CO_2 or SO_2: Should it stay, or should it go?

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Abstract

A broad computational analysis of carbon-centered radical formation via the loss of either CO_2 or SO_2 from the respective RXO_2 radical precursors (X = C or S) reveals dramatic differences between these two types of dissociative processes. Whereas the C-C scission with the loss of CO_2 is usually exothermic, the C-S scission with the loss of SO_2 is generally endothermic. However, two factors can make the C-S scissions thermodynamically favorable: increased entropy, characteristic for the dissociative processes, and stereoelectronic influences of substituents. The threshold between endergonic and exergonic C-S fragmentations depends on subtle structural effects. In particular, the degree of fluorination in a radical precursor has a notable impact on the reaction outcome. This study aims to demystify the intricacies in reactivity regarding the generation of radicals from sulfinates and carboxylates, as related to their role in radical cross-coupling.

Introduction

In chemical synthesis, the ability to harness various functional handles for controlled and chemoselective transformations is of paramount importance. [1] In turn, making use of functional groups that are endogenous to cheap carbon feedstocks gives leverage to synthetic chemists for exploiting the most efficacious retrosynthetic disconnections.[2] This certainty allows practitioners to avoid functional group interconversion, protecting groups, and lengthy, circuitous assembly of carbogenic skeletons. To this end, the radical cross-coupling of both carboxylic acids and sulfinate[3] salts has emerged as a powerful tool for the concise synthesis of complex molecules both of historical and translational importance.[2c]

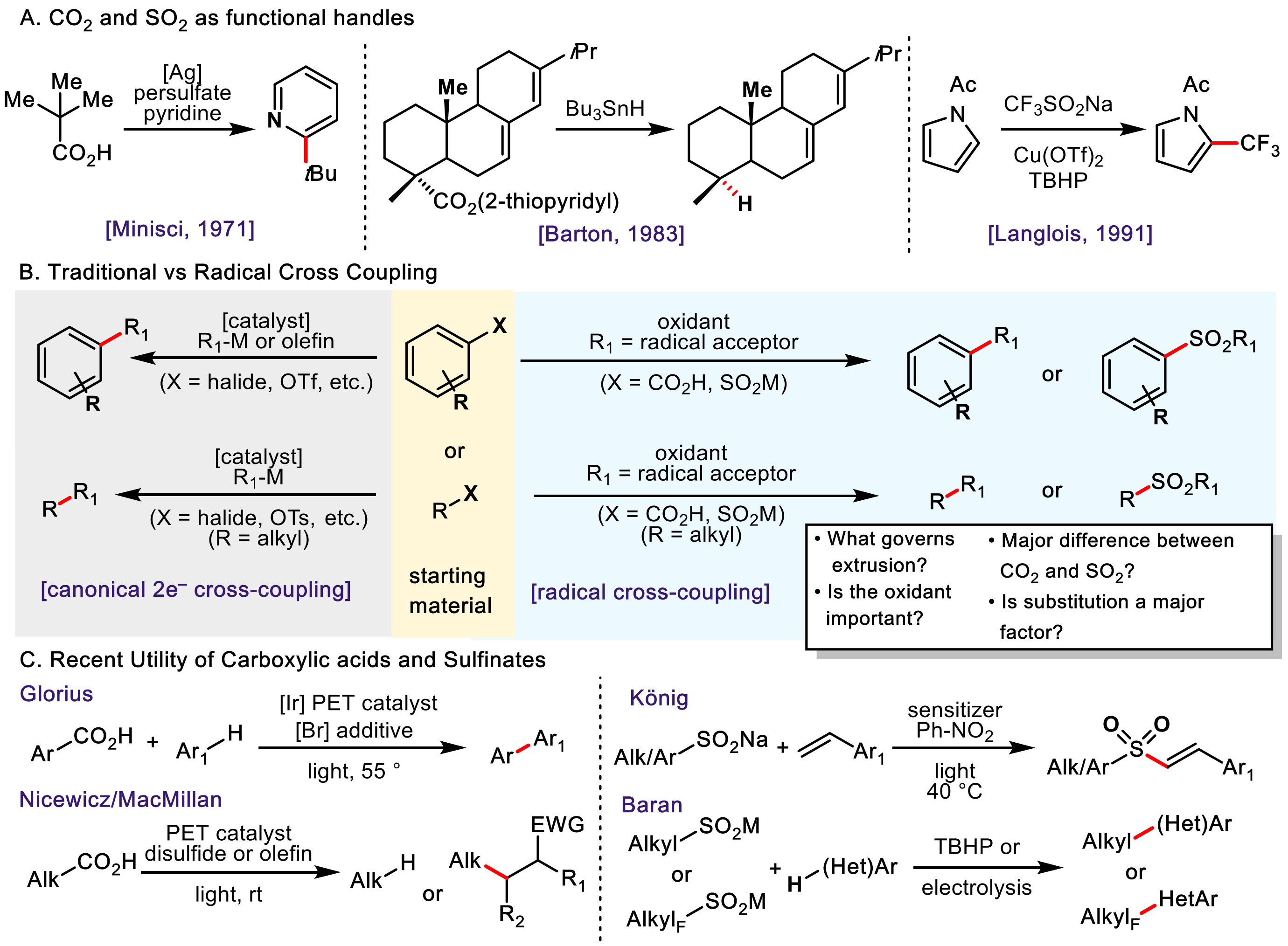


Figure 1: (A) Historic examples of utilizing carboxylic acids and sulfinates as synthetic handles. (B) Traditional cross-coupling compared to decarboxylative and desulfonylative radical cross-coupling. (C) Selected literature reports of (photo)oxidative coupling reactions with aryl and alkyl carboxylates and sulfinate salts. Abbreviations: B = base; Ar = Aryl; AlkylF = fluorinated alkyls; (Het)Ar = heteroarenes.

Since the mid-19th century, carboxylic acids have had a special role as abundant and ubiquitous starting materials for effective tactical and strategic synthesis.[4] With regard to carboxylic acids serving as progenitors for carbon-centered radicals, work of Minisci pioneered their utilization in the functionalization of electron-poor arenes (Figure 1A).[5] As this reaction was revolutionary for its day, radical decarboxylation has seen a resurgence in recent years, both from the direct oxidative decarboxylation of acids,[6] and the reductive manipulation of redox-active esters akin to the pioneering Sn-mediated work of Barton in 1983.[7] As a parallel, a synthetic relative to the carboxylate is the sulfinate, which Langlois exploited in the early 1990s for the C–H trifluoromethylation of arenes. [8] This technology was later popularized and made broadly useful by Baran in recent years.[9] Principally, the utilization of both sulfinates and carboxylic acids in radical cross coupling has shown important advantages over canonical cross-coupling tactics.

As traditional cross-coupling typically utilizes a starting halide or pseudohalide combined with an organometallic coupling partner, the radical cross coupling of sulfinates and carboxylic acids most often employs a radical acceptor as the reactive partner (Figure 1B).[7–10] Intriguingly, the nature of the arene or alkyl unit bearing the acid or sulfinate can have a drastic effect on the radical formation and downstream coupling event. This is most reflected in whether the CO_2 or SO_2 unit is retained in the coupled product, or lost as a gaseous byproduct. For example, the work of Glorius and coworkers showed that radical coupling of carboxylic acids proceeded through photoinduced electron transfer, but decarboxylation only occurred in the presence of a mild brominating agent such as NBS (Figure 1C).[11] Typically, decarboxylation (either two-electron or radical) of benzoic acids requires higher temperatures and/or stronger oxidants.[12,6a] Similarly, photoinduced electron transfer (PET) has promoted the decarboxylation of alkyl carboxylic acids in the work of Nicewicz and MacMillan. The resulting radical can either be trapped, for example, with a hydrogen atom[13] or an electron-deficient alkene.[14] With the case of sulfinates, König showed that the use of PET with alkyl and aryl sulfinates resulted in cross coupling with styrenes, however with retention of the SO_2 group in both cases.[15] Baran's sulfinate chemistry, which mostly employs TBHP as a simple oxidant, generates (fluoro)alkyl radicals that are subsequently trapped by heteroaryl radical acceptors.[3,9]

Given this mixture of outcomes, a deeper understanding of these phenomena would be ultimately beneficial towards the future utilization of these functionalities. Computational methods will probe the sensitivity of these homolytic C-C and C-S scissions to the nature of the departing carbon-centered radicals. By comparing and contrasting the two dissociative approaches to radical formation, we will establish general guidelines for the use of sulfinates as radical precursors. The dramatic electronic differences in the two types of fragmentations will be shown to be particularly important for the design of radical reactions mediated by the loss of SO_2. It is anticipated that the results should allow practitioners to predictably design desired radical cross-coupling events enabling exploration of desired chemical space.

Computational methods:

DFT calculations were carried with the *Gaussian 09* software package,[16] using the (U)M06-2X DFT functional[17] (with an ultrafine integration grid of 99,590 points) with the 6-311++G(d,p) basis set for all atoms. Grimme's D3 version (zero damping) for empirical dispersion[18] was also included. Frequency calculations were conducted for all structures to confirm them as either a minimum or a Transition State (TS). Intrinsic Reaction Coordinates (IRC)[19] were determined for the TSs of interest. Full (U)MP2[20] with cc-pVTZ basis set for all atoms was also employed in selected cases. Natural Bond Orbital[21] (NBO) analysis was performed on key intermediates and transition states. Spin density was evaluated from the NBO analysis data. The Gibbs Free energy values are reported at 298 K, unless noted otherwise. For selected systems, DLPNO-CCSD(T)[22] calculations were performed with *ORCA 4.0*[23] (see SI for details). Three-dimensional structures were produced with CYLView 1.0.1.[24]

Results:

First, let us compare the trends for the C-C and C-S BDEs over the broad range of neutral carboxylic and sulfinic acids. As one would expect, the homolytic scission is much more energetically costly for the C-C bonds than for the C-S bonds. The differences are very large - the fragmentations of the C-C bond are 30-50 kcal/mol more endothermic at the M06-2X level.

