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CO2 or SO2: Should It Stay or Should It Go

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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 substituent stereoelectronic effects. 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]

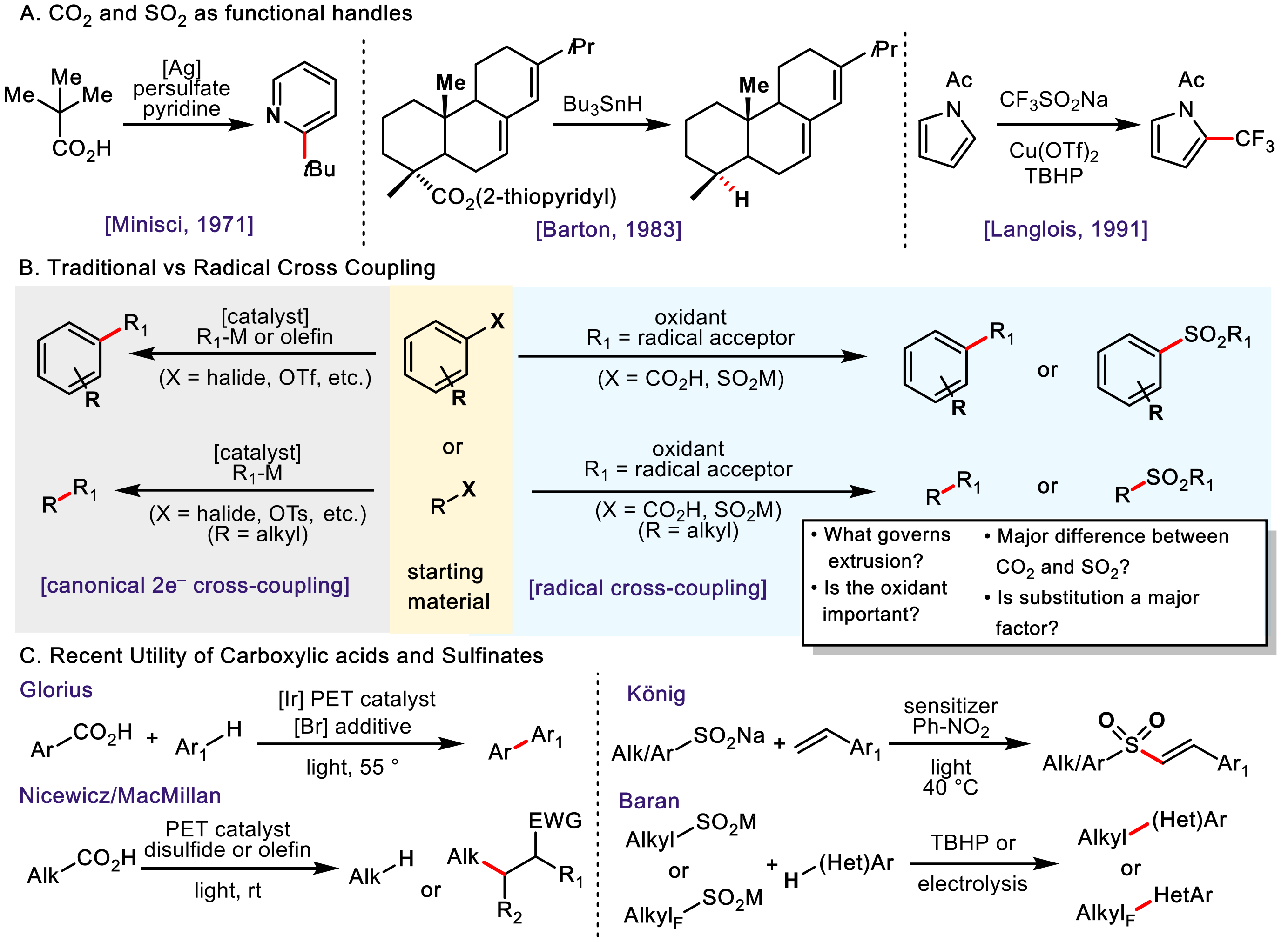


Figure 1: (A) Historic examples of utilizing carboxylic acids and sulfinates as synthetic handles. (B) Traditional cross-coupling compared to decarboxylative and desulfonylative radical cross-coupling. (C) Selected literature reports of (photo)oxidative coupling reactions with aryl and alkyl carboxylates 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 TS of interest. Natural Bond Orbital[20] (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. DLPNO-CCSD(T)[21] calculations (with Tight PNO) were performed with *ORCA 4.0*[22], with the aug-cc-pVTZ basis set for all atoms. RIJCOSX was used to accelerate the HF steps during the SCF evaluation. Three-dimensional structures and orbital plots were produced with CYLView 1.0.1,[23] Chemcraft 1.8[24] and UCSF Chimera.[25]

Results:

First, the trends for BDEs of breaking C-C or C-S bonds over the broad range of neutral carboxylic and sulfinic acids will be compared. 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.

