Radical Stimulated Nucleophile Release

*John C. Walton**

EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, Fife, KY16 9ST, United Kingdom

Supporting Information

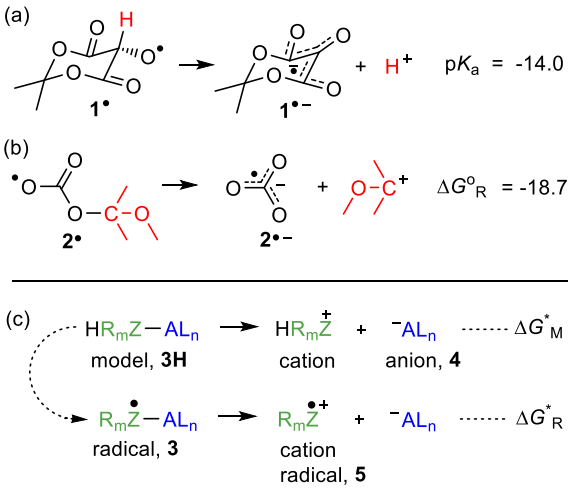
ABSTRACT. Experimental and computational results had shown that deprotonation was enhanced for precursors containing radical centers (RED-shift). An examination of whether the *inverse* heterolytic dissociations that release nucleophiles instead of electrophiles could also be stimulated by suitably sited radicals is reported in this paper. A DFT method was employed to assess the free energies of heterolytic dissociations releasing C-centered and O-centered nucleophiles. In most instances a radical adjacent to the incipient positive charge in the precursors led to significant enhancement of heterolytic dissociation; but inhibition was found in some cases. Greater enhancements were obtained with C-centered, rather than O-centered radicals. Exergonic dissociations for both O- and C-centered nucleophiles could be achieved with fluorenylmethyl- and cyclohepta-2,4,6-trienylmethyl-containing precursors. Heterolytic phosphate release from ribose and deoxyribose nucleotide C4' radicals was also found to be enhanced. This provided supporting evidence of the importance of these radicals in DNA and RNA strand breaking. The effect of ethyne, ethene and phenyl spacer units between the radical

center and the incipient positive charge was examined. Evidence was obtained that the key factor promoting heterolytic dissociation was the resonance stabilization of the co-released radical-cations.

INTRODUCTION

Experimental results[1] and computational studies[2] demonstrated that proton donor molecules become much more acidic when a radical center is generated appropriately close to the proton site within the molecule. This effect, dubbed a "RED-shift" (Radical Enhanced Dissociation), occurs with radicals centered on a variety of different atoms and with sundry different H-donor types. It can be very large, as for example with the Meldrum's-oxyl radical **1•** (see Scheme 1(a)) where the radical center induced a decrease of 17 units in the pK_a, compared to a non-radical model compound, resulting in a pK_a of -14.0 that's in the range for superacids.[3] This increased acidity of radical species has practical consequences in, for example, promoting facile base-promoted homolytic aromatic substitution reactions (BHAS reactions) with cyclohexadienyl type radical intermediates.[4] Radical enhanced acidity is also a key contributor to some enzyme catalysed dehydration processes.[5]

Scheme 1. Actual and potential radical stimulated heterolytic dissociations.[a]



[a] Energies in kcal/mol

A computational study established that carbocation release would also be strongly radical enhanced from functionalized Meldrum's acids, from dithianes, from carbonate and other esters.[6] For exergonic heterolytic dissociations, carbocations containing electron-releasing substituents were necessary. For example, the free energy for release of the 2-methoxypropylium cation from the carbonate radical (**2•**) derived from 2-methoxypropan-2-yl hydrogen carbonate was enhanced by about 13 kcal/mol in comparison with the non-radical model (see Scheme 1(b)).

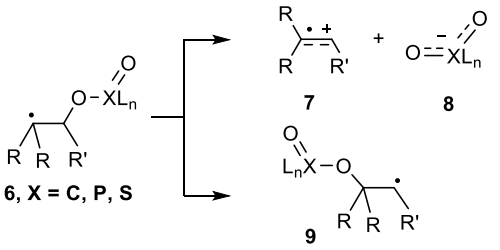
The magnitudes of these enhancements raised the intriguing question as to whether the *inverse* heterolytic dissociations, that released nucleophiles instead of electrophiles, could also be stimulated by suitably sited radicals. Scheme 1(c) presents a generalized description of this where the model compound **3H** contains a potential radical center, or unit, HR_mZ attached to a group capable of becoming a nucleophile **4** (^-AL_n). Removal of the H atom provides the radical intermediate **3** for which heterolytic dissociation to the cation-radical **5** together with anionic nucleophile **4** could be significantly easier than in the model compound. It is by no means a foregone conclusion that this type of heterolysis would also be radical enhanced.

Thermodynamic stabilization of the released anion-radicals is the major cause of the RED-shifts exemplified by processes (a) and (b). Whereas any enhancement of heterolysis (c) will depend on stabilization of the released cation-radical. In anion-radicals such as $\mathbf{1}^{-\bullet}$ and $\mathbf{2}^{-\bullet}$ the unpaired electrons (upe) will be accommodated in frontier orbitals dissimilar to those of radical-cations **5.** Clearly the structural features required for electron delocalization/stabilization will be rather different in the two cases.

Nucleophiles are extremely important reagents for a huge variety of organic synthetic applications. All manner of nucleophilic substitutions, additions and conjugate additions are workhorses for preparations of carbon-carbon and carbon-heteroatom bonds. Nucleophiles with one or more stabilizing substituents have found most use and of these, enolates and azaenolates are particularly popular. If radical enhancement were so large as to make the heterolysis exergonic, then spontaneous release of the nucleophile could take place concerted with radical generation. Radicals are normally generated by "soft" initiation employing heat or light. Potentially therefore, radical stimulated heterolytic dissociation offers the opportunity for 'clean' generation of nucleophiles avoiding the use of strong, corrosive or pyrophoric organometallic bases.