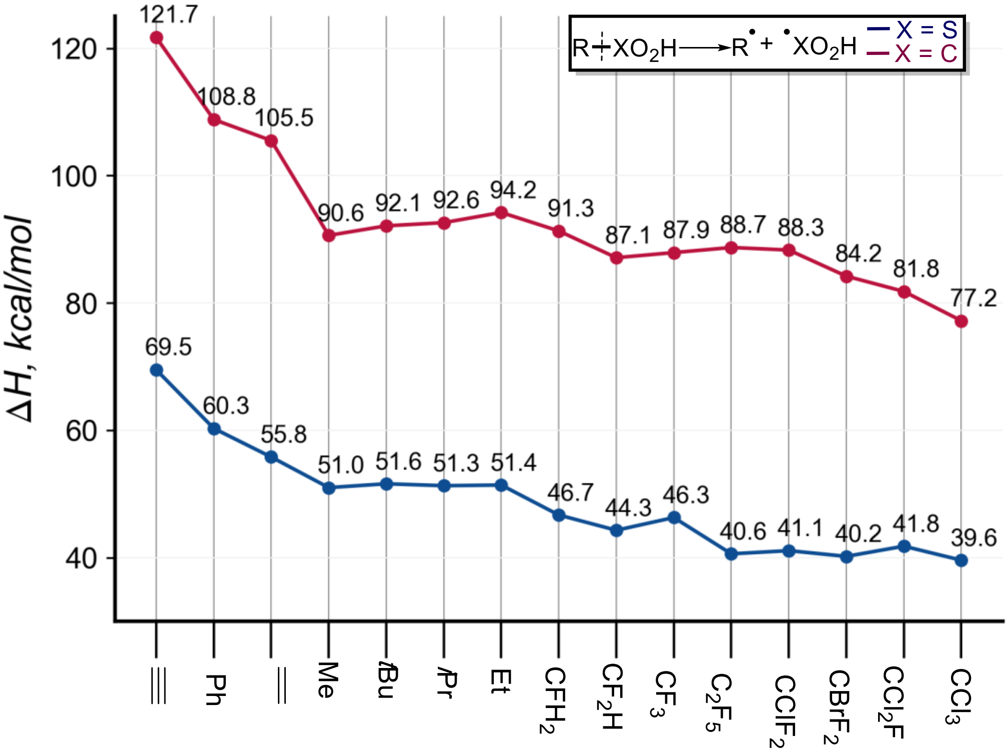


Figure 2: Bond Dissociation Energies (BDEs, as ΔH energies) for C-X (X = C or S) scission in neutral carboxylic and sulfinic acids.

In this context, it is especially remarkable how dramatically does the situation change for the fragmentation of the RXO_2 radicals produced by oxidation of the carboxylate and sulfinate anions. Counterintuitively at first, it is the C-S bond scission that now comes with a *greater* thermodynamic penalty. Furthermore, the difference in the BDEs for the C-C and C-S scissions remains dramatic, even though the trend is inverted! Whereas most of the C-C scissions with the loss of CO_2 are exothermic, the C-S scissions with the loss of SO_2 are generally endothermic.

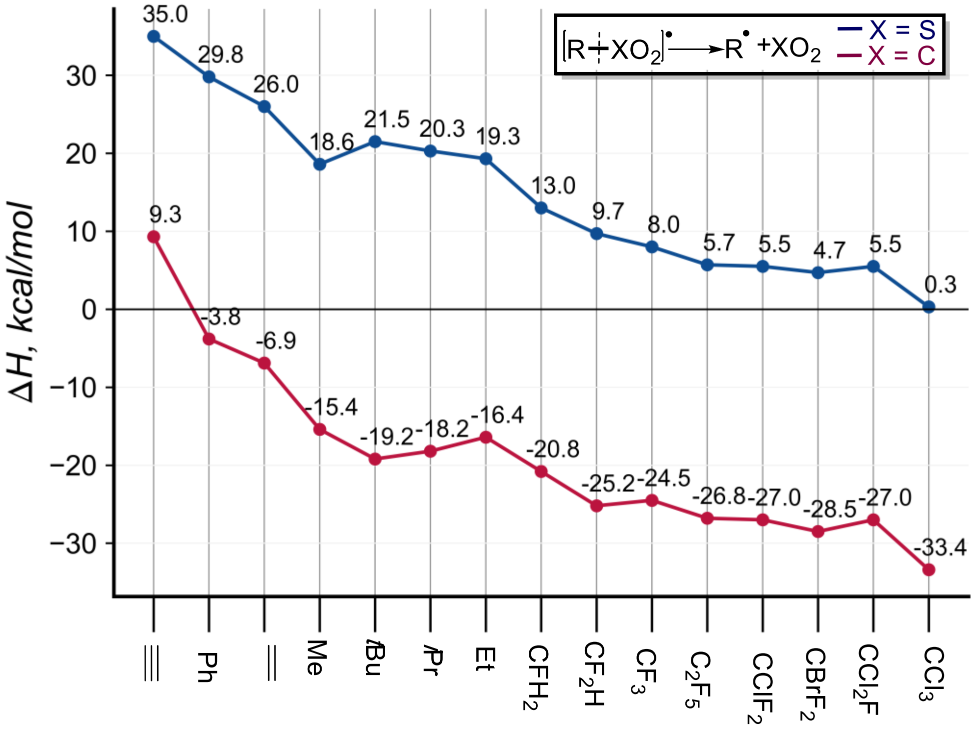


Figure 3: Comparison of the enthalpies for the C-S and C-C bond scissions in the radicals formed from carboxylic and sulfinic acids. The data are organized by decreasing ΔH for the C-S scission.

The thermodynamics of the two types of bond scission depends strongly on the nature of the forming radical. In particular, Figure 3 illustrates that the C-S scission is made much more favorable by acceptor substitution at the carbon atoms of the C-S bond. Furthermore, it is also greatly assisted by entropic factors. As is typical for dissociative processes, the entropic contribution is large, and can render the overall process an exothermic at the right temperature.[25] However, even with the help of entropy, free energy for the C–S bond dissociation remains positive for many important systems, e.g. aryl and alkyl radicals.

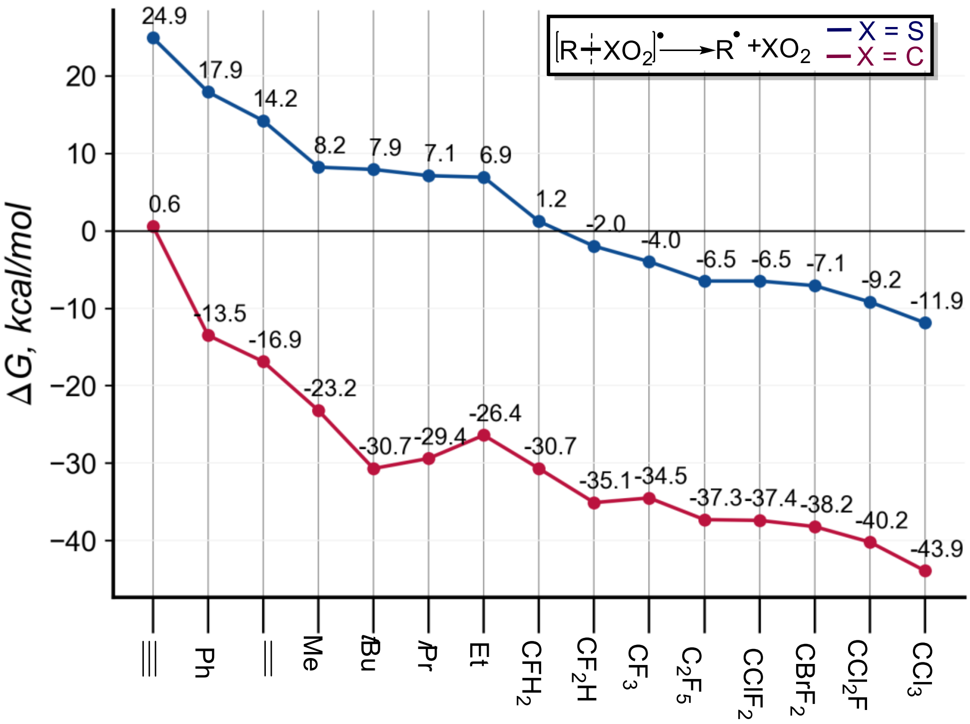


Figure 4. Comparison of the Gibbs energies for the C-S and C-C bond scissions in the radicals formed from carboxylic and sulfinic acids. The data are organized by decreasing $\Delta\boldsymbol{G}$ for the C-S scission.

These results provide a rationale for the diverging reactivity of non-aromatic sufinates upon their oxidation into RSO_2 radicals. The fluorinated $AlkF_nSO_2$ systems reported by Baran underwent clean C-S scission with the formation of CF_3 and CF_2H radicals,[3,9] but the $AlkSO_2$ radicals by Konig reacted further without SO_2 loss.[15] Whereas the loss of SO_2 is exergonic for CF_3 and CF_2H formation, the same process is uphill for each of the four alkyl radicals included in Figure 4. The monofluorinated FCH_2 radical formation is a borderline case in terms of fragmentation thermodynamics. However, experimental data from Baran suggests that radical generation is facile under oxidation with TBHP.[3]

It also must be noted that the uphill fragmentations are not impossible. However, the endergonicity of such processes imposes an additional thermodynamic penalty on reaction efficiency. At equilibrium, if the SO_2 by-product does not escape, the equilibrium constant is small, and the concentration of reactive intermediates (alkyl radicals) is low. For example, the 7 kcal/mol penalty for the formation of *i*-Pr radical from the *i*-$PrSO_2$ radical would make the equilibrium constant lower than 10^{-5} M (less than 0.001% of the *i*-$PrSO_2$ radical will be dissociated). Of course, the equilibrium can be shifted by using Le Chatelier's principle, i.e., by removal of SO_2 from the reaction sphere (either physically or chemically).

Discussion:

So, what controls the observed BDE trends? There are two main questions that will be addressed. First, we will address the difference in BDE magnitudes in the RXO_2 radical systems relative to those in the parent acids. Second, we will discuss why fluorination decreases both the C-C and the C-S BDEs to the extent where even the C-S scissions become thermodynamically favorable.

By definition, BDEs come from two sources: energy of the reactant and energy of the two bond-dissociation products. In this regard, considering only the product stability (i.e., stability of alkyl radical as a predictor of the C-H BDEs) can only predict the BDE trends when delocalization effects of substituents in the starting material are relatively small. Such approximation is often reasonable because delocalization effects are more important for species that lack a stable octet than they are for stable molecules.[26] This is why undergraduate students are taught that the C-H bonds at tertiary carbons are weaker "because the tertiary radical are more stable". However, predictions based on the product stability can fail for those cases where the starting materials are stabilized by delocalization more than the products, i.e., the case of the C-F BDEs in alkyl fluorides (BDE (C-F): Me-F < t-Bu-F, Figure 5).[27,28]

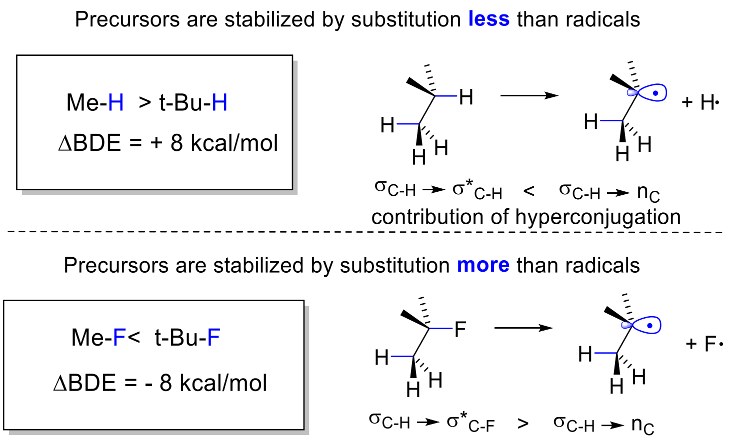


Figure 5: Contrasting effects of alkyl substitution on BDEs for C-H, and C-F bonds. The BDEs increase for the more substituted alkyl fluorides but decrease in respective alkanes

When both reactants and products are radicals, the balance of electronic effects can be quite delicate. For the systems studied herein, both reactants and products are odd-electron species. Neither can satisfy the octet rule, and both have to rely strongly on delocalizing interactions as a supplement source of stability. If delocalizing effects between the radical center and the substituents in the reactant are stronger than they are in the product, the counterintuitive trends in the C-S BDEs that go against the C-centered product radical stability are possible.