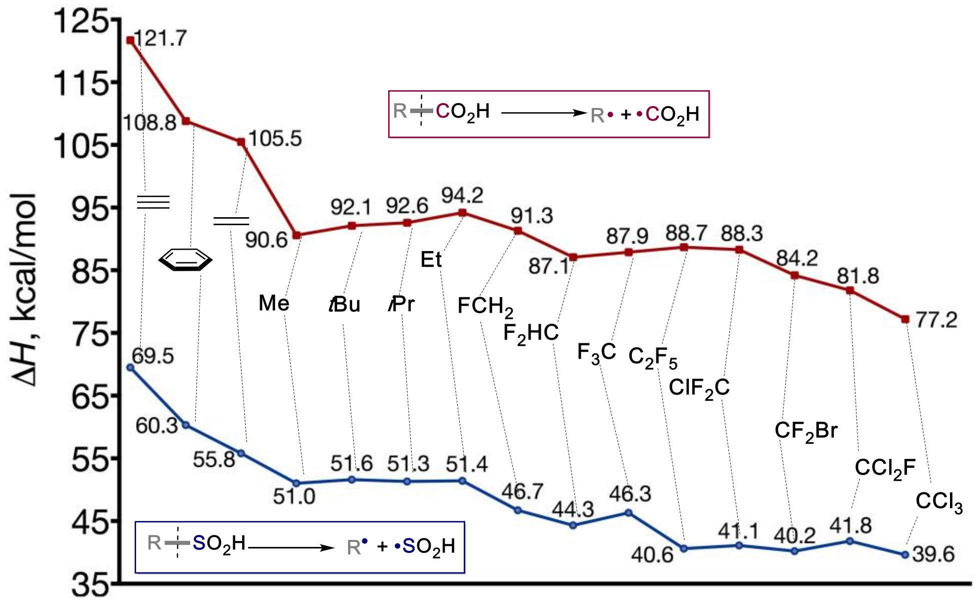


Figure 2: Bond Dissociation Energies (BDEs, as ΔH energies) for C-X (X = C or S) scission in neutral carboxylic and sulfinic acids.

However, the situation changes dramatically 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 is also 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.

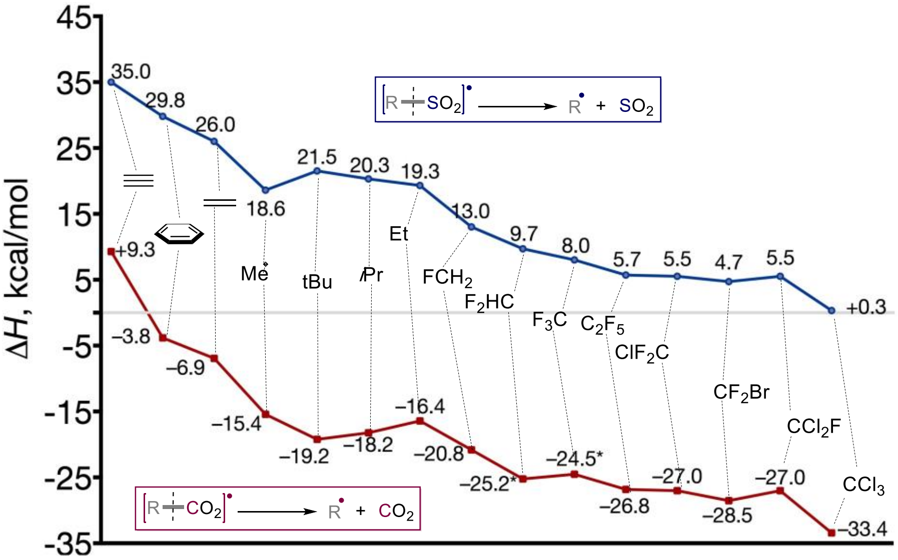


Figure 3: Comparison of the enthalpies for the C-S and C-C bond scissions in the radicals formed from carboxylic and sulfinic acids. The data are organized by decreasing ΔH for the C-S scission.