Carboxylate anions are a particular class of nucleophiles for which there already exists experimental evidence that they can be released by heterolytic fragmentation of β-(acyloxy)alkyl radicals (**6**, X = C; Scheme 2).

Scheme 2. Heterolytic dissociations and 1,2-migrations of β-(acyloxy)alkyl and β-(phosphatoxy)alkyl radicals.



EPR spectroscopic and electrochemical, as well as product studies, provided good evidence of heterolytic fragmentation to radical cations **7** together with carboxylate anions **8** (X = C).[7] This takes place in competition with the 1,2-migration of the ester moiety to yield rearranged radical **9** (Scheme 2). β-(Phosphatoxy)alkyl radicals **6** (X = P) are also known to fragment in analogous fashion.[8] This process is of particular significance because the nucleotide C4' radicals, formed by radical damage of oligonucleotides, are of this type and their heterolytic fragmentation is implicated in RNA and DNA strand breaks. Several important studies of model nucleotide radicals provided good evidence they fragment to the corresponding radical cations together with phosphate anions.[9] Beckwith, Crich et al. have provided an enlightening and comprehensive review bringing together the intricate reaction landscapes of these and related processes.[10] There is sound evidence, therefore, that ester type nucleophiles can indeed be generated by heterolytic dissociation of appropriate radical precursors.

The research reported in this paper employed a computational method to test the principle of Scheme 1(c) and to seek out the structural features needed in the $HR_mZ\text{-}AL_n$ precursors to ensure enhanced heterolysis. Significant enhancements were indeed predicted for release of thermodynamically stabilized nucleophiles. A method of quantifying the magnitude of the effect was applied to assess the ease of generation of a wide variety of anionic nucleophiles.

RESULTS AND DISCUSSION

The Gibbs free energies of the heterolyses of radicals **3** in solution (ΔG^*_R) with production of the desired nucleophiles **4** will be strongly influenced by the thermodynamic stabilization of the released radical-cations **5**. Heterolytic dissociations of the corresponding model compounds **3H** release the same nucleophiles **4** and the free energies for this will be ΔG^*_M. The difference in the Gibbs free energies of the model and radical dissociations $\Delta\Delta G$ provides a quantitative measure of any enhancement by the radical center:

$$\Delta\Delta G = \Delta G^*_M - \Delta G^*_R \qquad (1)$$

Positive $\Delta\Delta G$ values signify that nucleophile release is enhanced by the presence of the radical; whereas negative values correspond to radical inhibition of nucleophile release. A DFT computational method known to give reliable results for first and second row free radical species was chosen to evaluate the energies. The PBE0 functional with the 6-311+G(2d,p) basis set was employed to compute the optimum structures and the energetics of the heterolytic dissociations. Solvent effects were modelled with the SMD variant of the polarizable continuum solvation model (see below).

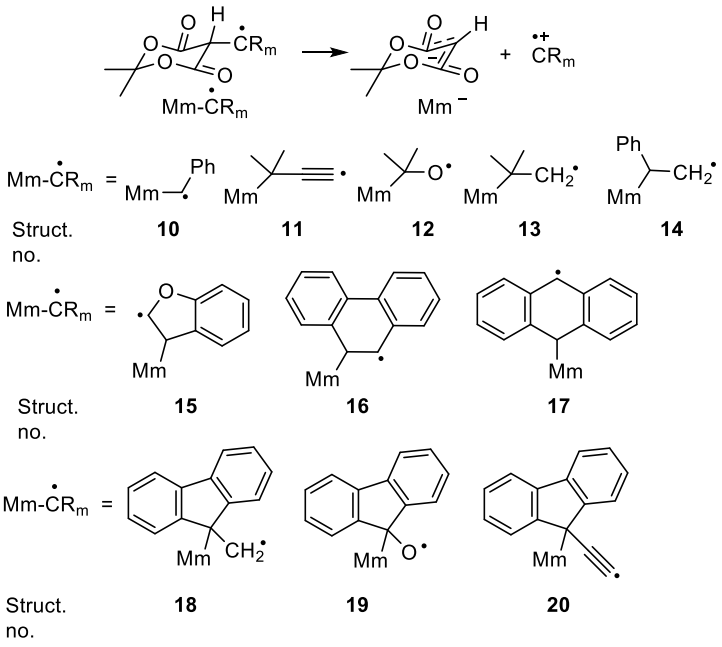
Evaluation of Radical Unit Suitability

From the perspective of preparative chemistry, it is most desirable that release of the nucleophile be spontaneous and concerted with generation of the radical center. This outcome can be expected, provided the heterolysis of the radical $R_mZ^{\bullet}-AL_n$ is enhanced ($\Delta\Delta G$ positive) and is also exergonic (ΔG^*_R negative). It seemed probable that this would only be achieved for release of nucleophiles that were strongly stabilized. Therefore, two L_nA^- types possessing this property were initially chosen as partners with a variety of radical moieties to probe the extent of enhancement. The Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione)[11,12] derived 'Meldrumate' anion was chosen to represent C-centered nucleophiles and the 2,2,2-

trifluoroacetate anion was chosen to represent O-centered nucleophiles. The structures and energetics of dissociation of precursors, combining these nucleophiles with a good range of radical units, were computed by the method outlined above.