As one can see, the trends in the BDEs can originate from a complicated combination of factors. Let's start our analysis with reactants. There are two types of delocalizing interactions that will be considered: 1) radical delocalization, and 2) interaction of the π-system of XO_2 groups with the substituents R.

Radical stabilization in the R-XO_2 reactants:

The carboxyl free radicals have been a topic of many investigations.[29] These species are quite complex from the electronic point of view due to the presence of several low-lying electronic states. Furthermore, the lowest energy $^2B_2$ state was suggested to distort from C_{2v} to a C_s symmetry due to a Jahn-Teller instability that localizes spin substantially at one of the oxygen atoms.[30] However, the analysis of McBride and Merrill demonstrated that the benzoyloxyl radical has a $^2B_2$ ground state with the symmetrical spin distribution.[31]

The in-depth discussion of the electronic structure of the RSO_2 radicals will be left for a future theoretical study and will limit our current work to the comparison of spin-density delocalization in two radicals, namely, $MeCO_2$ and $MeSO_2$. In the carboxy-radical, the unpaired electron is delocalized between the *in-plane* lone pairs of the two oxygen atoms. In this σ-radical, the radical center is aligned perfectly the C-C bond that needs to be broken in the decarboxylation process. Such kinetic stereoelectronic assistance is typical for radical beta-scission reactions.[32] However, communication of the radical center with substituent R in the RCO_2 species is inefficient due to the lack of spin density at the central carbon.[33]

In contrast, the $MeSO_2$ radical is of a p-type where the radical density is delocalized between a non-bonding orbital at sulfur and the two *out-of-plane* p-orbitals of the two oxygen atoms. In this case, the S-radical can communicate with the vicinal substituent orbitals via either conjugation or hyperconjugation (Figure 6).[26]

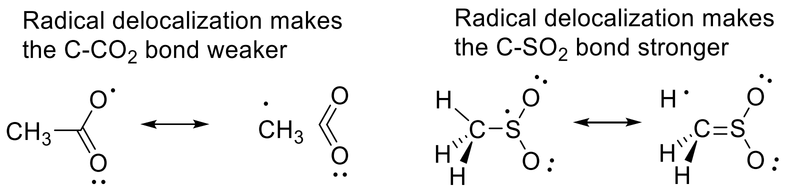


Figure 6: The distribution of spin density in RCO_2 and RSO_2 radicals and resonance structures explaining the contrasting substituent effects at the R-CO_2 and R-SO_2 BDEs (only electrons directly participating in radical delocalization are shown in the resonance structures).

Furthermore, the radical center in the RSO_2 radical is stabilized by conjugation (3c-5e) within the SO_2 moiety. Loss of such interaction in the product may also contribute to the counter-intuitive greater thermodynamic penalty for the C-S bond scission relative to the C-C bond scission in the RCO_2-analog.

In the following discussion, we will show how the difference in the radical delocalization patterns can explain the contrasting trends in Me group substitution at the C-X BDEs for the RSO_2 and RCO_2 systems.

The general trends in the stability of alkyl radicals (Me < Et < i-Pr < t-Bu) are, of course, well understood, and BDEs for the C-C scission in radical decarboxylation do follow these expectations. In the RCO_2 species, the C-C BDEs decrease as the forming radical becomes more substituted (~ 4 kcal/mol difference between Me and t-Bu). However, the C-S BDE for the loss of *SO_2* follows the *opposite trend.* The C-S BDE is ~3 kcal/mol greater for the formation of t-Bu radical than for the formation of Me radicals. *The striking feature of these C-S scissions is that the BDEs increase as the stability of forming radicals becomes greater!*

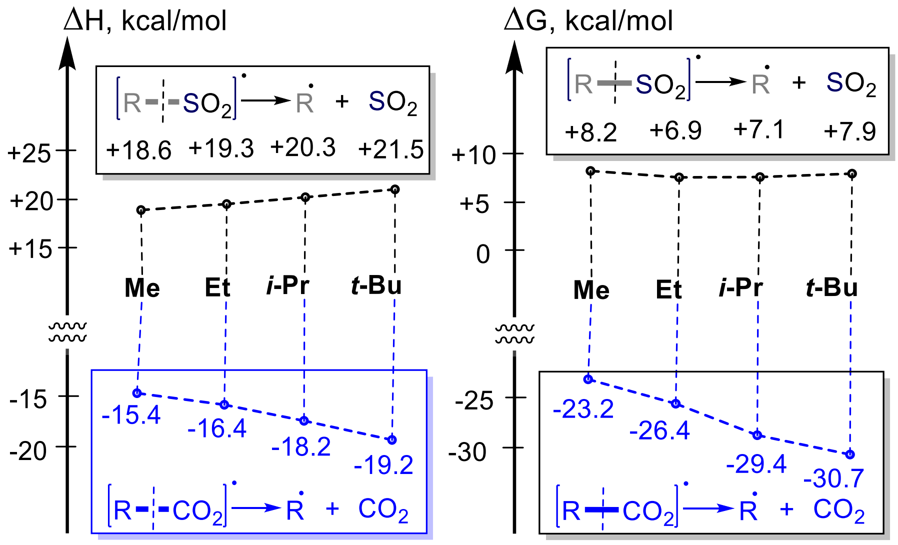


Figure 7: Enthalpies (left) and free energies (right) for the C-S bond fragmentations in the alkyl-SO_2 radicals are insensitive to the structure of the alkyl group whereas the fragmentation of C-C bonds in alkyl-CO_2 radicals are more favorable for the formation of more substituted radicals R.

Why do the two C-X bond scissions display such contrasting trends? The C-C BDE directly reflects the stability of forming radicals because the radical center in the RCO2 radicals is stereoelectronically isolated from the substituent R as shown in Figure 6. In contrast, the radical center in the RSO_2 species directly communicates with the substituent R. Increased BDE for the more substituted radicals for the C-S bond scission simply means that the stabilizing effects of Me groups in the RSO_2 reactant is *greater* than it is in the product.

The ΔG trends illustrate that entropic effects can either mask or amplify the enthalpy trends. When the free energy is used for the comparison, the increase in the alkyl radical stability has a small (~1 kcal/mol) and irregular effect at the free energy of the C-S bond scission (Me = t-Bu > Et = i-Pr). In contrast, the effect of Me substitution at the free energy of C-C bond becomes even larger (> 7 kcal/mol).

Hybridization effects: As expected, scission of the stronger C(sp)-S and C(sp^2)-S bonds is more thermodynamically unfavorable than scission of the C(sp^3)-S bond. This finding agrees well with the known stability of the $ArCO_2$, alkynylCO_2, and vinyl-CO_2 radicals towards the loss of CO_2.[34] These hybridization effects[35,36] at bond stability continue to apply to the bond scission in the R-SO_2 radicals, albeit to a slightly different extent. For example, the differences for the alkyne-XO_2 and Ph-XO_2 bonds are noticeably larger for X=C (14 kcal/mol) than for X=S (7 kcal/mol). On the other hand, the differences for the Ph-XO_2 and Me-XO_2 BDEs are about the same (~10 kcal/mol) for both X=C and S.

Additional hybridization effects are associated with Bent's rule, a well-established connection between hybridization and electronegativity.[37] This rule states that "s-character concentrates in orbitals directed toward electropositive substituents" or, alternatively, that "atoms direct hybrid orbitals with more p-character towards more electronegative elements". Bent's rule explains a variety of rehybridization effects[35,38] in reactivity in organic[39] and main group[40] compounds.

Figure 8 illustrates the role of Bent's rule in contributing to the relative instability of fluorinated RSO_2 radicals. According to Bent's rule, the C-F bonds usually get an increased amount of p-character. Use of the higher energy p-electrons by carbon facilitates polarization of the C-F bonds towards fluorine. This rehybridization is readily seen in the decreased FCF angle of fluoroform (~108°). At the same time, the HCF angle opens up relative to the ideal tetrahedral geometry due to the allocation of additional s-character in the C-H bond. The electronic origin of these geometric changes can be tracked by analyzing variable fractional orbital hybridization of CF_3H with Natural Bond Orbital (NBO) analysis. The carbon hybrid in the C-SO_2 bond of a $MeSO_2$ radical is even more p-rich ($sp^{4.5}$) than each of the carbon hybrids in the C-F bonds of CF_3H ($sp^{3.4}$). This p-character increase is consistent with the acceptor character of the SO_2 moiety and is amplified further by the large size of S orbitals.[40] Such rehybridization effects can make the C-F and the C-S bonds stronger and more polar. However, in the case of CF_3SO_2, rehybridization is difficult. Fluorines and sulfur compete for the p-character and neither one is "happy" with the hybridization of carbon in their bonds (Figure 8). The C-S bond scission can partially alleviate this "hybridization frustration", explaining why such scission is assisted by the fluorine substitution.

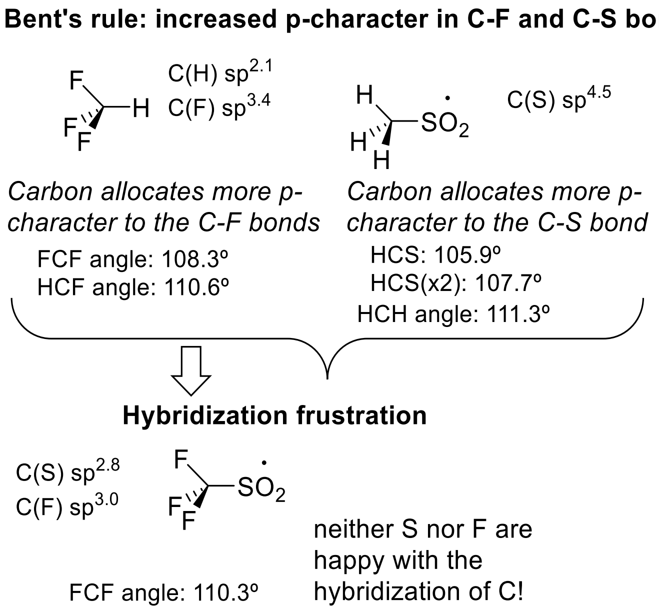


Figure 8: Illustration of "hybridization frustration" in the CF_3SO_2 radical. Average NBO hybridization from the α- and β-spin NBOs are given

Although the above effects are not negligible, they are not large enough to explain the dramatic differences between the C-C and C-S bond dissociation energies in the RXO_2H/RXO_2 systems. Hence, we need to look at the contribution of products to the observed BDE trends. There are two factors: the nature of the gaseous co-products, CO_2 vs. SO_2, and the stability of radical R forming from RXO_2.