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.[26] 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.

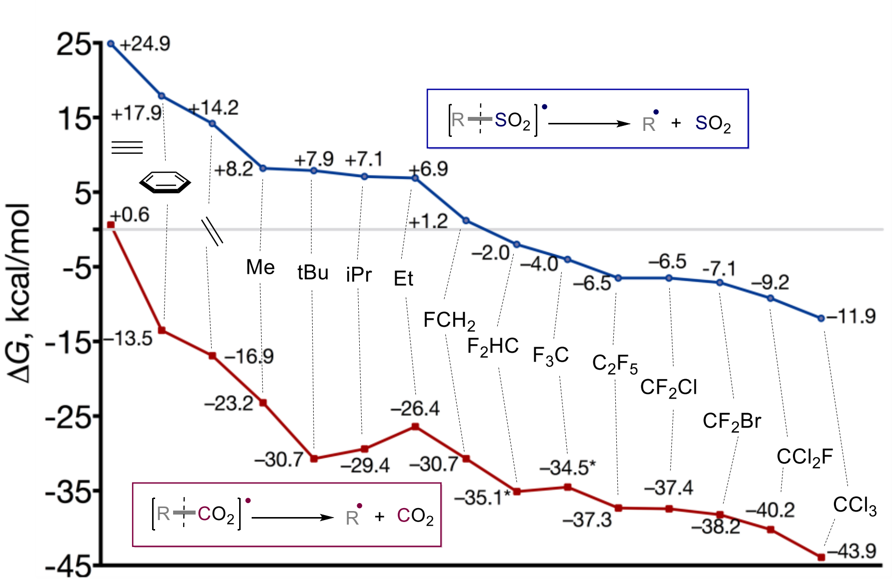


Figure 4. Comparison of the Gibbs energies for the C-S and C-C bond scissions in the radicals formed from carboxylic and sulfinic acids. The data are organized by decreasing ΔG for the C-S scission.

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).

CCSD(T) corrections to the DFT results:

In order to evaluate the performance of the chosen DFT method, it has been compared with the results of DPLNO-CCSD(T) calculations. DLPNO-CCSD(T) can recover 99.9% of the CCSD(T) energy at a fraction of its computational cost.[27] The aug-cc-pVTZ basis set was chosen as a sufficiently large one to cover the orbitals involved in the systems of interest, particularly the ones for sulfur. The DLPNO-CCSD(T) (labelled as simply CCSD(T) in Figure 5) data suggest that M06-2X(D3)/6-311++G(d,p) (labelled as DFT in Figure 5) systematically overestimates endergonicity of the fragmentation. For fluorinated radicals, the CCSD(T) correction reaches up to 7.5 kcal/mol, with an average of 6.1 kcal/mol. Understanding of DFT's overestimation will be important for the formation of partially fluorinated radicals and other borderline cases (vide infra).

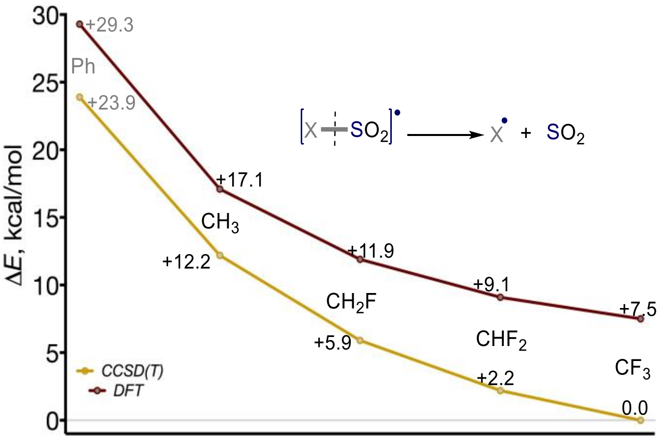


Figure 5: Comparison between UM06-2X(D3) and DLPNO-CCSD(T) reaction electronic energies for C-S scissions for fluorinated systems.

