Reflex Carbocation Release from Covalent Molecules by Endogenous Free Radicals

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Supporting Information

ABSTRACT: Carbocations are pervasive in contemporary organic synthesis, so new and innocuous methods of making them are always desirable. A theoretical approach revealed that compounds in which radical generation takes place may release carbocations advantageously. The radical types and molecular substructures that promote this effect were identified. The best substructures were found to be 1,3-dicarbonyl compounds, particularly those based on the Meldrum’s acid theme. Sulfate esters and dithiane rings could also be employed. Radicals generated on oxygen atoms or ethyne units were particularly effective. For these species, carbocation release could be reflex, that is, concurrent with radical generation. Only small radical enhancements were observed for release of lithium cations because of the ionic character of most of the precursors. Ethyne units could be incorporated as spacers between the radical center and the site of carbocation generation. Moreover, the enhancement was transmitted down polyethyne chains of at least six units.

INTRODUCTION

In a 1974 review, Hayon and Simic drew attention to the greater propensity of certain free radicals to deprotonate compared with parent compounds.1 Theoretical studies have since confirmed the reality of this enhanced acidity phenomenon.2,3 The importance of the effect as a key step in processes such as base-promoted homolytic aromatic substitution reactions4−6 and certain one-electron redox transformations of Coenzyme A esters7−9 has also been pointed out. Recently, my group demonstrated that suitably sited radical centers enhanced the acidity not only of carboxylic acids but also of sulfinic and sulfonic acids. The acidity of other proton donor molecules, particularly 1,3-dicarbonyl compounds, could also be formidably increased by similar means.10 The label “RED-shift” (for radical enhanced dissociation) was coined as a short and handy acronym to refer to the phenomenon. Radicals centered on C-, N-, and O-atoms induced RED-shifts, provided they were sufficiently close to the acid group and appropriately oriented. Huge enhancements were induced by alkoxyl radical centers and by ethynyl radical units such that 1,3-dicarbonyl compounds connected to them became carbon-based superacids.11 Microhydration studies had revealed that acids with negative pKₐ values, that is, pKₐ in the range of mineral acids, spontaneously dissociated on association with only a few (four or five) water molecules.12 The authenticity of the computed RED-shifts of bicarbonate,13 carboxyl, carboxyethynyl, and hydroperoxyl radicals was substantiated by computations of their microhydration behavior.14

The large magnitudes of many of the deprotonation enhancements suggested the intriguing possibility that radical centers might also induce dissociation of neutral species with release of a carbocation instead of a proton.

The process is generalized in Scheme 1 where the model compound 1 consists of a potential radical center X attached to a substructure A, capable of supporting a negative (−ve) charge, connected with a potential carbocation +CR₃. The corresponding radical 4 is then an intermediate for which heterolytic dissociation to the carbocation and radical anion could be significantly enhanced. A sufficiently large enhancement might lead to spontaneous release of the cation at the moment of radical generation. Carbocation generation for Friedel–Crafts and other preparative processes usually requires the use of strong and corrosive Lewis or Brønsted acids. A likely advantage of this radical-stimulated approach would be...
that carbanions could be generated by the "soft" initiation methods usually applied for radicals, that is, heat, photoredox catalysis, or UV-vis irradiation.

Computational methods were employed to examine the basic premise of Scheme 1 applied to different X–A structures and with a variety of cation types. It was found that significant enhancements were indeed predicted for release of thermodynamically stabilized cations. This paper describes a method of assessing the magnitude of the effect and an investigation of what structural features in the precursors are needed for the phenomenon to occur.

RESULTS AND DISCUSSION

Quantification of Enhancement of Cation Production from Radical Precursors. Most radical intermediates are short-lived, so experimental methods for determination of the dynamics of their heterolytic cation generation would inevitably be problematic. A theoretical approach was therefore used to map the outlines of the structural and energetic constraints on the process. A computational method that would be applicable to free radicals and would be easy to apply was sought.