The gaseous co-product stability: CO_2 vs. SO_2

The general strategy for making an unstable molecular species (e.g., a radical) is to couple this process with the formation of a stable co-product. This strategy finds numerous applications in chemistry.[41,42] In this section, we will compare the two such "thermodynamic auxiliaries", CO_2 and SO_2, and show that they are dramatically different.

In this regard, it is instructive to compare the BDEs for RXO_2H and RXO_2. The inversion of the relative BDE magnitudes for the C-C and C-S bond scissions in the radicals comes from the fact that BDE is lowered by the introduction of radical much more for the loss of CO_2 (~110 kcal/mol) than for the loss of SO_2 (~35-40 kcal/mol). The situation is summarized schematically in Figure 9. As discussed earlier, the BDEs reflect two components: stability of the reactants and stability of the products. The effect of product stability can be evaluated from the H-atom transfer equation shown in the Figure. It illustrates that the product stability plays a major role in the observed trend (~55 kcal/mol). The largest part of this effect is likely to stem from the high thermodynamic stability of CO_2[43] as the result of the greater strengths of the C=O bonds and the efficiency of the $n_{O1} \rightarrow \pi^*_{C2O3}$ resonance.[44] The rest should come from the intrinsic differences in the C-C and C-S bond strength in the reactants and, possibly, from the differences in the radical stabilization discussed in the previous section.

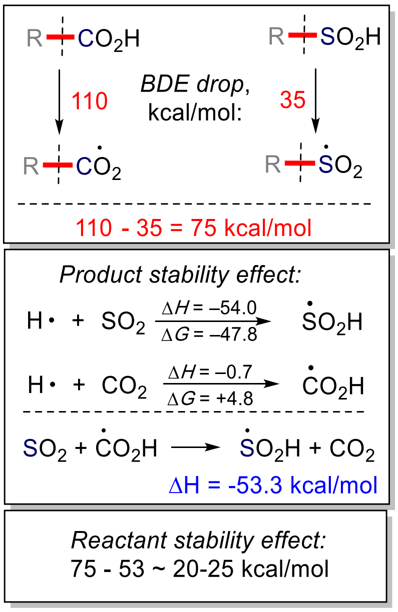


Figure 9: The dramatic difference in the radical effect at the C-C and C-S bond scissions in the R-XO2 systems

Nature of the departing radical.

Like true chameleons, radicals display a wide range of stabilities and reactivities, as a function of many possible delocalization effects. In the following sections, we will concentrate on several types of substrates with the goal of highlighting the underlying electronic factors that are responsible for the observed trends.

Effect of acceptors:

In order to evaluate the importance of donor/acceptor interactions of substituent at the departing radical with the pi-system of CO_2 (and SO_2), we have calculated BDEs for a group of para-substituted aryl radical precursors (Figure 10). These systems are convenient since they help to separate the effects of delocalization from the effects of hybridization.

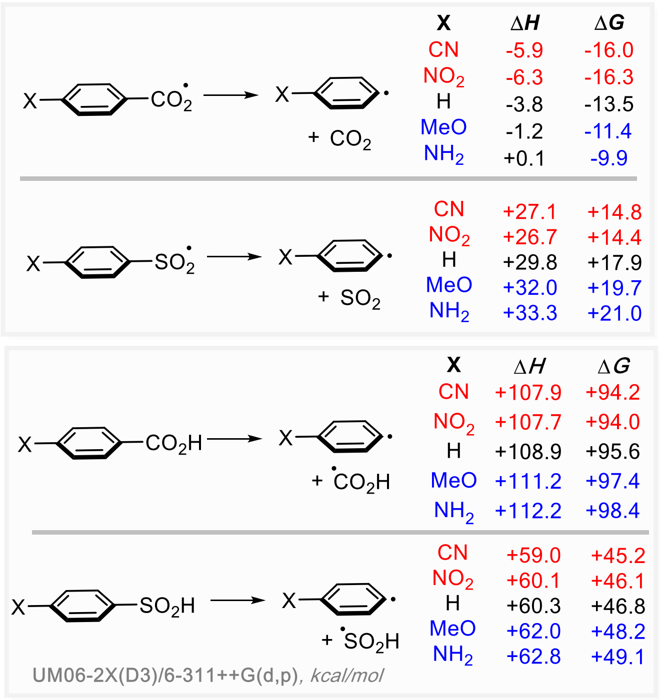
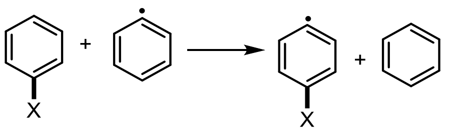


Figure 10: Substituent effects on the BDEs for the group of *para*-substituted aryl radical precursors. Note that delocalizing interactions that do not involve the radicals still have a large effect at the BDEs.

Although it is natural to concentrate on delocalizing interactions that involve the radical centers, one should not forget that other effects contribute to the observed BDEs as well. In particular, both the CO_2R and SO_2R groups are strong π-acceptors as illustrated by their relatively large and positive Hammett σ_{para} values (CO_2H = 0.45, CO_2Et =0.45, SO_2Me=0.72[45]).

The calculated energies in Figure 10 include both the π-effects and the effects of radical delocalization. The individual contributions from the two effects in the RCO_2 and RSO_2 systems should be quite different. Nevertheless, Figure 10 illustrates that the *net* substituent effects on the CO_2 and SO_2 loss are remarkably similar. For the loss of CO_2, the donor NH_2 group increases BDE by 3.9 kcal/mol whereas the acceptor nitro group decreases the BDE by (up to) 2.5 kcal/mol. The effects of the same groups (-3.5 kcal/mol and +2.1 kcal/mol) on the C-S BDE in the RSO_2 species are essentially the same.

For comparison, we have also included the C-H BDEs for the formation of the same radicals from the respective monosubstituted benzenes. As one can see, the effects are much smaller because the $\sigma_{C\text{-}H}$ bond is orthogonal to the aromatic π-system and has to interact with the para substituents either through-space or through the σ-framework.[46]



UM06-2X(D3)/6-311++G(d,p), *kcal/mol*

X	ΔH	ΔG
OMe	0.7	0.7
NH_2	1.1	1.1
H	0.0	0.0
NO_2	0.7	0.7
CN	0.5	0.5

Figure 11: Isodesmic equation evaluating the impact of *para*-substituted phenyl radicals. Both donor and acceptor groups offer little difference when compared to H.

An analogous set of systems was tested for the formation of substituted vinyl radicals. Formation of the parent vinyl radicals is similar to the formation of the Ph radical. Again, acceptor substitution decreases the C-S BDE. The effect is moderate for the formation of trifluorovinyl radicals where the p-donating properties of fluorine atoms partially compensate for their σ-accepting power. In agreement with the decrease in p-donation for Cl and Br,[27] these substituents provide less stabilization to the starting RSO_2 species and render fragmentation less unfavorable. The greatest facilitating effect is observed in the presence of π-acceptors. For example, the fragmentation of tricyano precursor is predicted to be ~3 kcal/mol exergonic.

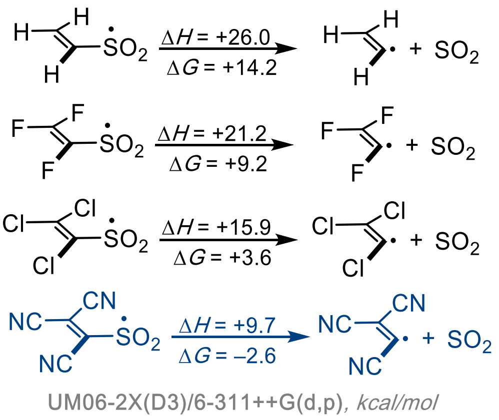


Figure 12: Substituent effects on the BDEs of alkene sulfonyl precursors

σ-Acceptors: fluoroalkyls vs. alkyls

Our computations suggest that for all alkyl radical formations, the loss of SO_2 is uphill! This result agrees very well with the results of Konig et al. who observed that reactions of sulfinyl radicals are *not* accompanied by the loss of SO_2.[15] On other hand, they bring mechanistic questions about the chemically induced oxidation of sulfinate salts reported by Baran. An additional factor in these reactions may be a different oxidation mechanism of the sulfinate anion by hydroperoxides. So far, no detailed mechanistic studies have been reported for the chemical oxidation of sulfinate anions.

This situation changes when acceptor groups are introduced at the scissile bond. The formation of halogen-containing radicals is less endothermic than the formation of simple alkyl radicals. This finding is especially important for the C-SO_2 scissions where, with the help of entropic factors, fluorination allows this process to become thermodynamically favorable. For the loss of SO_2 at 298 K, the threshold occurs between CH_2F/CF_2CH_3 and CF_2H. Higher temperatures should help to shift the equilibrium further in favor of dissociated products even for CH_2F.

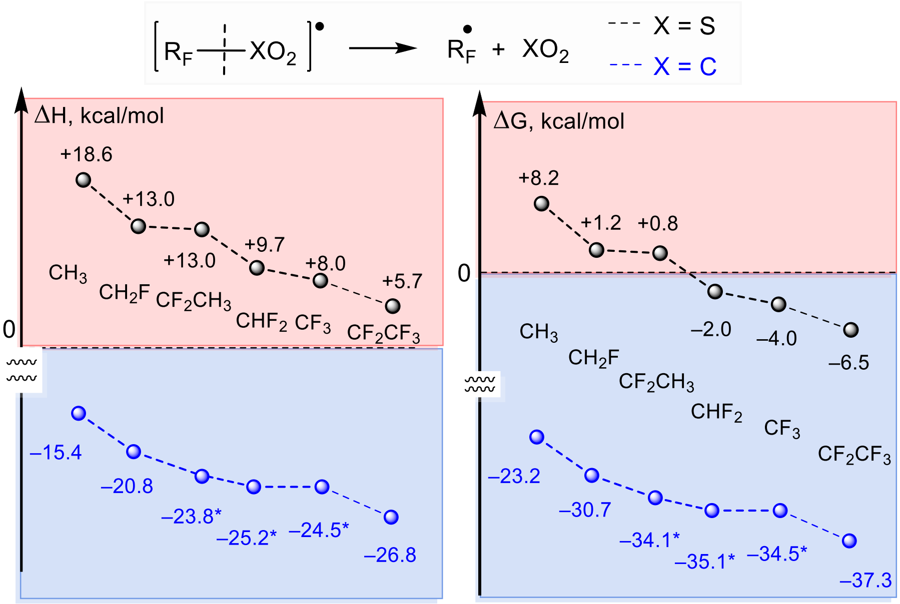
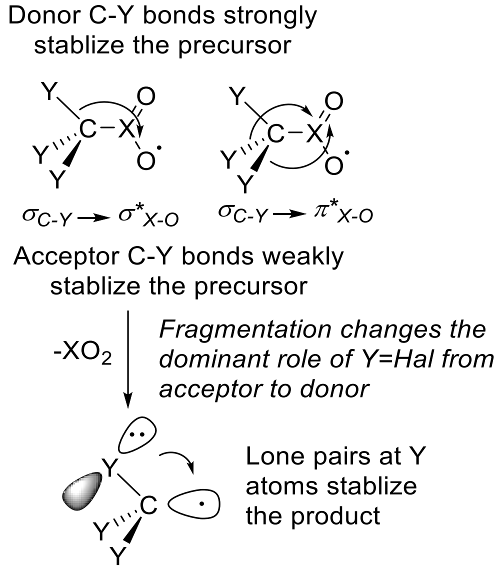


Figure 13: Enthalpies and free energies for the R_F-XO_2 (X = S, top, or C, bottom) bond fragmentations in the fluoroalkyl-XO_2 radicals.