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 where even 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, product stability is only revealing when delocalization effects of substituents in the starting material are relatively small, *e.g.*, the C-H BDEs (BDE (C-H): Me-H > t-Bu-H) for the transformation of closed-shell molecules to radicals. Such approximation is reasonable because delocalization effects are often more important for species that lack a stable octet.[28] However, it 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 6).[29,30]

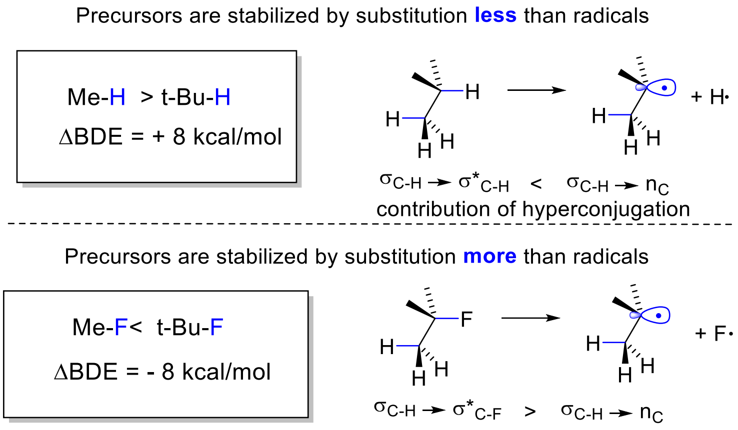


Figure 6: Contrasting effects of alkyl substitution on BDEs for C-H, and C-F bonds. The BDEs increase for the more substituted alkyl fluorides but decrease in respective alkanes

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 that go against the C-centered 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.[31] 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.[32] However, the analysis of McBride and Merrill demonstrated that the benzoyloxyl radical has a $^2B_2$ ground state with the symmetrical spin distribution.[33]

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.[34] However, communication of the radical center with substituent R in the RSO_2 species is inefficient due to the lack of spin density at the central carbon.[35]

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 radical centers can communicate with the substituent orbitals via vicinal conjugation or hyperconjugation (Figure 7).[28]

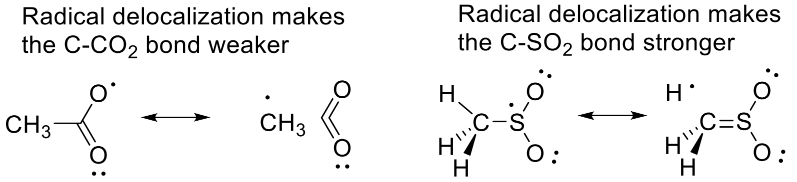


Figure 7: The distribution of spin density in RCO_2 and RSO_2 radicals and resonance structures explaining the contrasting substituent effects at the R-CO_2 and R-SO_2 BDEs (only electrons directly participating in radical delocalization are shown in the resonance structures)

Furthermore, the radical center in the RSO_2 radical is more stabilized by conjugation (3c-5e). Loss of such interaction in the product may 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!*

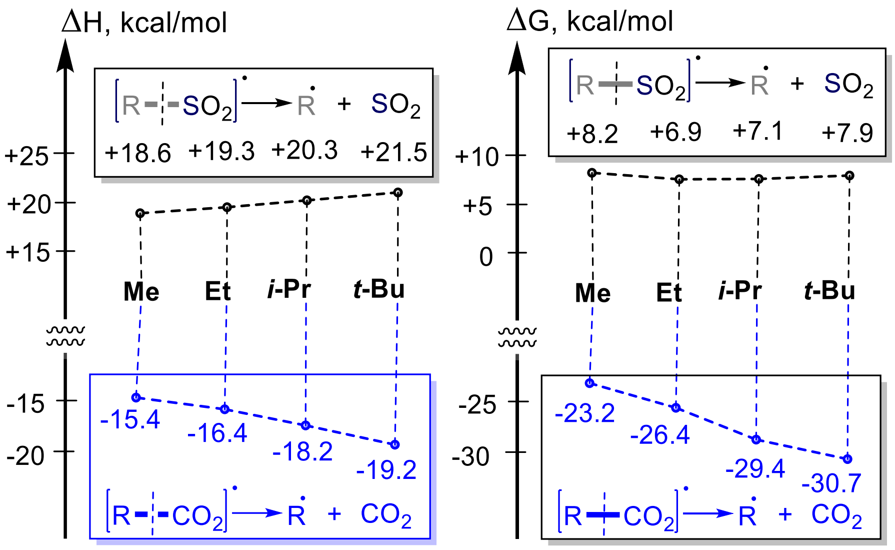


Figure 8: Enthalpies (left) and free energies (right) for the C-S bond fragmentations in the alkyl-SO_2 radicals are insensitive to the structure of the alkyl group whereas the fragmentation of C-C bonds in alkyl-CO_2 radicals are more favorable for the formation of more substituted radicals R.

