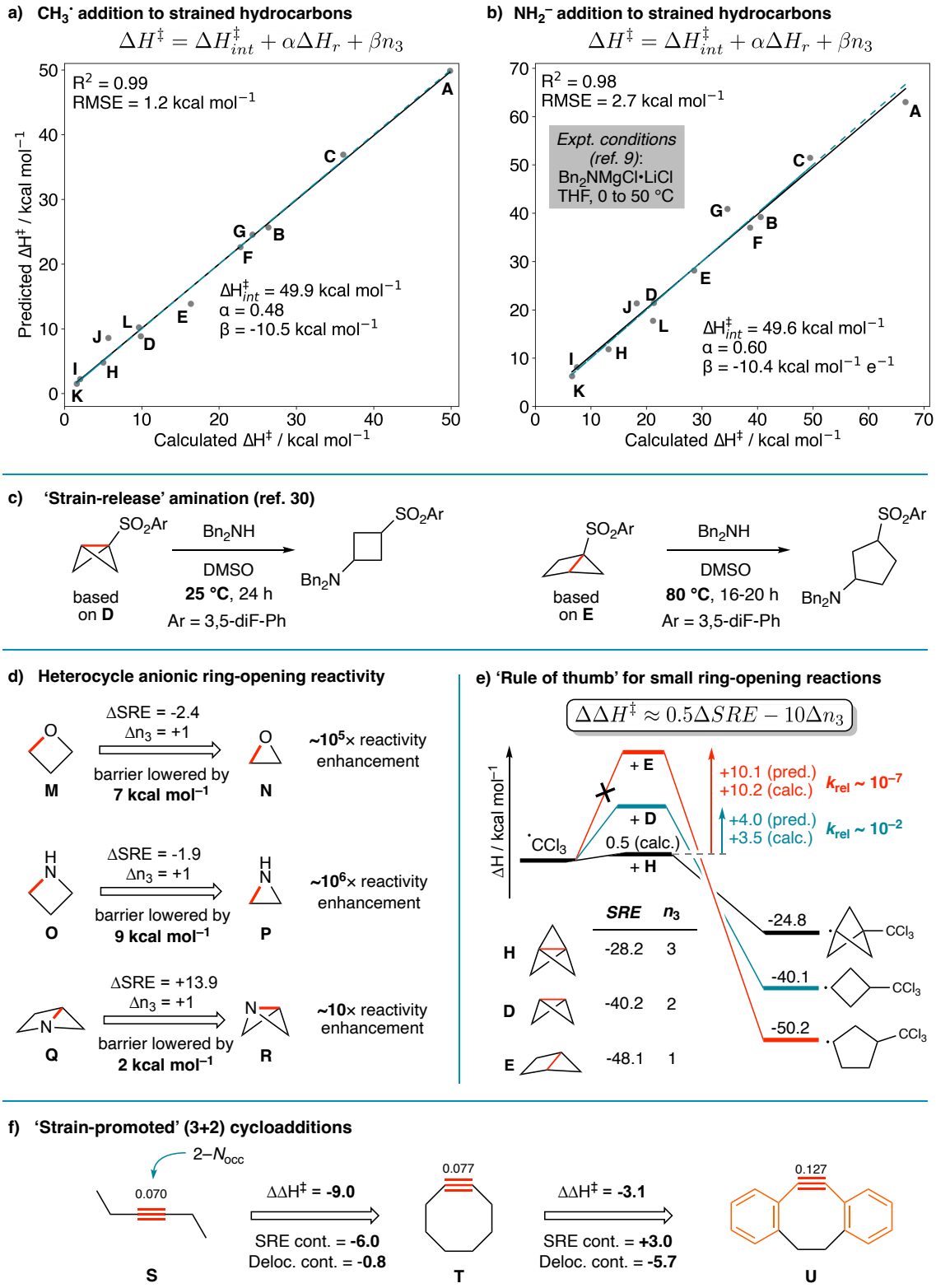

Fig. 4: Implications of strain and delocalisation on general reactivity. Multiple linear regression plots for the prediction of $\Delta H^{\ddagger}$ from ΔH_r and n_3 for the hydrocarbon test set with $CH_3^{\bullet}$ (**a**) and NH_2^- (**b**) using Eq. 5. The blue dashed lines denote perfect correlation. **c** Increased delocalisation lowers the required reaction temperature for the amination of a bicyclo[1.1.0]butane sulfone compared with housane. **d** Delocalisation in three-membered heterocycles leads to increased reactivity over their four-membered homologues. **e** Predicted relative activation enthalpies ($\Delta\Delta H^{\ddagger}_{pred}$, kcal mol^{-1}) based on SRE and n_3 using Eq. 5. **f** Delocalisation, not strain release, explains the enhanced reactivity of dibenzocyclooctyne over cyclooctyne in (3+2) cycloadditions. All *k* values estimated at 298 K.