Although the exact position of the threshold is affected by the computational uncertainty of the current methods, the M06-2X data do agree with the scarcity of the literature reports describing formation of the CH_2F radical via this approach.

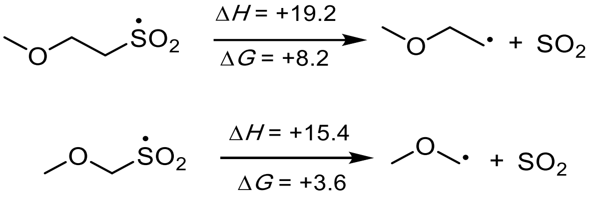
Stereoelectronic analysis can explain why the fragmentations of radical precursors with the σ-acceptors at the incipient radical centers (i.e., the C-F and C-Cl bonds) are more favorable than fragmentations that produce alkyl radicals. The origin of these effects lies in the chameleonic[47] behavior of C-Halogen moieties (Scheme 1). In contrast to the C-H and C-C bonds in the alkyl groups that serve as hyperconjugative donors in stabilizing interactions with the π* and σ* CO and CS orbitals in the reactants and with the carbon radical in the dissociated product (Scheme 1), the dominant electronic effect of halogen groups undergoes a reversal in the process of fragmentation. Although the C-F and C-Cl bonds are strong σ-acceptors[48] and do not stabilize the adjacent XO_2 groups, the same substituents act as donors (via the n(X)→n(C) interactions) towards the R radicals formed after the fragmentations. In other words, the "chameleonic" properties of the halogen groups originate from the switch from being a σ-acceptor relative to a β-substituent to become a p-donor relative to an α-substituent.



Scheme 1. The chameleonic change of the halogen substituents from $\sigma_{C\text{-}Y}$ acceptors to n_Y donors in the process of C-X bond fragmentations

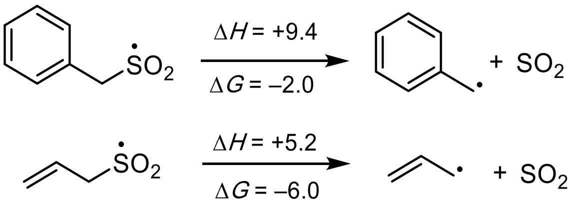
Additional substituent effects:

A similar effect was observed for the oxygen-containing substrates in Scheme 2. In ethers, the formation of anomeric radicals at the α-carbon is ~4-5 kcal/mol less endergonic (less unfavorable) than formation of radicals at the β-carbon. This result illustrates that donation from the S-centered radical to the σ*CO is less important than the *2c,3e* stabilization[49] by the interaction of the MeOCH$_2$ radical with the α-oxygen lone pair.



Scheme 2. Evaluation of systems that invoke anomeric stabilization

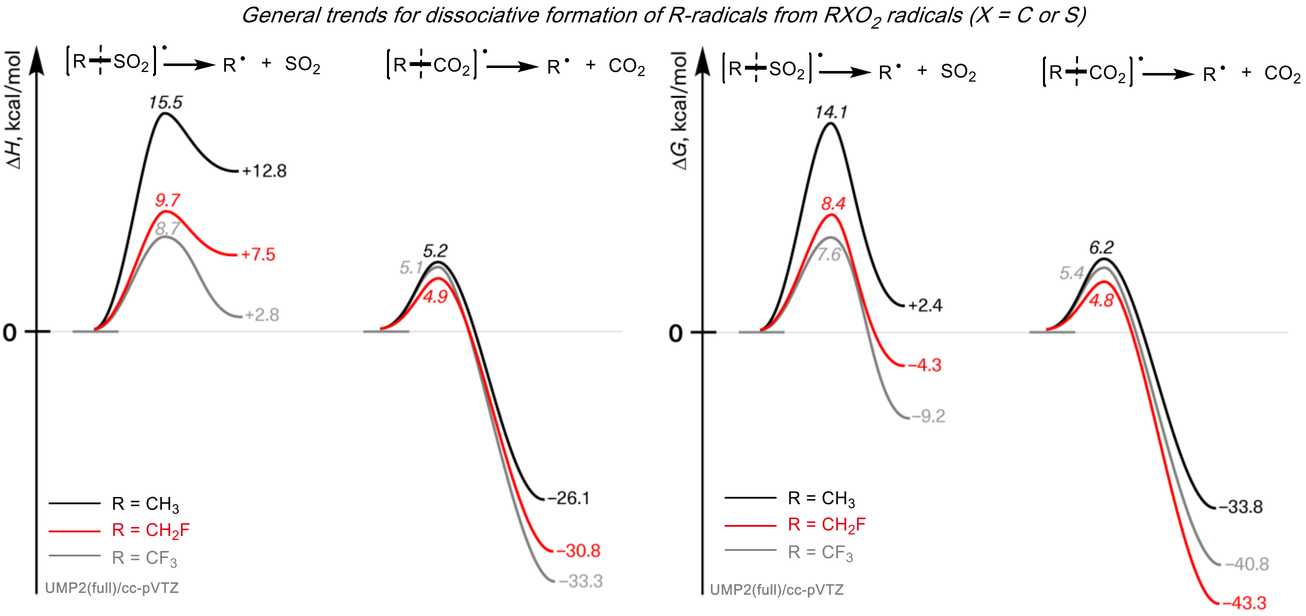
Stabilization of the C-centered radical product by an adjacent π-system renders the SO$_2$-extrusion exergonic. In agreement with the greater stabilization of radical center by an alkene,[50] the formation of allyl radical is slightly more favorable than the formation of benzylic radical (-6 vs. -2 kcal/mol, Scheme 3).



Scheme 3. Evaluation of systems that invoke benzylic and allylic stabilization

Selected barriers for the C-C and C-S scission in the RXO_2 (X=C,S) systems:

Analysis of the activation barriers is more difficult in RXO_2 systems. Since our initial attempts using DFT methods were unsuccessful, we have chosen the UMP2(full)/cc-pVTZ method as an alternative approach. The barriers for the C-C and C-S bond scissions were found by performing a full relaxed scan for the interatomic distances corresponding to the breaking bonds. The results are presented in Scheme 4. Although the introduction of fluorine atoms significantly decreases the barrier for the C-S bond scission, the fluorine substitution has only a small (<1 kcal/mol) effect on the C-C scission. In the RXO_2 species, the C-S scission barriers are higher than the C-C barriers and affected much more by the change in the nature of the substitution in radical R.



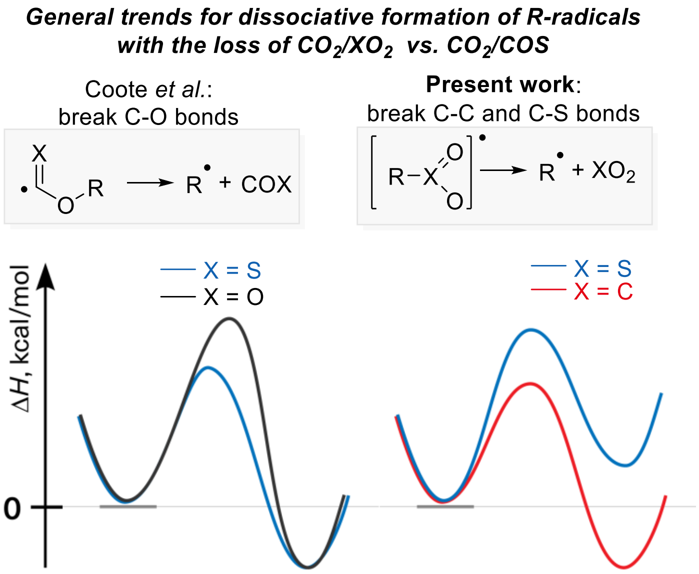
Scheme 4. Effect of fluorine substitution on kinetics and thermodynamics of XO_2 extrusion from RXO_2 radicals. (X=S,C)

General trends for radical formation via the extrusion of triatomic heterocumulenes: comparison with the literature systems

It is interesting to compare the above trends with the alkoxycarbonyl and alkoxythiocarbonyl radicals reported by Coote and coworkers.[51] Although both of these earlier studied systems had similar fragmentation enthalpies and breaking the same type of bond (the O-R), the alkoxycarbonyl precursors displayed higher activation barriers for the β-scission. The difference in the barriers has been attributed to the radical greater stabilization in the alkoxycarbonyl starting materials. As the C=O bond is shorter than the C=S bond, oxygen is more effective at engaging the radical center in a *2c,3e* bond than its sulfur counterpart. Since this stabilizing effect is weakened in the TS, this cost has to be paid as an increase in the activation barrier. From the point of view of the Marcus theory, the observed trends indicate that the intrinsic barriers for the fragmentation are different.[50]

In the present case, the types of the breaking bonds are different (C-C vs. C-S) and the reaction enthalpy for the C-C scission is 30-40 kcal/mol more negative than it is for the C-S scission (Scheme 5). The relative activation barriers for C-C and C-S scissions follow the same trend as thermodynamics. However, one should know that the barrier difference (3-10 kcal/mol) is much smaller than differences in the reaction energies.