A previous study of 12 radical reaction types compared results from the high-level composite ab initio G4 method,15 with those obtained with 23 different density functional theory (DFT) functionals (plus the MP2 ab initio method).13 The CAM-B3LYP functional16 was found to perform best with radical species and gave lowest mean absolute deviations (MADs). A second benchmarking study was carried out, this time including second row elements, specifically sulfur.17 Free energies were obtained for 9 diverse radical reactions with 31 different DFT functionals and compared with both G4 and the extrapolated complete basis limit of a series of CCSD(T)18–20 calculations. Comparisons of the MADs from both high-level methods indicated that M05,21 PBE0 (PBE1PBE),22 and LC-oPBE23 were the most accurate and that CAM-B3LYP also gave very satisfactory results. The CAM-B3LYP and the PBE0 functionals were chosen for this study, and full optimizations were carried out with the 6-311+G(2d,p) basis set. Solvent effects were modeled with radii and non-electrostatic terms from Truhlar and co-workers’ solvent density (SMD) solvation model and/or with the conductor-like polarizable continuum model (CPCM) model.24

The ease with which neutral radical 4 ionizes to carboxylation 3 will certainly depend on the stabilization of the accompanying radical anion 5. The free energies for ‘CR₃ production from a radical (4) (ΔG°ₕ) and from the corresponding model (1) (ΔG°ₘ) in which the unpaired electron (upe) had been replaced by an H-atom were computed for sets of representative molecules. The difference in these quantities, ΔΔG°, afforded a useful measure of the enhancement

\[ \Delta \Delta G^° = \Delta G^°_M - \Delta G^°_R \]  

(1)

Positive ΔΔG° values indicate radical enhancement of cation release, whereas negative values would correspond to radical inhibition of cation release.

Search for Suitable Radical Platforms. Heterolytic generation of ‘CR₃ carbanions from 1 will release the same radical anion ‘X–A~ (5) as that when an acid radical ‘X–A~–H deprotonates. As a starting point, therefore, X–A units that had been found to provide large deprotonation RED-shifts¹¹ were chosen for study. Scheme 2 displays the set selected to investigate release of the t-butyl-cation. This included carbonate ester radical 6, propiolate ester radical 9, sulfonate ester radical 10, peroxyl radical 11, the 5-methylenemeldrum’s acid 12, 5-oxyl-Meldrum’s acid 13 and 5-ethynyl-Meldrum’s acid 14 derivatives [5-(t-tert-buty1)-5-hydroxy-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives], as well as the 2-ethyl-1,3-dithiane derivative 15. The computed enthalpies ΔH°ₕ and free energies ΔG°ₕ for Me₃C⁺ release are in Table 1, along with the enhancement factors ΔΔG°.

Table 1. Energetics of Release of the t-Butyl Cation in Water as Solvent

| Precursor | Radical Pre | Ions |
|-----------|-------------|------|
| HO–O–CMe₃ | 6           | O–O  |
| 9H        | 9           | O–O  |
| 10H       | 10          | O–O  |
| 11H       | 11          | O–O  |
| 12H       | 12          | O–O  |
| 13H       | 13          | O–O  |
| 14H       | 14          | O–O  |
| 15H       | 15          | O–O  |

Table 2. Release of tert-Butyl Cation from Selected Radical Platforms

| Model Precursor | Radical Precursor | Ions |
|-----------------|------------------|------|
| HO–O–CMe₃       | *O–O–CMe₃        | O–O  |
| 6               | 6                | O–O  |
| 9               | 9                | O–O  |
| 10              | 10               | O–O  |
| 11              | 11               | O–O  |
| 12              | 12               | O–O  |
| 13              | 13               | O–O  |
| 14              | 14               | O–O  |
| 15              | 15               | O–O  |

Energies in kcal/mol. b(i) CAM-B3LYP/6-311+G(2d,p); (ii) BPE1PBE/6-311+G(2d,p).
Modest enhancements (3–13 kcal/mol) were calculated for heterolytic generation of Me₂C⁺ from carbonate radical 6, propiolate radical 9, hydrogen sulfate radical 10, peroxyl radical 11, and 5-methylenyl-Meldrum’s acid 12. However, four of these ionizations were endenthalpic and endergonic and so would not be practicable under mild conditions. t-Butyl cation release from the 2-ethyl-1,3-dithiane radical 15 showed a very large enhancement (47.8 kcal/mol) relative to the model, but again the process was too energetically uphill for it to occur spontaneously.