So 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 7. 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. As the result, 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.[36] These hybridization effects[37,38] 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.[39] 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[37,40] in reactivity in organic[41] and main group[42] compounds.

Figure 9 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.[42] 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. The C-S bond scission can partially alleviate this "hybridization frustration", explaining why such scission is assisted by the fluorine substitution.

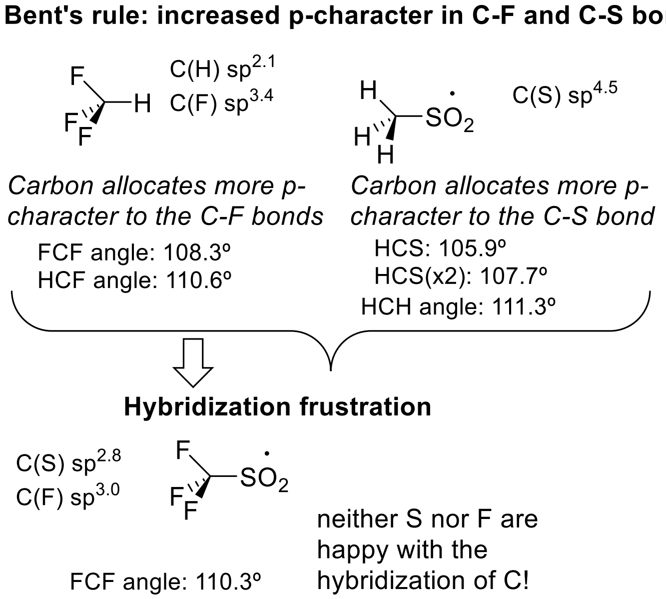


Figure 9: Illustration of "hybridization frustration" in the CF_3SO_2 radical. Average NBO hybridization from the α- and β-spin NBOs are given

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.[43,44] 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 10. 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[45] as the result of the greater strengths of the C=O bonds and the efficiency of the $n_{O1}\rightarrow\pi^*_{C2O3}$ resonance.[46] 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.

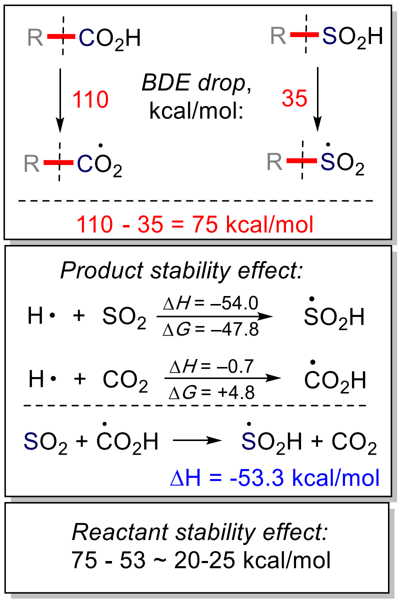


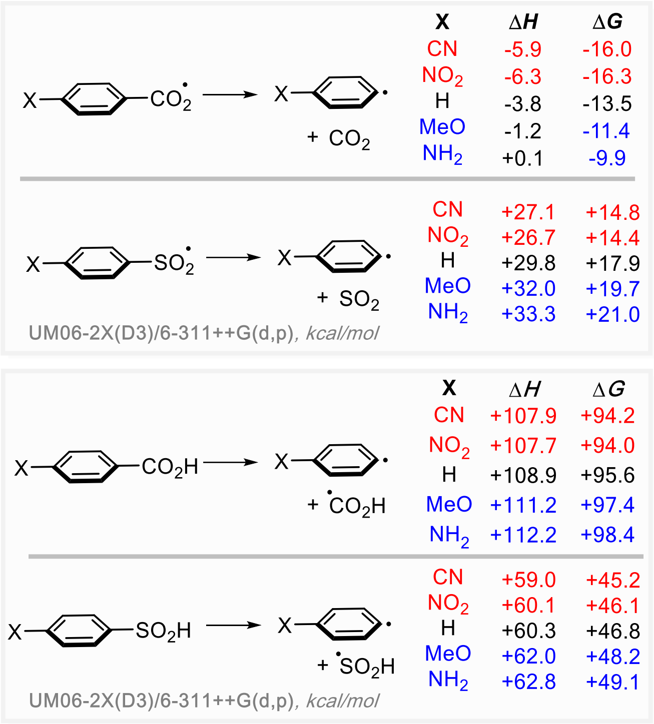
Figure 10: The dramatic difference in the radical effect at the C-C and C-S bond scissions in the R-XO2 systems

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 11). These systems are convenient since they help to separate the effects of delocalization from the effects of hybridization.