The energies associated with heterolytic dissociations of the Meldrum's model and radical species are presented in Table 1. For the Meldrumate structure (Mm) linked to a benzyl group (**10**) the radical-cation released on heterolysis ($R_mC^{+\bullet}$) has both its upe and charge associated (formally) with the same C-atom. This process was computed to be strongly endothermic and endergonic and, furthermore, the radical center inhibited dissociation ($\Delta\Delta G$ negative; Table 1). Release of tertiary alkyl radical-cations from the radical precursors **11** and **12** respectively was also found to be energetically unfavorable and inhibited by the contained alkynyl and oxyl radicals.

Table 1. Radicals linked with Meldrum's acid units and energetics for release of Meldrumate carbanion.[a]



Structure	ΔG^*_M	ΔH°_R	ΔG^*_R	$\Delta\Delta G$	r(C–C)/Å[b]
10	41.02	83.64	67.84	-26.82	1.487
11	24.85	43.92	28.49	-3.64	1.586
12	5.23	20.80	5.72	-0.49	1.590
13	19.97	25.05	11.75	8.21	1.607
14	26.58	24.14	10.05	16.53	1.537
15	22.29	19.50	5.02	17.27	1.537
16	20.06	14.07	-1.08	21.14	1.556
17	3.78	6.81	-8.11	11.89	1.553
18	11.37	7.28	-7.72	19.09	1.554
19	0.86	6.88	-8.78	9.64	1.539
20	13.74	22.39	6.99	6.75	1.561

[a] DFT computations with PBE1PBE/6-311+G(2d,p) in water; energies in kcal/mol.

[b] Length of the bond undergoing heterolytic dissociation.

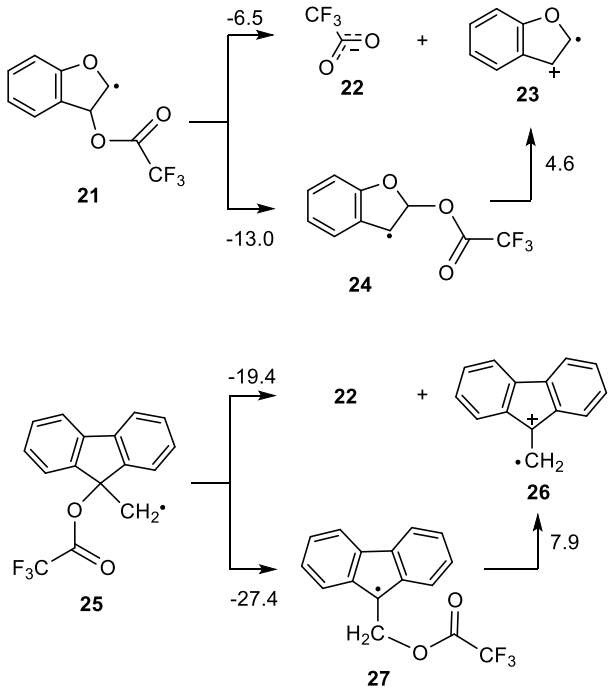
Heterolysis of radical **13** released a tertiary radical-cation with its radical center and positive (+ve) charge formally on adjacent C-atoms. This configuration resulted in significant enhancement ($\Delta\Delta G$ = 8.21 kcal/mol) although the process was endergonic. In structures **14** and **15** the radical and +ve charges were also formally on adjacent C-atoms in the released carbo-cations with the benzyl type π-systems offering delocalization. This led to increased enhancement of the heterolyses; but they remained endergonic. With radicals **16** to **19** the π-systems were extended, resulting in significant $\Delta\Delta G$ enhancements. The radical-cations released from precursors **17-19** contained double benzyl type π-delocalization and this led to the desired exergonic heterolyses. For radical **20** the (formal) radical center was separated from the +ve charge, in the released radical-cation, by an ethyne unit. This decreased the enhancement (in comparison with **18**) and the heterolysis was also endergonic (Table 1).

In assessing radical species containing ester groups the possibility of rearrangement must be taken into account. Research from the groups of Surzur,[13] Tanner,[14] Beckwith,[15] Giese[16] and others demonstrated that certain β-(acyloxy)alkyl radicals undergo 1,2-migrations of their ester

groups. Similarly, Crich and co-workers[17] and Giese and co-workers[18] discovered that β-(phosphatoxy)alkyl radicals undergo an even faster analogous 1,2-migration. Important work on these reactions from the groups of Schulte-Frohlinde,[8a] Giese,[19] Crich[9] and others proved that these 1,2-migrations take place in competition with heterolytic dissociations that release the ester nucleophile (Scheme 2).[10]

Only vicinal radicals undergo 1,2-ester migrations and usually the rearranged radical must be significantly thermodynamically stabilized relative to the unrearranged radical. In the Meldrumate series, radicals containing the benzodihydrofuranyl unit and the fluorenylmethyl unit were particularly successful. Precedent suggested, however, that rearrangement, rather than dissociation, would be favored for analogous trifluoroacetate linked radicals **21** and **25** (Scheme 3). The Gibbs free energies (kcal/mol) computed for the dissociation and 1,2-migration pathways of these potential precursors in water are displayed in Scheme 3. Heterolytic dissociation of the benzodihydrofuranyl species **21** was found to be exergonic (-6.5 kcal/mol), but the rearranged radical **24** has benzyl stabilization, such that the 1,2-migration is even more exergonic (-13.0 kcal/mol) and will probably be the preferred reaction path. Heterolytic dissociation of rearranged radical **24** was endergonic (4.6 kcal/mol) so radicals of type **21** are not suitable for generation of ester nucleophiles.