On the other hand, the releases of Me₂C⁺ by the 5-oxyl-Meldrum’s radical 13 and by 5-ethynyl-Meldrum’s radical 14 were strongly exergonic, and large enhancements (38.0 and 33.4 kcal/mol) were predicted. The Meldrum platform appeared to be the most promising as a core structure for radical-to-cation transformations. In accord with expectation, these results also indicated that significant thermodynamic stabilization of the released cation would be needed for spontaneous release.

**Investigation of Carbocation Suitability.** In view of the favorable results obtained for Me₂C⁺ release, Meldrum’s linked radicals were chosen as platforms to study release of a range of cations with differing thermodynamic stabilities. The computed energies and enhancement factors for release of some primary, allyl, benzyl, and tertiary carbocations by 5-oxyl-Meldrum’s 16 (process H1) and 5-ethynyl-Meldrum’s 17 (process H2) are listed in Table 2. Interestingly, the table demonstrates that the radical center enhances cation release in every case. No examples of radical inhibition of cation release were discovered.

Although allyl and benzyl cation releases (entries 4 and 6) were strongly enhanced by the radical center, both were endergonic and so experimentally impracticable. Introduction of the electron-donating MeO group led to exergonic processes for release of the primary methoxymethyl cation (both radical platforms; entries 2 and 3). Similarly, release of the 1-methoxymethyl and 4-methoxybenzyl cations (entries 5 and 8) was also exergonic. As might be expected, introduction of the MeO group to the t-butyl cation led to very favorable energetics (entries 9 and 10). The optimization for structure 16 (CR₃ = Me₂(MeO)C⁺) led directly to the dissociation products radical anion 13⁻ and carboxylation Me₂(MeO)C⁺. This implied that generation of radical 16 (CR₃ = Me₂(MeO)-C⁺) (and probably 17 (CR₃ = Me₂(MeO)C⁺) as well) would lead to concerted (spontaneous) carboxylation formation.

**Effect of Solvent on Carbocation Release.** The difference in solvation between the neutral radical precursors and the charged products was expected to have a considerable impact on the heterolytic cleavage. The magnitude of solvation effects was probed for two representative processes. First, release of the primary MeOCH₂⁺ cation from the carbonate radical precursor 18 (process H3 in Table 3) (together with the corresponding model) was examined. Second, the release of the t-butyl cation from the 5-oxyl-Meldrum’s radical 13 (and model) (process H4 in Table 3) was studied. The SMD method, on the basis of the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent, was employed. The free energies for the two processes, for solvents ranging from water to n-heptane, as well as the enhancement factors relative to the nonradical models, are recorded in Table 3.

The free energy for MeOCH₂⁺ release from radical 18 increased by nearly 70 kcal/mol (less favorable) as the polarity of the solvent decreased from water to n-heptane. No solvent was found in which this process would be exergonic. However, although the free energy of Me₂C⁺ release from radical 13 increased by about 60 kcal/mol through the series of solvents, the reaction was favorably exergonic in methanol, dimethyl sulfoxide (DMSO), and acetonitrile, as well as in water. The enhancement factors ΔΔG° for both processes H3 and H4 were positive and very substantial for H4. Interestingly, these enhancements changed by only a small amount as the solvent was varied. Not unexpectedly therefore, the change in solvation on going from the neutral model with charged products to the

![Diagram](https://example.com/diagram.png)