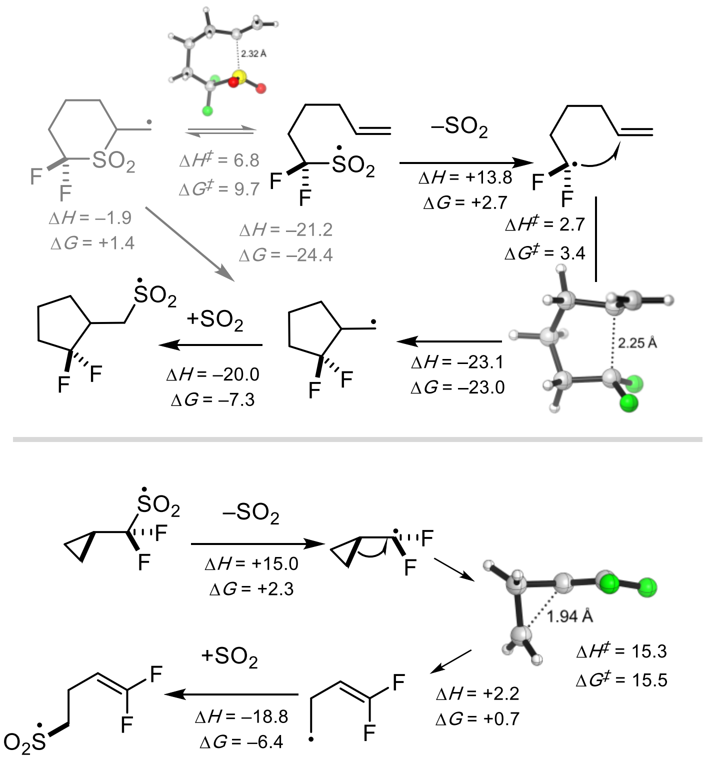
Analysis of these observations through the prism of Marcus theory[50] suggests that although the *intrinsic* bond scission barrier is lower for the C-S bonds, the *full* barrier is lower for the C-C bond scission due to much more favorable thermodynamic contribution for the CO_2 loss.


General trends for dissociative formation of R-radicals with the loss of CO_2/XO_2 vs. CO_2/COS

Scheme 5. Comparison of kinetic and thermodynamic trends in fragmentations producing an alkyl radical and a triatomic heterocumulene.

Implications for the design of isomerization cascades

The difference in the relative exergonicities of alkyl and fluoroalkyl radicl formation via the RXO_2 fragmentation may be possible to exploit for the design of isomerization cascades similar to those shown in Scheme 6.



UM06-2X(D3)/6-311++G(d,p), *kcal/mol*

Scheme 6. Possible radical isomerization cascades in substituted RXO_2 systems

The proposed cascades are based on the relative favorability of the C-S scission for the formation of fluorinated radicals. In the first example, the radical can be trapped by the alkene. Although one can suggest that the RXO_2 precursor can be also trapped by a 6-*exo* cyclization before the SO_2-extrusion, this process is uphill and, thus, can be reversed via the ring-opening. The loss of SO_2 should lead to a fast and irreversible 5-*exo* cyclization. Because the cyclization step produces an alkyl radical, this product should be capable of recapturing SO_2 by forming a new C-S bond, thus completing the isomerization cascade.

The second example combines C-S scission with a C-C fragmentation by involving a cyclopropyl radical clock. Again, the ring opening transforms a fluorinated radical (poor trap for SO_2) into an alkyl radical (a good trap for SO_2), rendering the overall isomerization thermodynamically favorable. Interestingly, the ring-opening proceeds is thermoneutral with a relatively high barrier. This finding suggests that in the presence of more efficient traps, the intermediate cyclopropyl radical can be intercepted, suggesting a new strategy for the usually problematic installation of cyclopropyl-CF_2 groups.

Conclusions and practical implications:

In summary, this study highlights the important differences between oxidative generation of C-centered radicals via loss of CO_2 and SO_2 from the respective radical precursors. Whereas the use of CO_2 is generally thermodynamically favorable, the loss of SO_2 does not enjoy the same thermodynamic assistance and, in many cases, is uphill. The paradoxical observation that the C-C bond is weaker than the C-S bond in these reactions is explained by the combination of conjugative and hybridization effects.

The differences in the spin density distribution illustrate that the radical centers in the RCO_2 radicals do not interact with the R group via conjugation. The lack of spin density at the central carbon is a stereoelectronic barricade that isolates the O-centered radicals from the rest of the molecule. In contrast, the sulfur atom in the RSO_2 radical has significant amount of spin density and can interact directly with the appropriately aligned orbitals at the substituent R.

The C-C scission in radical decarboxylation does follow the usual trends defined by in the stability of forming radicals. For example, the C-C BDEs decrease as the forming radical becomes more substituted (~ 4 kcal/mol difference between Me and t-Bu). However, the C-S BDE follows an *opposite trend* – it is ~3 kcal/mol *greater* than for the formation of t-Bu radical than for the formation of Me radicals.

Both RSO_2 and RCO_2 radicals are stabilized by the donor substituents and destabilized by the acceptor substituents in R. The stabilizing effects include both conjugation and hyperconjugation. In particular, progressive increase in the number of fluorine atoms makes the fragmentations more favorable.

The choice of conditions is crucial for radical fragmentation with SO_2 loss. One has to distinguish clearly between reactions that proceed via true “outer sphere” electron transfer, such as electrochemical oxidation and photoredox pathways, and chemical oxidation, e.g. by t-BuOOH, which may proceed via a mechanistically distinct scenario requiring a separate analysis in the future.

Thermodynamic limitations described in this work only apply to ground state fragmentations of true radicals. For the SO_2-centered radicals that are immune to the thermal loss of SO_2, additional photochemical activation of the RSO_2 precursor should be considered. It is possible that photochemical excitation of stable (or metastable) RSO_2 radicals can also assist to the loss of SO_2.

The differences in the two types of dissociative approaches to the formation of carbon-centered radicals are important for the design of radical reactions mediated by fragmentations. Loss of SO_2 can be a more selective process that loss of CO_2. Due to applications of RSO_2 radicals in synthesis,[52] the search for new approaches to their generations continues.[53] In this context, the reverse process, i.e. the reactions of SO_2 and alkyl and aryl radicals, may be useful for synthesis of RSO_2 radicals in the same way as reaction of radicals with carbon monoxide can be a source of acyl radicals.[54,55]

Supporting Information

Comparison of computational methods, as well as geometries and energies for all calculated structures reported in this work are available in the SI. This material is available free of charge via the Internet at http://pubs.acs.org

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References and Notes

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[1] Chemoselectivity: The Mother of Invention in Total Synthesis. Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.

[2] (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989. (b) Aiming for the Ideal Synthesis. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (c) Radical Retrosynthesis. Smith, J. M.; Harwood, S. J.; Baran, P. S. *Acc. Chem. Res.* **2018**, *51*, 1807.

[3] Practical and innate carbon-hydrogen functionalization of heterocycles. Fujiwara, Y.; Dixon, J. A.; O'hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

[4] Zersetzung der Valeriansäure durch den elektrischen Strom. Kolbe, H. *Annalen der Chemie und Pharmacie* **1848**, *64*, 339.

[5] Nucleophilic character of alkyl radicals-VI: A new convenient selective alkylation of heteroaromatic bases. Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron*, **1971**, *27*, 3575.

[6] For reviews, see: (a) Debarcoxylative coupling reactions: a modern strategy for C-C-bond formation. Roríguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (b) Minisci reactions: Versatile CH-functionalizations for medicinal chemists. Duncton*,* M. A. J. *MedChemComm* **2011***, 2,* 1135*.* (c) Mechanistic aspects: Catalysis of Radical Reactions: A Radical Chemistry Perspective. Studer, A.; Curran, D. P. Angew. Chem. Int. Ed., **2016**, *55*, 58.

[7] A novel giant palladium cluster. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Comm.* **1983**, *0*, 939.

[8] Trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions. Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett*. **1991**, *32*, 7525.

[9] (a) A New Reagent for Direct Difluoromethylation. Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) Innate C-H trifluoromethylation of heterocycles. Ji, Y.; Brueckl, T.; Baxter, R.D.; Fujiwara, Y.; Seiple, I.B.; Su, S.; Blackmond, D.G.; Baran, P.S. *PNAS*, **2011**, *108*, 14411. (c) Direct Synthesis of Fluorinated Heteroarylether Bioisosteres. Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3949. (d) Preparation and purification of zinc sulfinate reagents for drug discovery. O'Hara, F.; Baxter, R. D.; O'Brien, A. G.; Collins, M. R.; Dixon, J. A.; Fujiwara, Y.; Ishihara, Y.; Baran, P. S. *Nat. Protoc.* **2013**, *8*, 1042. (e) A Simple Litmus Test for Aldehyde Oxidase Metabolism of Heteroarenes. O'Hara, F.; Burns, A. C.; Collins, M. R.; Dalvie, D.; Ornelas, M. A.; Vaz, A. D. N.; Fujiwara, Y.; Baran, P. S. *J. Med. Chem.* **2014**, *57*, 1616. (f) C-H Methylation of Heteroarenes Inspired by Radical SAM Methyl Transferase. Gui, J.; Zhou, Q.; Pan, C. -M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853. (g) Radical-Based Regioselective C-H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.*, **2013**, *135*, 12122. (h) Enabling Efficient Late-Stage Functionalization of Drug-Like Molecules with LC-MS and Reaction-Driven Data Processing. Yao, H.; Liu, Y.; Tyagarajan, S.; Streckfuss, E.; Reibarkh, M.; Chen, K.; Zamora, I.; Fontaine, F.; Goracci, L.; Helmy, R.; Bateman, K. P.; Krska, S. W. *Eur. J. Org. Chem.* **2017**, 7122. (i) Terent'ev, A. O.; Mulina, O. M.; Pirgach, D. A.; Demchuk, D. V.; Syroeshkin, M. A.; Nikishin, G. I. Copper(I)-mediated Synthesis of b-hydroxysulfones from Styrenes and Sulfonylhydrazides: an Electrochemical Mechanistic Study. *RSC Adv*. **2016**, *6*, 93476-93485. (g) Terent'ev, A. O.; Mulina, O. M.; Pirgach, D. A.; Ilovaisky, A. I.; Syroeshkin, M. A.; Kapustina, N. I.; Nikishin, G. I. Electrosynthesis of Vinyl Sulfones from Alkenes and Sulfonyl Hydrazides Mediated by KI: an Electrochemical Mechanistic Study. *Tetrahedron*. **2017**, *73*, 6871-6879.

---

[10] For reviews on the Minisci reaction, see: (a) Minisci reaction: a Friedel-Crafts type process with opposite reactivity and selectivity. Selective homolytic alkylation, acylation, carboxylation and carbamoylation of heterocyclic aromatic bases. C. Punta and F. Minisci, *Trends Het. Chem.*, **2008**, *13*, 1. (b) Substitutions by nucleophilic free radicals: A new general reaction of heteroaromatic bases. F. Minisci, F. Fontana and E. Vismara, *J. Heterocycl. Chem.*, **1990**, *27*, 79. (c) Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. F. Minisci, E. Vismara and F. Fontana, *Heterocycles*, **1989**, *28*, 489. (d) Minisci reactions: Versatile CH-functionalizations for medicinal chemists. Dunction, M. A. J. *MedChemComm* **2011**, *2*, 1135.