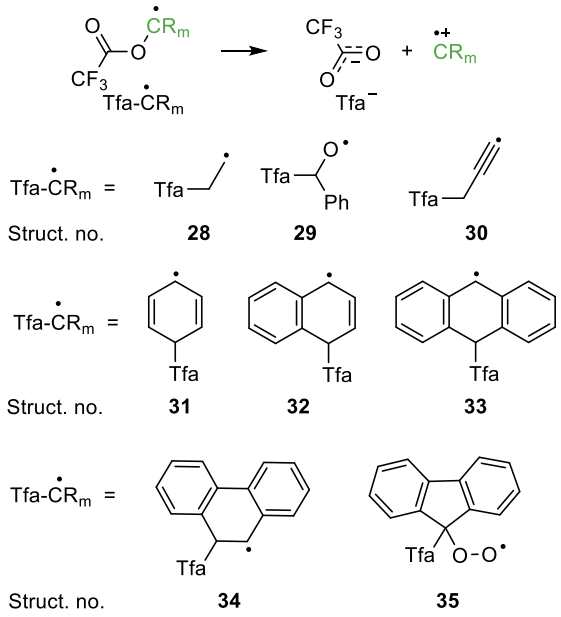
Scheme 3. Computed energetics (ΔG*/kcal/mol) for dissociative and rearrangement pathways of trifluoroacetate-linked radicals.



As expected, heterolytic dissociation of the fluorenylmethyl-linked trifluoroacetate radical **25** was found to be strongly exergonic (-19.4 kcal/mol). However, 1.2-migration yielding the extensively resonance-stabilized radical **27** was even more exergonic (-27.4 kcal/mol) such that this is likely to be the preferred reaction. Heterolytic dissociation of radical **27** was endergonic (7.9 kcal/mol) so again fluorenylmethyl-linked esters are unsuitable for generation of this type of nucleophile.

For successful heterolytic release of the trifluoroacetate nucleophile (and other carboxylate nucleophiles) precursor radical species for which the rearrangement is forbidden or disfavored are required. The set of potential such species shown above Table 2 was chosen such that the radical center is not vicinal or, if it is, as with radicals **28** and **34**, the 1,2-migration is degenerate with identical unrearranged and rearranged radicals.

Table 2. Trifluoroacetate-linked radicals and energetics for release of trifluoroacetate anion.[a]



Entry	Structure	ΔG^{*}_{M}	ΔH^{o}_{R}	ΔG^{*}_{R}	$\Delta\Delta G$	r(O–C)/Å[b]
1	**28**	34.02	36.68	23.84	10.18	1.459
2	**29**	1.28	16.08	0.95	0.34	1.467
3	**30**	38.88	57.20	43.97	-5.09	1.446
4	**31**	-7.79	12.14	-2.37	-5.42	1.504
5	**32**	-6.25	0.66	-13.2	6.94	1.504
6	**33**	-13.24	-8.50	-23.24	10.00	1.507
7	**34**	10.87	5.90	-8.23	19.10	1.507
8	**35**	-6.69	23.1	8.18	-14.87	

[a] DFT computations with PBE1PBE/6-311+G(2d,p) in water; energies in kcal/mol.

[b] Length of the bond undergoing heterolytic dissociation.

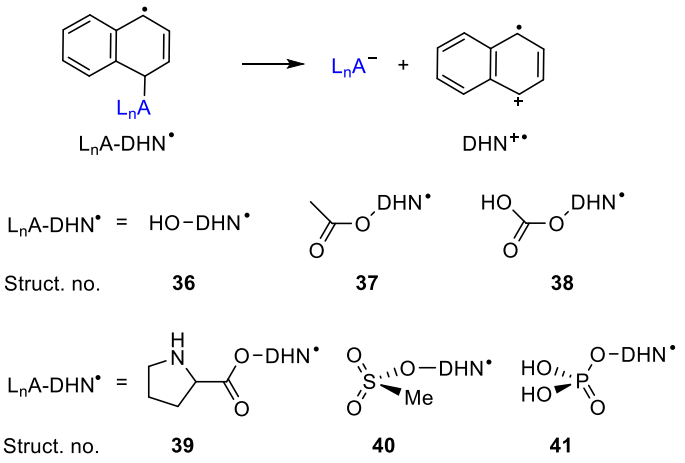
In the radical precursors **30** and **35** the radical center and incipient +ve charge are (formally) separated by two or more C- or O-atoms and, in each case, this led to inhibition of the heterolysis (Table 2, entries 3 and 8). All the other configurations delivered radical enhancements ranging from 6.94 to 19.1 kcal/mol. Furthermore, heterolyses were both substantially enhanced and exergonic for conjugated radical precursors **31-34** (entries 2 and 4-7). For trifluoroacetate, exergonic enhancements were more easily achieved, with less π-delocalization in the radical-cations, than for Meldrumate.

Considering the results for both the C-centered and O-centered series, it can be concluded that a C-centered radical adjacent to the incipient +ve charge in the precursor causes significant enhancement of heterolytic dissociation. O-Centered radicals were less effective. The presence of benzyl or greater conjugation in the trifluoroacetate-linked precursors was sufficient to make the dissociations exergonic. However, non-vicinal radicals or radicals such as **34** for which 1,2-migration was degenerate, were needed

Examining the Range of Achievable Nucleophile Releases

The dihydronaphthalenyl unit (DHN) was chosen as the radical carrier to partner various potential nucleophiles and hence to discover the range for which spontaneous heterolysis could be achieved. First, the set of O-centered anions depicted in Table 3 was investigated. With this radical carrier significant enhancements of dissociation, in the range 6.2-6.7 kcal/mol, were obtained for all the nucleophiles. Furthermore, except for hydroxide, all the heterolyses were exergonic. The exergonicities of acetate (**37**) and prolinate (**39**) were in the range -1.2 to -6.9 kcal/mol. The implication is that all carboxylates (RCO_2^-) would be spontaneously released from this platform on radical generation.