**Table 2. Energetics of Release of Diverse Carbocations in Water as Solvent**

| entry | process | RCR₃⁺ | ΔH° | ΔG° | ΔΔG° |
|-------|---------|-------|-----|-----|------|
| 1     | H2      | FCH₃⁺ | 44.0 | 32.3 | 33.5 |
| 2     | H2      | MeOCH₂⁺ | 1.6  | −10.1 | 33.1 |
| 3     | H1      | MeOCH₂⁺ | 2.6  | −8.7  | 47.3 |
| 4     | H1      | CH₂═CHCH₃⁺ | 23.3 | 11.1  | 43.2 |
| 5     | H1      | MeOCH₂=CHCH₂⁺ | −5.4 | −16.1 | 43.3 |
| 6     | H1      | PhCH₂⁺ | 14.7 | 2.6   | 42.6 |
| 7     | H1      | 4-MeOC₆H₆CH₂⁺ | 13.0 | 1.3   | 43.2 |
| 8     | H2      | 4-MeOC₆H₆CH₂⁺ | 6.0  | −5.6  | 33.3 |
| 9     | H₁ b    | Me₂(MeO)C⁺ b | b    | b     | b    |
| 10    | H₂      | Me₂(MeO)C⁺ | −27.3 | −42.1 | 33.3 |

a Energies in kcal/mol; DFT with CAM-B3LYP/6-311+G(2d,p).

b Dissociated straight to 13⁻ and Me₂(MeO)C⁺.

**Table 3. Effect of Solvents on Heterolytic Cation Release**

| solvent | Δδ⁺ | ΔΔG° | ΔG° | ΔΔG° |
|---------|-----|------|-----|------|
| H₂O     | 23.5 | −19.0 | 38.0 | 0.112 |
| MeOH    | 14.3 | −15.9 | 37.0 | 0.115 |
| DMSO    | 12.9 | −16.1 | 36.5 | 0.096 |
| MeCN    | 11.9 | −11.6 | 40.3 | 0.097 |
| Me₂C-≡O | 9.8  | 20.3  | 15.9 |
| THF     | 9.5  | 31.5  | 16.3 | 0.090 |
| n-C₃H₇ | 7.4  | 77.4  | 17.1 | 0.078 |

Δδ⁺ is the electronic solvation parameter in kcal/mol, ΔΔG° is the change in free energy of cation formation in kcal/mol, and ΔG° is the free energy of cation formation in kcal/mol.
neutral radical with charged products remained fairly constant, irrespective of solvent properties. Water was unquestionably the solvent of choice for advantageous energetics. However, methanol or acetonitrile could be used, with little or no diminution in enhancement, for covalent precursors insoluble in water.

The enhancement of ionic dissociation of the 5-oxyl-Meldrum’s radical (13) was accompanied by a lengthening of the bond from its CMe$_3$ group to its Meldrum’s unit compared to that in the nonradical model (13H). Furthermore, there was a trend toward greater bond extension $\Delta r$(CC) in Table 3] as the exergonicity increased for the more polar solvents (see Table 3). For the carbonate series (18) the C−O bond from the MeOCH$_2$ group to the carbonate unit was also longer in the radical than in the model but the extension, 0.011−0.015 Å, depending on solvent, was much smaller.

**Release of Acylium and Lithium Cations.** Radical enhancement of release of acylium and benzoylium cations was also studied for the set of precursor radicals (and corresponding models) shown in Scheme 3.

| Heterolysis | $\Delta H^\circ_R$ (kcal/mol) | $\Delta G^\circ_R$ (kcal/mol) | $\Delta G^\circ$ (kcal/mol) |
|-------------|------------------------------|-------------------------------|-----------------------------|
| 19a $\rightarrow$ 19a$^-$ + RCO$^+$ | 65.2                          | 52.8                          | 13.2                        |
| 21a $\rightarrow$ 21a$^-$ + RCO$^+$ | 54.5                          | 45.1                          | 19.0                        |
| 21b $\rightarrow$ 21b$^-$ + RCO$^+$ | 57.1                          | 47.3                          | 19.8                        |
| 22a $\rightarrow$ 13$^-$ + RCO$^+$ | 0.9                           | $-$10.7                       | 37.3                        |
| 22b $\rightarrow$ 13$^-$ + RCO$^+$ | 6.2                           | $-$4.5                        | 26.4                        |
| 23a $\rightarrow$ 14$^-$ + RCO$^+$ | $-$9.6                        | $-$21.7                       | 35.4                        |
| 23b $\rightarrow$ 14$^-$ + RCO$^+$ | $-$8.3                        | $-$20.8                       | 35.6                        |

"Energies in kcal/mol; PBE1PBE/6-311+G(2d,p); scrf = SMD-(acetonitrile)."