X	ΔH	ΔG
CN	-5.9	-16.0
NO_2	-6.3	-16.3
H	-3.8	-13.5
MeO	-1.2	-11.4
NH_2	+0.1	-9.9

X	ΔH	ΔG
CN	+27.1	+14.8
NO_2	+26.7	+14.4
H	+29.8	+17.9
MeO	+32.0	+19.7
NH_2	+33.3	+21.0

X	ΔH	ΔG
CN	+107.9	+94.2
NO_2	+107.7	+94.0
H	+108.9	+95.6
MeO	+111.2	+97.4
NH_2	+112.2	+98.4

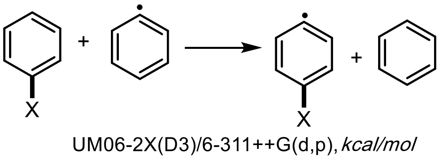
X	ΔH	ΔG
CN	+59.0	+45.2
NO_2	+60.1	+46.1
H	+60.3	+46.8
MeO	+62.0	+48.2
NH_2	+62.8	+49.1

Figure 11: 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[47]).

The calculated energies in Figure 11 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, the *net* substituent effects on the CO_2 and SO_2 loss are remarkably similar. For loss of CO_2, the donor NH_2 group increases BDE by 3.9 kcal/mol whereas the acceptor nitro group decreases BDE by (up to) 2.5 kcal/mol. The effects of the same groups (-3.5 kcal/mol and +2.1 kcal/mol) on 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 σ_{C-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.



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 12: 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 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,[29] 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.

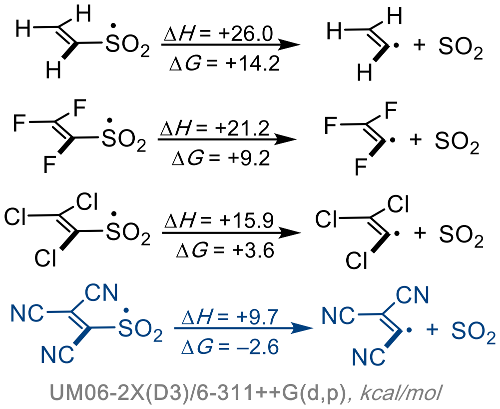


Figure 13: Substituent effects on the BDEs of alkene sulfonyl precursors

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.

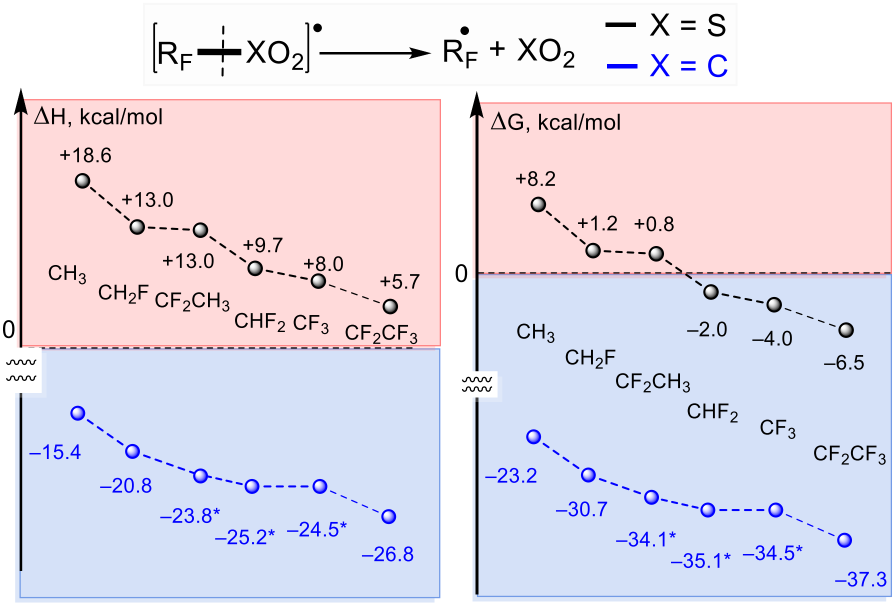
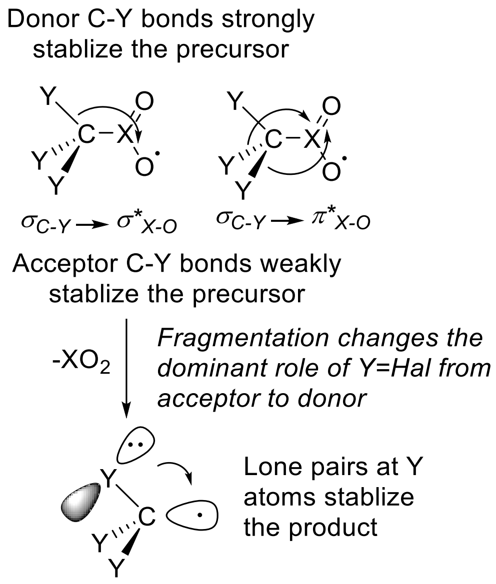