Table 3. Heterolytic dissociations of dihydronaphthalenyl-linked nucleophiles.[a]



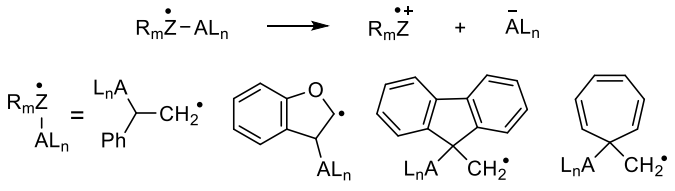
Structure	Nucleophile	ΔG^*_M	ΔH^o_R	ΔG^*_R	$\Delta\Delta G$
36	HO^-	25.2	30.5	19.0	6.2
37	$MeCO_2^-$	5.2	11.1	-1.2	6.4
38	$H0CO_2^-$	-2.6	4.4	-9.3	6.7
39	RCO_2^- [b]	-0.5	6.7	-6.9	6.3
40	$MeSO_3^-$	-16.1	-9.5	-22.5	6.4
41	$H_2PO_4^-$	-11.2	-4.0	-17.6	6.4

[a] DFT computations with PBE1PBE/6-311+G(2d,p) in water; energies in kcal/mol. [b] R = pyrrolidinyl.

The exergonic heterolyses were with carboxylate, bicarbonate (**38**), sulfonate esters (**40**) and phosphate (**41**). Soft production of these nucleophiles via the dihydronaphthalenyl and other radical platforms should therefore be readily achievable.

The radical units shown in Tables 4 and 5 were chosen as carriers for a representative set of carbon nucleophiles; including enolates. All four radical platforms **42-45** showed substantial enhancements (13.0 to 18.7 kcal/mol) in comparison with their corresponding non-radical models. The heterolyses were only exergonic, however, such that spontaneous enolate release would be expected at room temperature, for enolates linked to the cyclohepta-2,4,6-trienylmethyl structure (**45a** and **45b**).

Table 4. Heterolytic dissociations of radical-linked enolates.[a]



42 **43** **44** **45**

a, L_nA^- = CH_2=C(Me)O^-

b, L_nA^- = CH_2=C(OMe)O^-

Structure	^-AL_n	ΔG^*_M	ΔH^o_R	ΔG^*_R	$\Delta\Delta G$
42a	CH_2=C(Me)O^-	30.25	32.14	18.66	17.53
43a	"	33.47	29.23	15.37	18.09
44a	"	24.29	21.60	7.3	16.99

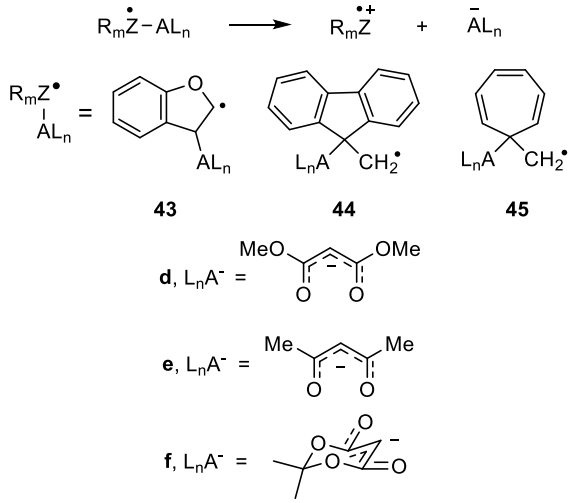
45a	"	5.64	7.94	-7.34	12.98
42b	CH_2=C(OMe)O^-	29.8	25.35	12.48	17.32
43b	"	27.39	22.99	9.33	18.06
44b	"	18.25	13.26	-0.47	18.72
45b	"	29.8	-0.70	-15.89	13.01

[a] DFT computations with PBE1PBE/6-311+G(2d,p) in water; energies in kcal/mol.

The heterolyses releasing the ester-derived nucleophile were also substantially radical enhanced (Table 4, col. 6). With this nucleophile, heterolysis of precursor **44b** had a ΔG^*_R value close to thermoneutral. Hence, equilibria between CH_2=C(OMe)O^- plus its accompanying radical-cation with the neutral radical precursors, could probably be achieved. Nevertheless, cyclohepta-2,4,6-trienylmethyl was the radical carrier of choice for both types of nucleophile.

Results for release of carbon-nucleophiles derived from 1,3-dicarbonyl precursors are presented in Table 5. Again, the presence of the radical center led to substantial enhancements of all the heterolyses. Exergonic dissociations were obtained in the case of the Meldrumate anions (**43f** to **45f**; Table 5) linked to all the structures and for all three 1,3-dicarbonyls linked to the cyclohepta-2,4,6-trienylmethyl structure (**45d**, **45e** and **45f**).