The computed enthalpies, free energies, and enhancement factors are in Table 4. The 1,5-dihydro-2$H$-pyrrol-2-one unit of 19a was chosen because of the potential resonance stabilization of the anions produced on ionization. A modest enhancement of acylium release from radical 19a was obtained, but the process was impractically endergonic (Table 4). Similarly, although the releases of both PhCO$^+$ and MeCO$^+$ were significantly enhanced for the ethynyl platforms 21a,b, the energetics were again very unfavorable. However, acylium release was exergonic from both 5-oxyl-Meldrum’s 22a and 5-ethynyl-Meldrum’s 23a precursors and large enhancement factors were observed for the radicals. Release of PhCO$^+$ was also favorable for both 22b and 23b.

Because of the importance of lithium ions in battery technology, release of this alkali metal cation from carbonate 24, carboxyethynyl 25, ethynyl 26, and Meldrum’s radical-containing platforms was also examined (Scheme 4). The computed energies are in Table 5. For all of these platforms, the heterolyses were endergonic. The smallness of the enhancement factors obtained for Li$^+$ release from the radical forms of the carbonate and carboxyethynyl species (Table 5) can be attributed to their salt-like character. The calculated long C−Li bond (2.18 Å) in model-lithiated Meldrum’s acid 27H, together with the large positive charge on Li (0.88), indicated it was virtually an ionic compound. The C−Li bond was slightly shorter (2.07 Å) in the radical 27 and the charge on Li was smaller (0.65), suggesting lower ionic character. In conformity with this, the computed $\Delta \Delta G^\circ$ was actually computed energies are in Table 5.
marginally negative (−3.6). For the ethynyl-Meldrum’s platform, the minimum energy structure of the model had the Li-atom attached to one of the O-atoms and in the optimized radical 28, it was attached to the terminal ethyne C atom. Not only was the process endergonic but virtually no enhancement was found (Table 5).

Influence of Ethyne Radicals and Multiple Ethyne Spacer Units. The cation release process was tolerant of the introduction of the two-carbon ethyne spacer between the upe and the cation (see tables above). The effect of lengthening this spacer by more ethyne units was therefore studied. Small hydrocarbon cages are known to transmit spin density across their centers.25,26 The huge γ-H-atom hyperfine splitting in the electron paramagnetic resonance spectrum of the bicyclo[1.1.1]pent-1-yl radical pointed to its cage as by far the most effective.27,28 This spacer unit was also investigated.

Scheme 5 compares the computed ΔG°M and ΔG°R values and the enhancement factors ΔΔG°, for release of the 2-methoxyprop-2-yl cation but accompanied by CO2 and the C2O radical anion. Not only was the process endergonic but virtually no enhancement from the upe was completely suppressed. On the other hand, with the ethyne spacer, heterolytic dissociation was computed to release the 2-methoxyprop-2-yl cation from carbonate radical, with data for spacer units were added is illustrated in Figure 1.

Because the ethyne spacer was so effective, the result of increasing the number of ethyne spacer units was also explored. Release of the t-butyl cation from Meldrum’s precursor radicals with up to 6 ethyne spacers (14n; n = 1−6) and release of the 2-methoxyprop-2-yl cation from similar precursors with up to 6 ethyne spacers (29n) were examined. Additionally, release of 2-methoxyprop-2-yl cation from the 1,3-dithiane radicals 15n was studied. Finally, release of lithium ions from the ethynyllithium precursors 26n, having up to 7 spacers, was investigated in tetrahydrofuran (THF). The computed free energies are in Tables 6−9 (see also the Supporting Information).

Release of the t-butyl cation from Meldrum’s species 15H-1 and 15-1 was investigated using both the CAM-B3LYP and PBE1PBE methods (Table 6, top two rows). The respectable agreement of the energies obtained demonstrates the comparability of the two methods. The tables show that ΔG°M for all model precursors became less endergonic (or more exergonic) as the length of the polyethyne spacer increased. The dissociations of radicals 14n to Me2CCa became less exergonic as the spacer increased in length, whereas the dissociation of analogous 29n to Me2(MeO)C became little in exergonicity (Tables 6 and 7). Loss of the Me2(MeO)C from dithiane radical 15n became more exergonic as the length of the spacer increased (Table 8), but ΔG°M decreased in parallel such that the enhancement decreased by only a small amount. ΔG°R for loss of Li+ from precursors 26n varied little with spacer length (Table 9). The variation in the ΔΔG° enhancements as the additional spacer units were added is illustrated in Figure 1.