Importantly, the principle that more delocalised bonds are more reactive can be extended to other reactions purported to be driven by strain release, for example 'click' (3+2) azide-alkyne cycloadditions.[34] To demonstrate this, we constructed a set of SREs and $2–N_{occ}$ values for each bond in a range of commonly-employed strain release molecules including carbocycles, heterocycles, cycloalkynes and cycloalkenes, summarised in §S2. Strategies to enhance the 'click' reactivity of alkynes (**S**, Fig. 4f) have generally focused on increasing the strain of the alkyne, *e.g.*, by incorporating the alkyne in an eight-membered ring (**T**).[35] Further reactivity enhancement can be achieved through dibenzo annulation (**U**), which has been proposed to increase the strain release driving force by increasing the number of sp^2 centres in the cyclooctyne ring. Our model suggests that this enhanced reactivity is explained by alkyne delocalisation rather than strain release (Figs. 4f and §S1): while the activation enthalpy for **U** is 3 kcal mol^{-1} lower than **T**, the reaction enthalpy is 6 kcal mol^{-1} *smaller* for the former, which should *increase* its activation barrier by 3 kcal mol^{-1}. However, alkyne delocalisation is 0.05 *e* greater in **U** than **T** due to π-conjugation, leading to a 6 kcal mol^{-1} barrier-lowering effect. The net result is an overall 3 kcal mol^{-1} lowering of the activation barrier – delocalisation therefore compensates for the reactivity-suppressing strain contribution.

In conclusion, strain energy is often invoked to rationalise trends in reactivity, but is insufficient to explain trends in reaction kinetics. Bond delocalisation is an equally important factor necessary to understand the 'spring-loaded' reactivity often associated with strain release in small carbo- and heterocyclic rings, and cycloalkynes. Evaluation of small-ring radical and anionic additions, and azide / cycloalkyne click reactions, reveals that delocalisation effects are critical for the success of these reactions. We anticipate that this new understanding of the reactivity of strained molecules will lead to new directions in ‘strain release’ tactics for application for organic synthesis, medicinal chemistry, polymer science and chemical biology.

Methods

QM calculations were run using ORCA (v 4.2.1)[36] 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).[37–41] 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).[42] All data processing was carried out using the *Scikit-learn* package with Python 3.7.[43] 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. Values of $2–N_{occ}$ were found to be in good agreement with an alternative density-based delocalisation parameter, 1–ELF, where ELF is the electron

localisation function at the bond critical point (§S1).[44] For further details, see the Supplementary Methods.

Data Availability

A script to generate all linear regression data and plots discussed in this paper, and cartesian coordinates and energies of all stationary points, are available at https://github.com/duartegroup/strain-delocalisation.

Acknowledgements

We thank Dr T. Harris, S. Zavitsanou, N. Frank and M. de la Puente for suggestions and discussions. A. J. S. thanks the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine for a studentship (EP/L015838/1), generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. A. J. S. also thanks the Oxford-Radcliffe Scholarship for a studentship, and the EPSRC Doctoral Prize (EP/T517811/1) for support. E. A. A. thanks the EPSRC for support (EP/S013172/1). This work used the Cirrus UK National Tier-2 HPC Service at EPCC (http://www.cirrus.ac.uk) funded by the University of Edinburgh and EPSRC (EP/P020267/1), and we thank the EPSRC Centre for Doctoral Training for Theory and Modelling in Chemical Sciences (EP/L015722/1) for providing access to the Dirac cluster at Oxford.

Author contributions

A.J.S., E.A.A. and F.D. conceptualised the study, analysed the data and wrote the manuscript. A.J.S. implemented the models and carried out the calculations. F.D., E.A.A. and R.C.S. supervised the study.

Competing interests

The authors declare no competing interests.