Table 5. Heterolyses of radical-linked 1,3-dicarbonyl precursors.[a]



Structure	ΔG^*_M	ΔH^o_R	ΔG^*_R	$\Delta\Delta G$

43d	41.21	36.49	23.89	17.32
44d	33.55	27.53	12.88	20.67
45d	8.61	11.24	-1.52	10.13
43e	34.38	31.18	17.14	17.25
44e	27.96	23.70	9.4	18.56
45e	3.37	7.58	-6.47	9.84
43f	22.29	19.50	5.02	17.27
44f	11.37	7.28	-7.72	19.09
45f	-9.91	-9.11	-22.73	12.82

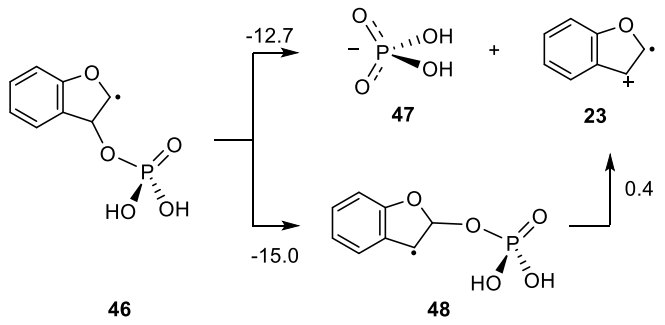
[a] DFT computations with PBE1PBE/6-311+G(2d,p) in water; energies in kcal/mol.

It can be concluded that spontaneous generation of many O-centered nucleophiles will readily take place from a variety of radical platforms. However, for enolates and 1,3-dicarbonyl anions only a limited range of radical structures are suitable and linkage to the cyclohepta-2,4,6-trienylmethyl structure is preferred.

Release of Phosphate Nucleophiles and Cleavage of DNA and RNA.

The DFT results in Table 3 demonstrated that, with the dihydronaphthalenyl-precursor **41**, release of dihydrogen phosphate [$(HO)_2P(=O)O^-$, **47**] was strongly exergonic (-17.6 kcal/mol) and significantly enhanced even though the radical center was *three bonds* removed from the breaking bond. Phosphate heterolytic dissociations would probably be even more facile with precursors based on the fluorenylmethyl or cycloheptatrienylmethyl units. 1,2-Migration of the phosphate radical would, however, almost certainly be the preferred reaction mode for these vicinal radicals. The dihydrogen phosphate-dihydrobenzofuran-linked radical **46** (Scheme 4) was examined as a test of the competition between rearrangement and heterolytic dissociation.

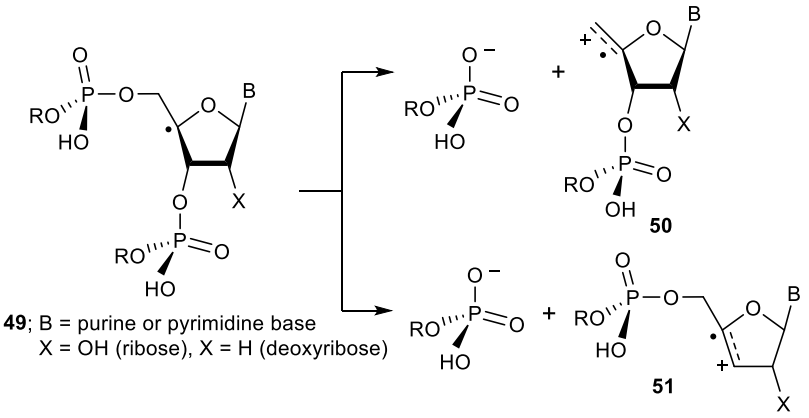
Scheme 4. Computed energetics (ΔG*/kcal/mol) for the dissociative and rearrangement pathways of dihydrogen phosphate-dihydrobenzofuran-linked radical.



The heterolytic dissociation was computed to be exergonic by -12.7 kcal/mol but the 1,2-migration to radical **48** was even more thermodynamically favorable (-15.0 kcal/mol). Thus, the preferred reaction would be the rearrangement. Furthermore, this would not be followed by dissociation of **48** because this is endergonic (0.4 kcal/mol, Scheme 4). It can be concluded that radical precursors such as the dihydronaphthalenyl-linked **41**, or the dihydrogen phosphate analogs of **33** and **34** (see Table 2), would be needed for facile radical enhanced delivery of phosphate nucleophiles.

It is well established that diradicals generated from enediyne antitumor agents,[20] including calicheamicin, esperamicin and neocarzinostatin, abstract H-atoms from C4' sugar sites of DNA and RNA to produce C4'-nucleotide radicals **49** (Scheme 5).[10,21] Hydroxyl radicals are less selective in their reactions with nucleic acids but a minor proportion also produce the same type of species,[22] as do peroxyl radicals.[23] Furthermore the nucleotide C4' radicals generate DNA single and double strand breaks by heterolytic dissociation of their phosphate substituents.[24]

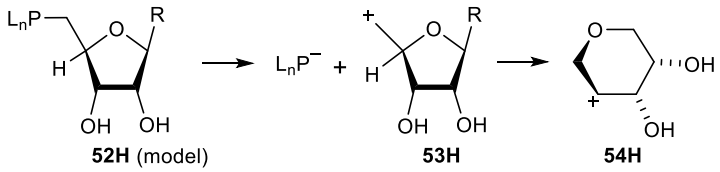
Scheme 5. C4' Nucleotide radicals and alternative heterolytic dissociations.

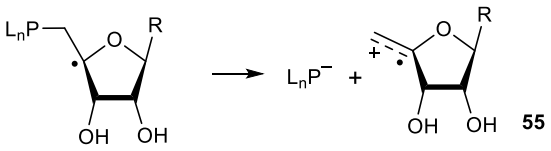


1,2-Migration of phosphate in C4' nucleotide radicals is disfavored because the rearranged radicals would be thermodynamically less stable. In DNA, RNA and oligonucleotides in general dissociation of the C3' phosphate will be preferred because of the greater stability of the resulting radical cation **51**. However, in radicals generated from AMP, ATP and analogues, dissociation of C5' phosphate types with production of radical cations of type **50** is a possibility.