Figure 14: Enthalpies and free energies for the R_F-XO_2 (X = S, top, or C, bottom) bond fragmentations in the fluoroalkyl-XO_2 radicals.

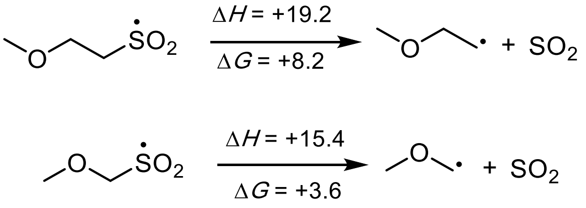
Although the exact position of the threshold is affected by the computational uncertainty of the current methods, the M06-2x data do agree with the scarcity of the literature reports describing formation of the CH_2F radical via this approach.

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[48] 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[49] that 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.



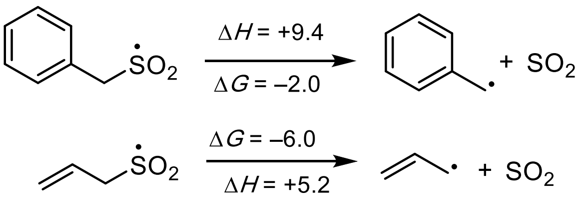
Scheme 1. The chameleonic change of the halogen substituents from $\sigma_{C\text{-}Y}$ acceptors to n_Y donors in the process of C-X bond fragmentations

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[50] in the $MeOCH_2$ radical.



Scheme 2. Evaluation of systems that invoke anomeric stabilization

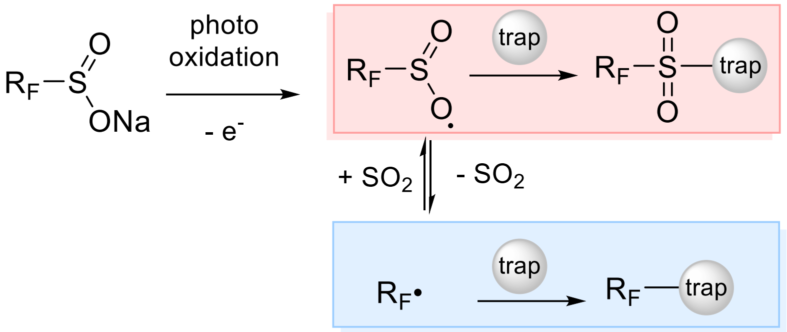
Stabilization of the C-centered radical product by an adjacent π-system renders the SO_2-extrusion exergonic. In agreement with the greater stabilization of radical center by an alkene,[51] the formation of allyl radical is slightly more favorable than the formation of benzylic radical (-6 vs. -2 kcal/mol, Scheme 3).