As expected, ΔΔG° decreased for the dissociations of all radical species as the length of the polyethyne spacer chains increased. However, the remarkable result that became apparent was the ability of the spacer chains to transmit the

**Table 7. Energetics for Release of the ‘C(MeO)Me2 Cation (7) from Polyethynyl Meldrum’s Precursors 29n**

| n | ΔG° (model 29Hn) | ΔG° (radical 29n) | ΔΔG° | r(C−C)/Å |
|---|-----------------|-----------------|-------|----------|
| 1 | −8.80           | −42.05          | 33.25 | 1.613    |
| 2 | −11.90          | −46.08          | 34.18 | 1.614    |
| 3 | −13.14          | −46.30          | 33.17 | 1.614    |
| 4 | −14.64          | −46.40          | 31.76 | 1.614    |
| 5 | −16.22          | −47.56          | 31.34 | 1.614    |
| 6 | −15.62          | −45.64          | 30.02 | 1.614    |

*CAM-B3LYP/6-311+G(2d,p) with SMD(water) values in kcal/mol. *r(C−C) is length of the bond from the platform A to the leaving cation in the radicals (*XA-cation).*
Table 8. Energetics for Release of the °C(MeO)Me° Cation from Polyethynyl Dithiane Precursors 15n in Waterb

| n  | ΔG° (model 15Hn) | ΔG° (radical 15n) | ΔΔG° | r(C–C)/Å |
|----|-----------------|------------------|-------|----------|
| 1  | 36.81           | –8.22            | 45.03 | 1.562    |
| 2  | 29.97           | –11.95           | 41.91 | 1.567    |
| 3  | 24.12           | –16.45           | 40.57 | 1.569    |
| 4  | 19.83           | –19.00           | 38.83 | 1.569    |
| 5  | 16.64           | –19.91           | 36.56 | 1.569    |
| 6  | 16.33           | –22.20           | 38.53 | 1.570    |

bPBE1PBE/6-311+G(2d,p) with SMD(water); values in kcal/mol. b r(C–C) is length of the bond from the platform A to the leaving cation in the radicals (*XA-cation).

Table 9. Energetics for Release of the Li(+) Cation from Lithium Polyethynyl Radicals 26n in THF

| n  | ΔG° (model 26Hn) | ΔG° (radical 26n) | ΔΔG° | r(C–Li)/Å |
|----|-----------------|------------------|-------|----------|
| 1  | 35.32           | 24.95            | 10.37 | 1.993    |
| 2  | 32.80           | 26.29            | 6.51  | 2.003    |
| 3  | 31.05           | 25.23            | 5.82  | 2.005    |
| 4  | 30.48           | 25.25            | 5.22  | 2.005    |
| 5  | 29.20           | 25.13            | 4.07  | 2.005    |
| 6  | 27.95           | 25.67            | 4.08  | 2.003    |
| 7  | 27.79           | 22.65            | 4.14  | 2.002    |

bPBE1PBE/6-311+G(2d,p) with SMD(THF); energy values in kcal/mol. b r(C–Li) is length of the bond from the platform A to the leaving Li cation in the radicals (*XA–Li).

FIGURE 1. Plots of enhancement factors ΔΔG° (kcal/mol) as a function of the number of C atoms (Cn) in the chains of ethyne spacers for radicals 14n, 29n, 15n, and 26n.