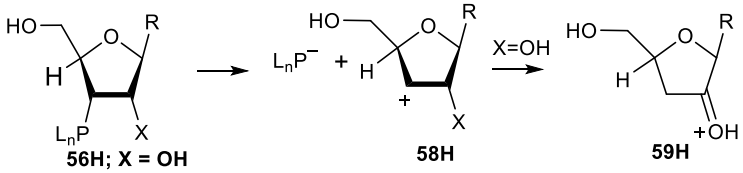
These nucleotide fragmentations appeared to be examples of radical enhanced dissociations so to study the scope this process the sets of phosphate-containing radicals shown in Scheme 6 were chosen.

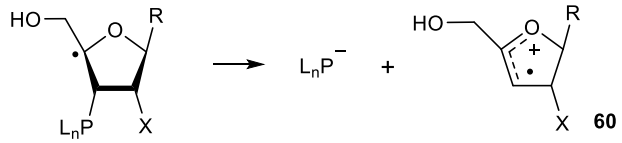
Scheme 6. Computed energetics (ΔG^*/kcal/mol) for dissociation of C4' nucleotide type radicals.





52	L_nP	R	G*	G
a:	$(HO)_2P(=O)O^-$	cytosine	-2.86	32.66
b:	$(HO)_2P(=O)O^-$	H	-2.17	29.77
c:	$HOPO_3^{2-}$	H	12.30	30.45
d:	PO_4^{3-}	H	61.36	30.64
e:	$(HO)_4P_3O_6^-$	H	-20.00	30.32
			trans -20.46	27.23





56	L_nP	R	X	G*	G
b:	$(HO)_2P(=O)O^-$	H	OH	-4.84	34.70
c:	$HOPO_3^{2-}$	H	OH	9.48	4.23
d:	PO_4^{3-}	H	OH	43.26	30.64
e:	$(HO)_4P_3O_6^-$	H	OH	-8.73	5.37
f:	$(HO)_2P(=O)O^-$	OH	OH	-0.75	5.79

57	L_nP	R	X	G*	G
b	$(HO)_2P(=O)O^-$	H	H	-9.38	2.42
c:	$HOPO_3^{2-}$	H	H	3.06	1.89
d:	PO_4^{3-}	H	H	43.06	1.89
e:	$(HO)_4P_3O_6^-$	H	H	-17.71	3.53

Radicals **52**, with their corresponding models **52H**, had C5' phosphate ligands in imitation of radicals derived from AMP, ATP etc. whereas radicals **56** and **57** contained C3' phosphate to represent RNA and DNA oligonucleotide species respectively. The computed Gibbs free energies of heterolyses of these species are displayed in Scheme 6 along with the $\Delta\Delta G$ enhancement factors. The ΔG^* values for the corresponding models **52H**, **56H** and **57H** are needed to derive these $\Delta\Delta G$ enhancements. The DFT optimizations of the carbo-cations derived

from dissociations of **52H**, **56H** and **57H** revealed that they spontaneously rearranged to more stable forms. For example, the primary 5-member ring carbo-cations **53H** rearranged to the secondary 6-member ring cations **54H**. Similarly, secondary carbo-cations **58H** rearranged to the resonance-stabilized oxocarbenium ions **59H** (see Scheme 6). On the other hand, radical cations derived from the radical precursors (**55** and **60**) did not rearrange. One consequence of this is that the ΔG^* values for dissociations of the non-radical model compounds correspond to structures different from those of the radical precursors. The derived $\Delta\Delta G$ values are not therefore a measure of the "true" enhancements but underestimate them because the rearrangements delivered more stable carbo-cations. Nevertheless, Scheme 6 shows that for every C4' nucleotide precursor a positive $\Delta\Delta G$ was obtained, so it is reasonable to conclude that vicinal radical centers do indeed enhance the heterolytic release of phosphate from both ribose and deoxyribose nucleotides.

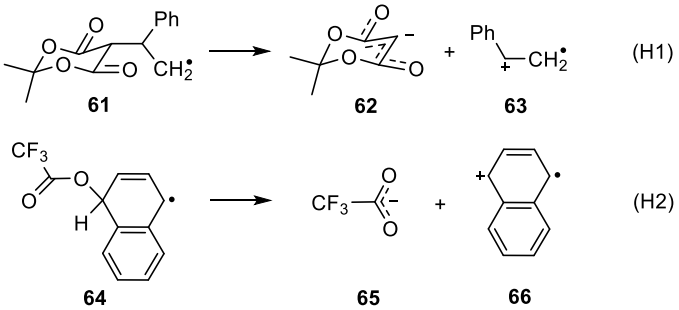
The Gibbs free energies show that, as expected, dissociations of the C3'phosphates are more exoergonic than dissociations of the C5' phosphates (compare **56b** and **57b** with **52b**). Also as expected, the presence of C1'-substituents (cytosine, OH) had only a small effect on the energetics of dissociation (compare **52a** with **52b** and **56b** with **56f**). Interestingly, the dissociations of the triphosphate group were, in each set, more exergonic than dissociations of the dihydrogen phosphate group (compare **52b** with **52e**, **56b** with **56e** and **57b** with **57e**). Dissociations of the dihydrogen phosphate and triphosphate group were more exergonic in the deoxyribose series than in the ribose series (compare **57b** with **56b** and **57e** with **56e**). This is in good accord with experimental results showing diminished reactivity of RNA compared to DNA.[10,25] In all three sets, while dissociations to $(HO)_2PO_2^-$ were exergonic, dissociations to $HOPO_2^{2-}$ became endergonic and dissociations to PO_4^{3-} were even more endergonic (Scheme 6).