[11] Mild, visible light-mediated decarboxylation of aryl carboxylic acids to access aryl radicals. Candish, L.; Freitag, M.; Gensch, T.; Glorius, F. *Chem. Sci.* **2017,** *8*, 3618.

[12] For an example, see: Silver-Catalyzed Arylation of (Hetero)arenes by Oxidative Decarboxylation of Aromatic Carboxylic Acids. Kan, J.; Huang, S.; Lin, J.; Zhang, M.; Su, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 2199.

[13] Hydrodecarboxylation of Carboxylic and Malonic Acid Derivatives via Organic Photoredox Catalysis: Substrate Scope and Mechanistic Insight. Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340.

[14] (a) Decarboxylative alkylation for site-selective bioconjugation of natice proteins via oxidation potentials. Bloom, S.; Liu, C.; Kölmel, K.; Qiao, J. X.; Zhang, M. A.; Poss, M. A.; Ewing, W. R.; MacMillan, D. W. C. *Nat. Chem.* **2017**, *10*, 205. (b) Decarboxylative Peptide Macrocyclization through Photoredox Catalysis. McCarver, S. J.; Qiao, J. X.; Carpenter, J.; Borzilleri, R. M.; Poss, M. A.; Eastgate, M. D.; Miller, M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2017**, *56*, 728. (c) Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin. Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886.

[15] Eosin Y (EY) Photoredox-Catalyzed Sulfonylation of Alkenes: Scope and Mechanism. Meyer, A. U.; Straková, K.; Slanina, T.; König, B. *Chem. Eur. J.* **2016**, *22*, 8694.

[16] Frisch, M. J. *et al.* Gaussian 09, Revision D.01; Gaussian: Wallingford, CT, 2009. Complete reference in the SI.

[17] (a) The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.,* **2008**, *120*, 215. (b) Density Functionals with Broad Applicability in Chemistry. Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.,* **2008**, *41*, 157.

[18] A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for 94 elements H-Pu Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *J. Chem. Phys.,* **2010**, *132*, 154104.

[19] The path of chemical reactions – the IRC approach. Fukui, K. *Acc. Chem. Res.*, **1982**, *14*, 363.

[20] MP2 energy evaluation by direct methods. Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.*, **1988**, *153*, 503.

[21] (a) Photocatalytic water splitting for solar hydrogen generation: fundamentals and recent advancements. Weinhold, F.; Landis, C. R.; Glendening, E. D. *International Reviews in Physical Chemistry* **2016**, *35*, 1. Natural localized molecular orbitals. Reed, A. E.; Weinhold, F. *J. Chem. Phys.,* **1985**, *83*, 1736. (b) Natural Bond Orbital Analysis of Internal Rotation Barriers and Related Phenomena. Reed, A. E.; Weinhold, F. *Isr. J. Chem.*, **1991**, *31*, 277. (c) Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.,* **1988**, *88*, 899. (d) Weinhold F. in Schleyer P.v.R. *Encyclopedia of Computational Chemistry*: Wiley: New-York, **1998**, *3*, 1792. Selected recent applications of NBO analysis towards analysis of organic structure and reactivity: a) Stereoelectronic Effects on α-Carbanions of Conformationally Constrained Sulfides, Sulfoxides, and Sulfones. Podlech, J. *J. Phys. Chem. A* **2010**, *114*, 8480. b) Simultaneous *gauche* Anomeric Effects in α-Substituted Sulfoxides. Freitas, M. P. *J. Org. Chem.* **2012**, *77*, 7607. c) Probing Hyperconjugation Experimentally with the Conformational Deuterium Isotope Effect. Greenway, K. T.; Bischoff, A. G.; Pinto, B. M. *J. Org. Chem.* **2012**, *77*, 9221. d) Theoretical Examination of the S-C-P Anomeric Effect. Juaristi, E.; Notario, R. *J. Org. Chem.* **2015**, *80*, 2879. e) Stereoelectronic source of the anomalous stability of bis-peroxides. Gomes, G. P.; Vil', V.; Terent'ev, A.; Alabugin, I. V. *Chem. Sci.* **2015**, **6**, 6783. f) Gold(I)-catalyzed allenyl Cope rearrangement: evolution from asynchronicity to trappable intermediates assisted by stereoelectronic switching. Vidhani, D.; Krafft, M.; Alabugin, I. V. *J. Am. Chem. Soc.*, **2016**, *138*, 2769. g) Interrupted Baeyer-Villiger Rearrangement: Building a Stereoelectronic Trap for the Criegee Intermediate. V. A. Vil', Gomes, G. P.;, O. V. Bityukov, K. A. Lyssenko, G. I. Nikishin, I. V. Alabugin, A. O. Terent'ev, *Angew. Chem. Int. Ed.,* **2018**, *57,* 3372.

[22] An efficient and near linear scaling pair natural orbital based local coupled cluster method. Riplinger, C.; Neese, F. *J. Chem. Phys.*, **2013**, *138*, 034106.

[23] Software update: the ORCA program system, version 4.0. Neese, F. *WIREs Comput Mol Sci* **2018**, 8:e1327.

[24] CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

[25] For an intriguing temperature effect that leads to a switch from SO_2 preservation to extrusion in photocatalytic reactions of sulfonyl chlorides, see: Temperature Controlled Selective C-S or C-C Bond Formation: Photocatalytic Sulfonylation versus Arylation of Unactivated Heterocycles Utilizing Aryl Sulfonyl Chlorides. Pagire, S. K.; Hossain, A.; Reiser, O. *Org. Lett*. **2018**, *20*, 648-651.

[26] Hyperconjugation. I. V. Alabugin, G. Gomes, M. A. Abdo, *WIREs: Comput. Mol. Sci.* **2018**, *in press,* 10.1002/wcms.1389.

[27] (a) Trends in R-X Bond Dissociation Energies (R = Me, Et, *i*-Pr, *t*-Bu; X = H, CH_3, OCH_3, OH, F): A Surprising Shortcoming of Density Functional Theory. Izgorodina, E.; Coote, M. L.; Radom L., *J. Phys. Chem. A*, **2005**, *109*, 7558–7566. (b) Alabugin, I. V. *Stereoelectronic Effects: the Bridge between Structure and Reactivity.* John Wiley & Sons Ltd, Chichester, UK, 2016.

[28] The CH/CF hyperconjugation explains other seeming paradoxes, such is why is CF_3 has a negative Radical Stabilization Energy (Effect of substituents on the stabilities of multiply-substituted carbon-centered radicals. Menon, A. S.; Henry, D. J.; Bally T.; Radom L. *Org. Biomol. Chem.* **2011**, *9*, 3636-3657); or why the C−H bond in $H-C_6F_5$ is stronger than the C-H bond in benzene

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whereas the C−F bond in $F-C_6F_5$ is weaker than in $F-C_6H_5$ (Selectivity of C-H Activation and Competition between C-H and C-F Bond Activation at Fluorocarbons. Eisenstein, O.; Milani, J.; Perutz, R. N.; *Chem. Rev.* **2017**, *117*, 8710-8753).

[29] Carboxyl Free Radicals: Formyloxyl (HCOO.bul.) and Acetyloxyl (CH3COO.bul.) Revisited. Rauk, A.; Yu, D., Armstrong, D. A., *J. Am. Chem. Soc.*, **1994**, *116*, 8222-8228.

[30] .sigma. Ground state of the benzoyloxy radical. Yim, M. B.; Kikuchi, O.; Wood, D. E. *J. Am. Chem. Soc.*, **1978**, *100*, 1869 and references therein.

[31] 2B2 benzoyloxy, a delocalized .sigma. radical. McBride, J. M.; Merrill, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1723.

[32] Selected examples: Changing the path of least resistance, or access to endo-dig products via a sequence of three exo-trig transition states: electronic effects in homoallyic ring expansion cascades of alkenyl isonitriles. Gomes, G. P.; Evoniuk, C.; Ly, M.; Alabugin, I. V. *Org. Biomol. Chem.,* **2017**, *15*, 4135-4143. Coupling radical homoallylic expansions with C-C fragmentations for the synthesis of heteroaromatics: Quinolines from reactions of o-alkenylarylisonitriles with aryl, alkyl and perfluoroalkyl radicals. Evoniuk, C.; Gomes, G. P.; Ly, M.; White, F.; Alabugin, I. V. *J. Org. Chem.,* **2017**, *82*, 4265-4278. Domino Fragmentations in Traceless Directing Groups of Radical Cascades: Evidence for the Formation of Alkoxy Radicals via C-O Scission. Harris, T.; Gomes, G.; Clark, R. J.; Alabugin, I. V. *J. Org. Chem.*, **2016**, *81*, 6007–6017. Traceless Directing Groups in Radical Cascades: From Oligoalkynes to Fused Helicenes without Tethered Initiators. Pati, K.; Gomes, G. P.; Harris, T.; Hughes, A.; Phan, H.; Banerjee, T.; Hanson, K.; Alabugin, I. V. *J. Am. Chem. Soc.* **2015**, *137*, 1165-1180. Conformationally Gated Fragmentations and Rearrangements Promoted by Interception of the Bergman Cyclization through Intramolecular H-Abstraction: A Possible Mechanism of Auto-Resistance to Natural Enediyne Antibiotics? Baroudi, A.; Mauldin, J.; Alabugin, I. V. *J. Am. Chem. Soc.,* **2010,** *132*, 967-979.

[33] There is also an interesting symmetry problem because the radical center populates an MO with the nodal structure that renders its interaction with the scissile C-C bond symmetry forbidden. Although this feature is likely to be of significance, a more detailed discussion of its consequences goes beyond the scope of the present work.

[34] First spectroscopic and absolute studies on (alkoxycarbonyl)oxyl radicals and an unsuccessful attempt to observe carbamoyloxy radicals. Chateauneuf, J.; Lusztyk, J.; Maillard, B.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 6727. First EPR spectroscopic detection of photochemically generated carbonyloxyl radicals in solution under steady-state conditions. Korth, H.-G.; Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 5929. Further spectroscopic and kinetic studies on carbonyloxyl radicals. Korth, H.-G.; Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1991**, *56*, 2405. Spectroscopic and kinetic characteristics of aroyloxyl radicals. 1. The 4-methoxybenzoyloxyl radical. Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 2877. Spectroscopic and kinetic characteristics of aryloxyl radicals: 2. Benzoyloxyl and ring-substituted aryloxyl radicals. Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. *J. Am.Chem. Soc.* **1988**, *110*, 2886. Well-Resolved ESR Spectra of Arenecarboxyl Radicals in Solution. Korth, H.-G.; Muller, W.; Lusztyk, J.; Ingold, K. U. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 183. Direct observation of benzoyloxyl radicals in photodecomposition of dibenzoyl peroxides with a time-resoved ESR technique. Yamauchi, S.; Hirota, N.; Takahara, S.; Sakuragi, H.; Tokumaru, K. *J. Am. Chem. Soc.* **1985**, *107*, 5021 and references therein.