References

1. Clayden, J., Greeves, N. & Warren, S. Organic chemistry. (Oxford University Press, 2012).
2. Wiberg, K. B. The concept of strain in organic chemistry. *Angew. Chem. Int.* **25**, 312–322 (1986).
3. Stirling, C. J. M. Some quantitative effects of strain on reactivity. *Pure Appl. Chem.* **56**, 1781–1796 (1984).
4. Ebner, C. & Carreira, E. M. Cyclopropanation strategies in recent total syntheses. *Chem. Rev.* **117**, 11651–11679 (2017).
5. Herzberger, J., Niederer, K., Pohlit, H., Seiwert, J., Worm, M., Wurm, F. R. & Frey, H. Polymerization of ethylene oxide, propylene oxide, and other alkylene oxides: synthesis, novel polymer architectures, and bioconjugation. *Chem. Rev.* **116**, 2170–2243 (2016).
6. Sathe, D., Zhou, J., Chen, H., Su, H.-W., Xie, W., Hsu, T.-G., Schrage, B. R., Smith, T., Ziegler, C. J. & Wang, J. Olefin metathesis-based chemically recyclable polymers enabled by fused-ring monomers. *Nat. Chem.* **13**, 743–750 (2021).
7. Agard, N. J., Prescher, J. A. & Bertozzi, C. R. A strain-promoted [3 + 2] azide-alkyne cycloaddition for covalent modification of biomolecules in living systems. *J. Am. Chem. Soc.* **126**, 15046–15047 (2004).
8. Tokunaga, K., Sato, M., Kuwata, K., Miura, C., Fuchida, H., Matsunaga, N., Koyanagi, S., Ohdo, S., Shindo, N. & Ojida, A. Bicyclobutane carboxylic amide as a cysteine-directed strained electrophile for selective targeting of proteins. *J. Am. Chem. Soc.* **142**, 18522–18531 (2020).
9. Turkowska, J., Durka, J. & Gryko, D. Strain release - an old tool for new transformations. *Chem. Commun.* **56**, 5718–5734 (2020).

10. Gianatassio, R., Lopchuk, J. M., Wang, J., Pan, C.-M., Malins, L. R., Prieto, L., Brandt, T. A., Collins, M. R., Gallego, G. M., Sach, N. W., Spangler, J. E., Zhu, H., Zhu, J. & Baran, P. S. Strain-release amination. *Science* **351**, 241–246 (2016).
11. Morten, C. J., Byers, J. A., Dyke, A. R. V., Vilotijevic, I. & Jamison, T. F. The development of endo-selective epoxide-opening cascades in water. *Chem. Soc. Rev.* **38**, 3175–3192 (2009).
12. Earl, H. A., Marshall, D. R. & Stirling, C. J. M. Eliminative ring fission of cyclobutanes: evaluation of acceleration by strain and the comparison with cyclopropanes. *J. Chem. Soc., Chem. Commun.* 779 (1983).
13. Sella, A., Basch, H. & Hoz, S. Reactivity of strained compounds: is ground state destabilization the major cause for rate enhancement? *J. Am. Chem. Soc.* **118**, 416–420 (1996).
14. Sawicka, D., Wilsey, S. & Houk, K. N. The 16 kcal/mol anomaly: alteration of [2 + 2 + 2] cycloaddition rates by through-bond interactions. *J. Am. Chem. Soc.* **121**, 864–865 (1999).
15. Verhoeven, J. W. Sigma-assistance; the modulation of intramolecular reactivity by through-bond interaction. *Recl. Trav. Chim. Pays-Bas* **99**, 369–379 (1980).
16. Coulson, C. A. & Moffitt, W. E. I. The properties of certain strained hydrocarbons. *Lond. Edinb. Dubl. Phil. Mag.* **40**, 1–35 (1949).
17. Dewar, M. J. S. & McKee, M. L. Aspects of cyclic conjugation. *Pure Appl. Chem.* **52**, 1431–1441 (1980).
18. Weinhold, F. & Landis, C. R. Valency and bonding: a natural bond orbital donor-acceptor perspective. (Cambridge University Press, 2005).
19. Sterling, A. J., Dürr, A., Smith, R., Anderson, E. A. & Duarte, F. Rationalizing the diverse reactivity of [1.1.1]propellane through σ-π-delocalization. *Chem. Sci.* **11**, 4895–4903 (2020).
20. Bull, J. A., Croft, R. A., Davis, O. A., Doran, R. & Morgan, K. F. Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. *Chem. Rev.* **116**, 12150–12233 (2016).
21. Newcomb, E. T., Knutson, P. C., Pedersen, B. A. & Ferreira, E. M. Total synthesis of gelsenicine via a catalyzed cycloisomerization Strategy. *J. Am. Chem. Soc.* **138**, 108–111 (2016).
22. Limanto, J. & Snapper, M. L. Sequential intramolecular cyclobutadiene cycloaddition, ring-opening metathesis, and Cope rearrangement: total syntheses of (+)- and (−)-asteriscanolide. *J. Am. Chem. Soc.* **122**, 8071–8072 (2000).
23. Bielawski, C. W. & Grubbs, R. H. Living ring-opening metathesis polymerization. *Prog. Polym, Sci.* **32**, 1–29 (2007).
24. Stepan, A. F., Subramanyam, C., Efremov, I. V., Dutra, J. K., O'Sullivan, T. J., DiRico, K. J., McDonald, W. S., Won, A., Dorff, P. H., Nolan, C. E., Becker, S. L., Pustilnik, L. R., Riddell, D. R., Kauffman, G. W., Kormos, B. L., Zhang, L., Lu, Y., Capetta, S. H., Green, M. E., Karki, K., Sibley, E., Atchison, K. P., Hallgren, A. J., Oborski, C. E., Robshaw, A. E., Sneed, B. & O'Donnell, C. J. Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **55**, 3414–3424 (2012).
25. Bell, R. P. The theory of reactions involving proton transfers. *Proc. R. Soc. Lond.* **154**, 414–429 (1936).
26. Evans, M. G. & Polanyi, M. Inertia and driving force of chemical reactions. *J. Chem. Soc. Faraday Trans.* **34**, 11–24 (1938).
27. Marcus, R. A. On the theory of oxidation-reduction reactions involving electron transfer. I. *J. Chem. Phys.* **24**, 966–978 (1956).
28. Marcus, R. A. Theoretical relations among rate constants, barriers, and Broensted slopes of chemical reactions. *J. Phys. Chem.* **72**, 891–899 (1968).
29. Sinninghe Damsté, J. S., Strous, M., Rijpstra, W. I. C., Hopmans, E. C., Geenevasen, J. A. J., van Duin, A. C. T., van Niftrik, L. A. & Jetten, M. S. M. Linearly concatenated cyclobutane lipids form a dense bacterial membrane. *Nature* **419**, 708–712 (2002).