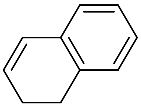
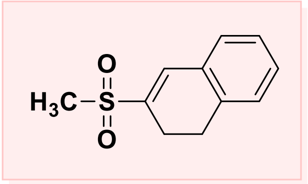
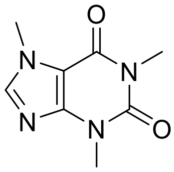
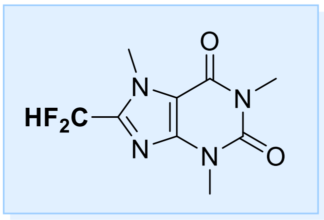
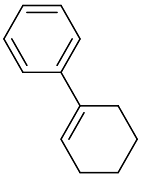
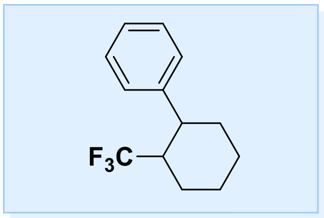


Scheme 3. Evaluation of systems that invoke benzylic and allylic stabilization

Experimental verification of CF_2H radical formation in photooxidation of CF_2SO_2Na.

In order to validate the computational prognosis for the bond fragmentations in the fluoroalkyl-SO_2 radicals, we performed a single-electron photo-oxidations of the respective sodium sulfinate salts (see the SI). Chemical trapping of the generated radicals can occur before or after extrusion of SO_2. In either scenario, it leads to stable cross-coupled products. As already reported, CH_3-SO_2Na does not extrude SO_2 upon single-electron photo-oxidation. The respective sulfonyl radical is trapped and forms the respective sulfonylated adduct (Entry 1, Scheme 4).[15] As suggested by the calculations, we found that CF_2H-SO_2Na loses SO_2 upon photo-oxidation and solely forms the desulfinylated adduct (Entry 2, Scheme 4). The single-electron photo-oxidation of CF_3-SO_2Na was already reported earlier to lead to the respective desulfinylated coupling products (Entry 3, Scheme 4).[52]

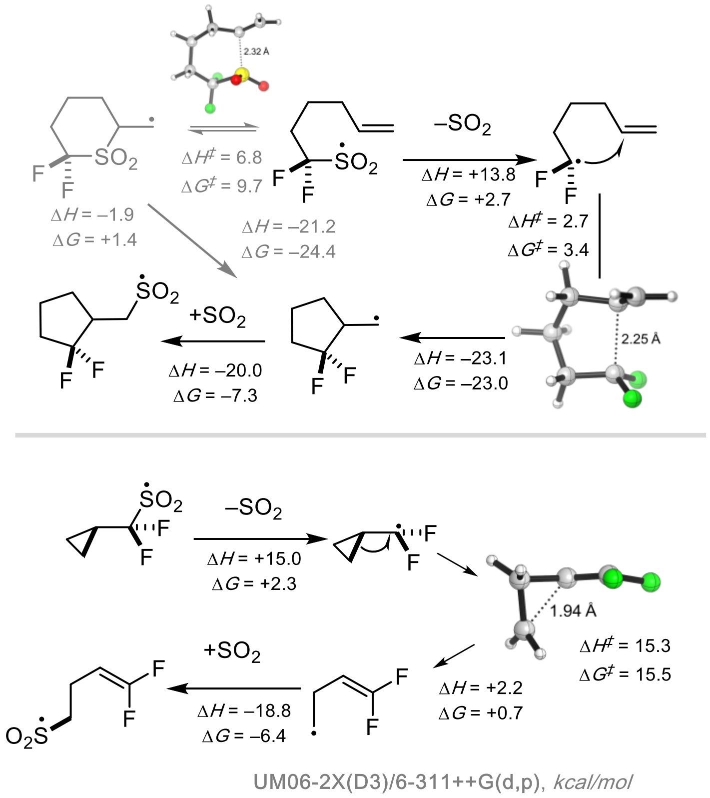


Entry	R_F-SO_2Na	Trap	Product
1	CH_3-SO_2Na		
2	CF_2H-SO_2Na		
3	CF_3-SO_2Na		

Scheme 4. Experimental studies of alkyl vs. fluoroalkyl RSO_2 systems

Implications for the design of isomerization cascades

The difference in the relative exergonicities of alkyl and fluoroalkyl radical formation via the RXO_2 fragmentation may be possible to exploit for the design of isomerization cascades similar to those shown in Scheme 5.



Scheme 5. 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 SO2), 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 is likely to 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,[53] the search for new approaches to their generations continues.[54] 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.[55,56]

Supporting Information

Comparison of computational methods, additional details of NBO analysis, as well as geometries and energies for all calculated structures reported in this work are available in the SI. Experimental conditions for the formation and trapping of CF_2H radicals by photooxidation of CF_2HSO_2Na. This material is available free of charge via the Internet at http://pubs.acs.org

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