[35] Orbital Hybridization: a Key Electronic Factor in Control of Structure and Reactivity. Alabugin, I. V.; Bresch S.; Gomes, G. P. *J. Phys. Org. Chem.,* **2015**, *28,* 147-162. Combining Traceless Directing Groups with Hybridization Control of Radical Reactivity: from Skipped Enynes to Defect-Free Hexagonal Frameworks. Pati, K.; Gomes, G.; Alabugin, I. V. *Angew. Chem. Int. Ed.,* **2016**, *55*, 11633-11636.

[36] Such effects can be useful in synthetic radical chemistry. For example, the greater strength of X-aryl bonds in comparison to that of X-alkyl bonds, was used to redirect the classic Barton- McCombie decarboxylation (A new method for the deoxygenation of secondary alcohols. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574. The Genesis of the Reversible Radical Addition-Fragmentation-Transfer of Thiocarbonylthio Derivatives from the Barton-McCombie Deoxygenation: A Brief Account and Some Mechanistic Observations. Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663), into an alternative C,O-transposition path: Radical O→C Transposition: a Metal-Free Process for Conversion of Phenols into Benzoates and Benzamides Baroudi, A.; Alicea, J.; Flack, P.; Kirincich, J.; Alabugin, I. V. *J. Org. Chem*. **2011**, *76*, 1521-37. Formaldehyde-Extruding Homolytic Aromatic Substitution via C→O Transposition: Selective 'Traceless-Linker' access to Congested Biaryl Bonds. P. Poonpatana, G. P. Gomes, T. Hurrle, K. Chardon, D. Marshall, S. J. Blanksby, S. Bräse, K.-S. Masters, I. V. Alabugin. *Chem. Eur. J.,* **2017**, *23*, 9091–9097.

[37] An Appraisal of Valence-bond Structures and Hybridization in Compounds of the First-row elements. Bent, H. A. *Chem. Rev.* **1961**, *61*, 275-311.

[38] Rehybridization as a general mechanism for maximizing chemical and supramolecular bonding and a driving force for chemical reactions. Alabugin, I.V.; Manoharan, M. *J. Comp. Chem.* **2007**, *28*, 1, 373.

[39] Cycloaromatization reactions: Substituent effects on the Bergman cyclization of (*Z*)-1,5-hexadiyne-3-enes: a systematic computational study. Prall, M.; Wittkopp, A.; Fokin, A. A.; Schreiner, P. R. *J. Comp. Chem.* **2001**, *22*, 1605. Matrix Isolation of Perfluorinated *p*-Benzene. Wenk, H. H.; Balster, A.; Sander, W.; Hrovat, D. A.; Borden, W. T. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2295. Halo-Enediynes: Probing the Electronic and Stereoelectronic Contributions tot he Bergman Cycloaromatization. Plourde, G. W.; Warner, P. M.; Parrish, D. A.; Jones, G. B. *J. Org. Chem.* **2002**, *67*, 5369. Concerted Reactions that Produce Diradicals and Zwitterions: Electronic, Steric, Conformational and Kinetic Control of Cycloaromatization Processes. Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V. *Chem. Rev*. **2013**, *113,* 7089. Cycloadditions: Second-Generation Difluorinated Cyclooctynes for Copper-Free Click Chemistry. Bertozzi, C. R.; Agard, N. J.; Baskin, J. M.; Codelli, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 11486. Selective Transition State Stabilization via Hyperconjugative and Conjugative Assistance: Stereoelectronic Concept for Copper-Free Click Chemistry. Gold, B.; Shevchenko, N. E.; Bonus, N.; Dudley, G. B.; Alabugin, I. V. *J. Org. Chem.* **2012**, *77*, 75. Moderating strain without sacrificing reactivity: Design of fast and tunable non-catalyzed alkyne-azide cycloadditions via stereoelectronically controlled transition state stabilization. Gold, B.; Dudley, G. B.; Alabugin, I. V. *J. Amer. Chem. Soc.,* **2013**, *135*, 1558. In reactivity

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of fluoroorganic compounds, see: Understanding organofluorine chemistry. An introduction to the C-F bond. O'Hagan, D. *Chem. Soc. Rev*. **2008**, *37*, 308.

[40] Hybridization Trends for Main Group Elements and Expanding the Bent's Rule Beyond Carbon: More than Electronegativity. Alabugin, I. V.; Bresch S.; Manoharan, M. *J. Phys. Chem. A* **2014**, *118*, 3663– 3677.

[41] Upconversion of Reductants. M. A. Syroeshkin, F. Kuriakose, E. A. Saverina, V. A. Timofeeva, M. P. Egorov, I. V. Alabugin. *Angew. Chem. Int. Ed.,* **2018**, *57,* https://doi.org/10.1002/anie.201807247.

[42] Many aromaticity-driven processes follow this logic as well: (a) Benzo[*b*]thiophene Fusion Enhances Local Berepin Aromaticity in Polycyclic Heteroaromatic Compounds. R. E. Messersmith, S. Yadav, M. A. Siegler, H. Ottosson and J. D. Tovar, *J. Org. Chem.*, **2017**, *82*, 13440; (b) The excited state antiaromatic benzene ring: a molecular Mr Hyde? R. Papadakis and H. Ottosson, *Chem. Soc. Rev.*, **2015**, *44*, 6472; (c) Triplet-State Aromaticity of 4*n*π-Electron Monocycles: Analysis of Bifurcation in the π Contribution to the Electron Localization Function. S. Villaume, H. A. Fogarty and H. Ottosson, *ChemPhysChem*, **2008**, *9*, 257; (d) How to Lose a Bond in Two Ways: The Diradical/Zwitterion Dichotomy in Cycloaromatization Reactions. P. W. Peterson, R. K. Mohamed, I. V. Alabugin, *Eur. J. Org. Chem.*, **2013**, *2013*, 2505; (e) The Missing C1−C5 Cycloaromatization Reaction: Triplet State Antiaromaticity Relief and Self-Terminating Photorelease of Formaldehyde for Synthesis of Fulvenes from Enynes. R. K. Mohamed, S. Mondal, K. Jorner, T. F. Delgado, V. V. Lobodin, H. Ottosson, and I. V. Alabugin, *J. Am. Chem. Soc.*, **2015**, *137*, 15441; (f) Synchronized Aromaticity as an Enthalpic Driving Force for the Aromatic Cope Rearrangement. D. J. Babinski, X. Bao, M. El Arba, B. Chen, D. A. Hrovat, W. T. Borden and D. E. Frantz, *J. Am. Chem. Soc.*, **2012**, *134*, 16139.

[43] A CO_2 Cloak for the Cyanide Dagger. Alabugin, I. V.; Mohamed, R. *Science*, **2014***, 344*, 45-46.

[44] This delocalization is a π-analogue of the n→σ*CO delocalization involved in the anomeric effect: 21e and Stereoelectronic Interactions as a Probe for the Existence of the α-Effect. E. Juaristi, G. P. Gomes, A. O. Terent'ev, R. Notario, I. V. Alabugin *J. Amer. Chem. Soc.*, **2017**, *139*, 10799–10813.

[45] J.E. Leffler and E. Grunwald, Rates and Equilibria of Organic Reactions, Wiley, **1963** (Dover reprint)

[46] For an example of substituent effects on the σ-radicals, see: Ortho Effect in the Bergman Cyclization: Electronic and Steric Effects in Hydrogen Abstraction by 1-Substituted Naphthalene 5,8-Diradicals.Pickard IV, F. C.; Shepherd, R. L.; Gillis, A. E.; Dunn, M. E.; Feldgus, S.; Kirschner, K. N.; Shields, G C.; Manoharan, M.; Alabugin I. V. *J. Phys. Chem. A,* **2006**, *110*, 2517-2526.

[47] Stereoelectronic Chameleons: The Donor-Acceptor Dichotomy of Functional Groups. Vatsadze, S. Z.; Loginova, Y. D.; Gomes, G.; Alabugin, I. V. *Chem. Eur. J.,* **2017**, *23*, 3225-3245.

[48] Stereoelectronic Effects and General Trends in Hyperconjugative Acceptor Ability of σ Bonds. Alabugin I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175-3185.

[49] For a dramatic effect of 2c,3e-stabilization on a radical fragmentation, see: Design of Leaving Groups in Radical C-C Fragmentations: Through-Bond 2c-3e Interactions in Self-Terminating Radical Cascades. Mondal, S.; Gold, B.; Mohamed, R. K.; Alabugin, I. V. *Chem. Eur. J.,* **2014**, *20*, 8664-8669. Alkenes as Alkyne Equivalents in Radical Cascades Terminated by Fragmentations: Overcoming Stereoelectronic Restrictions on Ring Expansions for the Preparation of Expanded Polyaromatics. Mohamed, R.; Mondal, S.; Gold, B.; Evoniuk, C. J.; Banerjee, T.; Hanson, K.; Alabugin, I. V. *J. Am. Chem. Soc.*, **2015**, *137*, 6335-6349.

[50] Thermodynamic and Strain Effects in the Competition Between 5-Exo-dig and 6-Endo-Dig Cyclizations of Vinyl and Aryl Radicals. Alabugin I.V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127*, 12583-12594. 5-Endo-dig Cyclizations – the "Poor Cousins" of the Radical Cyclization Family. Alabugin I.V.; Manoharan, M. *J. Am. Chem. Soc.* **2005**, *127,* 9534-9545.

[51] Factors Affecting the Relative and Absolute Rates of β-Scission of Alkoxythiocarbonyl Radicals and Alkoxycarbonyl Radicals. Coote, M. L.; Easton, C. J.; Zard, S. Z. *J. Org. Chem.* **2006**, *71*, 4996–4999.

[52] For example: (a) In Search of Efficient 5-Endo-dig Cyclization of a Carbon-Centered Radical: 40 Years from a Prediction to Another Success for the Baldwin Rules. Alabugin, I. V.; Timokhin, V. I.; Abrams, J. N.; Manoharan, M.; Ghiviriga, I., Abrams, R. *J. Am. Chem. Soc.*, **2008**, *130*, 10984-10995. (b) Silver-catalyzed stereoselective aminosulfonylation of alkynes. Y. Ning, Q. Ji, P. Liao, E. A. Anderson, X. Bi, *Angew. Chem. Int. Ed*. **2017**, *56*, 13805–13808.

[53] Convenient, Ambient Temperature Generation of Sulfonyl Radicals for Addition to Alkynes. Gilmore, K.; Gold, B.; Clark, R.; Alabugin, I. V. *Aust. J. Chem.,* **2013**, *66*, 336–340.

[54] Chemistry of Acyl Radicals. Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070.

[55] (a) Synthesis of sulfonated naphthols *via* C-H bond functionalization with the insertion of sulfur dioxide. Zhou, K.; Chen, M.; Yao, L.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 371–375. (b) Recent advances in the sulfonylation of C-H bonds with the insertion of sulfur dioxide. Qiu, G.; Zhou, K.; Wu, J. *Chem. Commun.* **2018**, *54*, 12561–12569.