30. Lopchuk, J. M., Fjelbye, K., Kawamata, Y., Malins, L. R., Pan, C.-M., Gianatassio, R., Wang, J., Prieot, L., Bradow, J., Brandt, T. A., Collins, M. R., Elleraas, J., Ewanicki, J., Farrell, W., Fadeyi, O. O., Gallego, G. M., Mousseau, J. J., Oliver, R., Sach, N. W., Smith, J. K., Spangler, J. E., Zhu, H., Zhu, J. & Baran, P. S. Strain-release heteroatom functionalization: development, scope, and stereospecificity. *J. Am. Chem. Soc.***139**, 3209–3226 (2017).
31. Wolk, J. L., Hoz, T., Basch, H. & Hoz, S. Quantification of the various contributors to rate enhancement in nucleophilic strain releasing reactions. *J. Org. Chem.* **66**, 915–918 (2001).
32. Wolk, J. L., Sprecher, M., Basch, H. & Hoz, S. Relative reactivity of three and four membered rings - the absence of charge effect. *Org. Biomol. Chem.* **2**, 1065–1069 (2004).
33. Wiberg, K. B., Waddell, S. T. & Laidig, K. [1.1.1]Propellane: reaction with free radicals. *Tetrahedron Lett.* **27**, 1553–1556 (1986).
34. Li, K., Fong, D., Meichsner, E. & Adronov, A. A survey of strain-promoted azide–alkyne cycloaddition in polymer chemistry. *Chem. Eur. J.* **27**, 5057–5073 (2021).
35. Harris, T. & Alabugin, I. V. Strain and stereoelectronics in cycloalkyne click chemistry. *Mendeleev Commun.* **29**, 237–248 (2019).
36. Neese, F. Software update: the ORCA program system, version 4.0. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **8**, 4–9 (2018).
37. Weigend, F. & Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297–3305 (2005).
38. Grimme, S., Antony, J., Ehrlich, S. & Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **132**, 154104 (2010).
39. Marenich, A. v., Cramer, C. J. & Truhlar, D. G. Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B.* **113**, 6378–6396 (2009).
40. Riplinger, C., Sandhoefer, B., Hansen, A. & Neese, F. Natural triple excitations in local coupled cluster calculations with pair natural orbitals. *J. Chem. Phys.* **139**, 134101 (2013).
41. Grimme, S. Semiempirical hybrid density functional with perturbative second-order correlation. *J. Chem. Phys.* **124**, 034108 (2006).
42. Lu, T. & Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* **33**, 580–592 (2012).
43. Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., Blondel, M., Prettenhofer, P., Weiss, R., Dubourg, V., Vanderplas, J., Passos, A., Cournapeau, D., Brucher, M., Perrot, M. & Duchesnay, É. Scikit-learn: machine learning in Python. *J. Mach. Learn Res.* **12**, 2825–2830 (2011).
44. Becke, A. D. & Edgecombe, K. E. A simple measure of electron localization in atomic and molecular systems. *J. Chem. Phys.* **92**, 5397–5403 (1990).