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CONCLUSIONS

The heterolytic dissociations of neutral covalent species were greatly enhanced for structures containing radical centers adjacent to potential cations. Such enhancements took place when the bonds breaking heterolytically were C–CR3, C–C(O), O–CR3, N–C(O), O–Li, and C–Li types. For exergonic heterolytic dissociations, tert-carbocations were required. Electron-releasing groups, particularly MeO substituents attached to the cationic centers, facilitated the process. Sulfate ester (10) and dithiane (15) radical platforms promoted exergonic releases of cations. However, the most successful substructures that gave exergonic heterolytic release of the widest variety of cations, were the 5-oxyl-Meldrum and 5-ethyl-Meldrum radical types (16, 17 etc.). It is very probable that other 1,3-dicarbonyl core structures would work nearly as well. Spontaneous cation release, concerted with radical generation, can be anticipated for 3-methoxyallylum and 2-methoxypropylum cations from these structures. Radical enhancements of Li cation release were small for all platforms, probably because the precursors were already salt like or at least partly ionic in character. It was no surprise that cation release took place most readily in water as solvent, but methanol, DMSO, and acetonitrile also permitted large enhancements.

In every case of carbocation generation examined, the presence of an upe either enhanced the process or had little effect. No case of radical inhibition of carbocation release was found. The only retardation discovered was for Li+ cation generation from Meldrum-lithium radical ([2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl]lithium, 27), and that was very small.

For large enhancements, the radical center X and spacer A in the *X–A–CR3 species needed to be single C, N, or O atoms. Sizeable enhancements were also achieved for X–A = O–C– O and O–S–O. The cage bicyclo[1.1.1]pentyl structure did not transmit the enhancement, and it is safe to conclude other saturated hydrocarbon spacers would also block the effect. A remarkable finding was that the ethyne spacer in almost every radical platform led to sizeable enhancements. Notably too, polyethynyl spacers gave rise to long-range enhancement. Radicals generated six or seven ethyne units away from the cationic center were still effective in enhancing cation release. It is worth mentioning the complementarity of these fragmentations to those of radical substrates that see anionic leaving groups, such as acetate anions or the loss of phosphate anions from deoxyribose radicals.

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Carbocations are extremely important in contemporary organic synthesis as well as in cationic polymerizations. Friedel–Crafts alkylation and acylation are amongst the most important routes to functionalized aromatic compounds. Wagner–Meerwein skeletal rearrangements, homoaallylic/cyclopropyl rearrangements, pinacol rearrangements, and others remain important in syntheses of numerous natural products. Chiral carbocation couplings with nucleophiles constitute valuable routes to asymmetric syntheses. To date, for most of these processes, either strong mineral acids or corrosive Lewis acids are required. Several of the radical platforms described above have the potential to deliver a specific carbocation as a reas on generation of the upe. No strong acids or toxic metals need to be involved, and neutral conditions will prevail. Excellent control of initiation can be achieved when the radicals are generated photochemically or by mild heating. Practical applications of the radical-induced production of carbocations can therefore be anticipated as mild alternatives for many of these preparations.

**EXPERIMENTAL SECTION**

DFT calculations were carried out using the Gaussian 09 suite of programs. Results were obtained with two different DFT methods. First, the CAM-B3LYP functional with the 6-311+G(2d,p) basis set was employed with the CPCM continuum model with water as solvent. This model is derived from the COSMO model. Default values of the keywords Alpha, Radii, TSNUM, and TSARE were employed. On the basis of previous work with free radicals, the CAM-B3LYP functional, which combines the hybrid qualities of B3LYP with the long-range correction proposed by Tawada et al., gave the best results in comparison with G4 (MAD: 2.5 kcal/mol). A second benchmarking study including second-row elements indicated that M05, PBE0 (PBE1PBE), and LC-PBE were the most accurate and that CAM-B3LYP also gave very satisfactory results. Full optimizations were carried out with the B3LYP/6-311+G(2d,p) method. Solvent effects were modeled with radii and non-electrostatic terms from Truhlar and co-workers’ SMD solvation model. Vibrational frequency calculations were implemented so that the effects in conformational flexible molecules were, in most cases, estimated from related molecules computed previously. The influence of the six-member ring conformation was shown previously to be small. In cases of doubt, the same conformation was employed for the model species as that for the radical species.

**ASSOCIATED CONTENT**

- Supporting Information
  The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02307.

- Computationally obtained structures and energetics (PDF)

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**Notes**

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