This accords well with the pH dependence found experimentally for various oligonucleotide fragmentations[10] and with the large decreases in rates (~ 3 orders of magnitude) of model phosphatoxy-substituted alkyl radicals reported by Schulte-Frohlinde as the charge on the phosphate groups increased.[8] A consistent picture emerges, therefore, in which fragmentations of C4' nucleotide radicals form a special class of radical enhanced heterolyses.

Effect of Solvent on Nucleophile Release

The heterolytic dissociations will be considerably influenced by the differing solvation between the neutral radical precursors and the charged products. The effect of solvation on the enhancement of heterolysis was therefore examined for two representative processes. First, release of the Meldrumate carbanion from the benzylmethyl radical precursor **61** (process H1 in Table 6) (together with the corresponding model) was examined. Second, the release of trifluoroacetate from the dihydronaphthyl radical **64** (and model; process H2 in Table 6) was studied. Truhlar's SMD method, based on the quantum mechanical charge density of a solute molecule interacting with a continuum description of the solvent, was employed.[26] The free energies for the two processes, for solvents ranging from water to *n*-heptane, as well as the enhancement factors relative to the non-radical models, are recorded in Table 6.

Table 6. Effect of solvents on radical enhancement of heterolytic nucleophile releases.[a]



Solvent	δ^b	Meldrumate$^-$ (H1)	$CF_3CO_2^-$ (H2)

		ΔG^*_R	$\Delta\Delta G$	ΔG^*_R	$\Delta\Delta G$
H_2O	23.5	6.93	15.79	-13.2	6.94
MeOH	14.28	16.71	16.73	-1.90	7.39
MeCN	11.92	16.48	16.79	-2.16	7.39
THF	9.52	26.09	16.82	8.25	7.32
n-C_7H_{16}	7.4	62.03	17.44	45.48	7.53

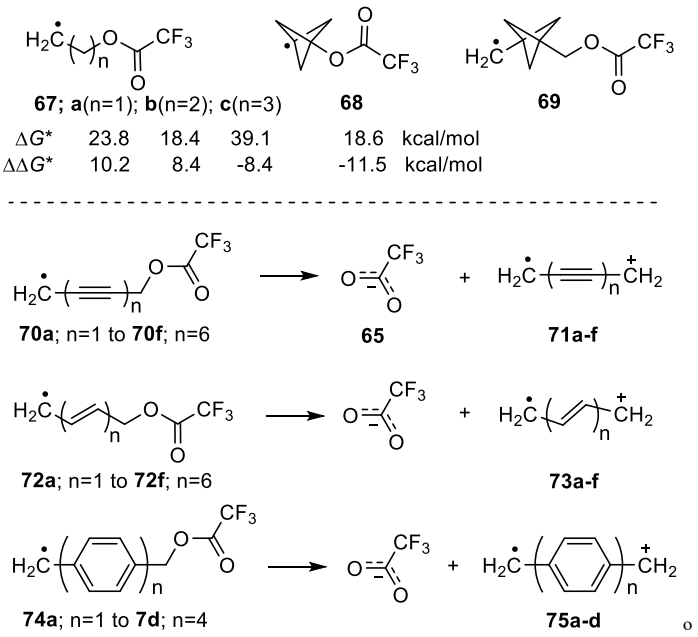
[a] Energies in kcal/mol; DFT with PBE1PBE/6-311+G(2d,p). [b] Standard Hildebrand solvent parameters in $cal^{1/2}\,cm^{-3/2}$.

The free energy for Meldrumate release from radical **61** increased by about 55 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. The free energy of trifluoroacetate release from radical **64** increased by nearly 60 kcal/mol through the series of solvents. Furthermore, the reaction was favorably exergonic in methanol and acetonitrile as well as in water. Significant enhancement factors ($\Delta\Delta G$) were obtained for both processes H1 and H2. It was found, however, that these enhancements were practically independent of the solvent. This can probably be attributed to the fact that the change in solvation on going from the neutral model to charged products compared to the neutral radical to charged products, remained fairly constant irrespective of solvent properties. For both processes a fairly smooth trend can be discerned towards increasing ΔG^*_R values as the Hildebrand solvent parameter δ decreased (Table 6). So, for example, for solvents such as DMF and DMSO with δ values of 12.14 and 12.93 respectively, the H1 process would certainly be endergonic but loss of trifluoroacetate (H2) would probably be marginally exergonic. Water was unquestionably the solvent of choice for advantageous energetics. However, mixed solvents of water with methanol, acetonitrile, DMF or DMSO could be used, with little diminution in enhancement, for covalent precursors insoluble in water.

The Effect of Spacers and the Reach of Radical Enhancement

Data in Table 1 shows that an ethyne spacer inhibited Meldrumate anion release from the 3-methylbutyne radical **11**. Similarly, the ethyne spacer inhibited trifluoroacetate release from the analogous radical **30** (Table 2). On the other hand, the dihydroanthracene spacer in structures **17** (Table 1), **33** (Table 2) and the dihydronaphthalene spacer in structures in Table 3, where the upe is separated from the breaking bond by ring π-systems, led to significant enhancements in every case; as well as favorable free energies of heterolysis. The influence of the selected set of spacer units, shown in Table 7, on the energetics of heterolysis was therefore investigated.

Table 7. Influence of spacers on radical promoted release of trifluoroacetate.[a]



	a, n=1	**b**, n=2	**c**, n=3	**d**, n=4	**e**, n=5	**f**, n=6
70, Δ*G**	18.9	25.3	22.0	20.7	21.1	22.8
ΔΔ*G*	8.0	6.7	3.7	3.8	2.3	3.6
72, Δ*G**	20.1	11.7	6.0	2.4	-2.8	-2.3
ΔΔ*G*	3.7	0.8	0.3	0.2	-0.1	0.5
74, Δ*G**	1.9	9.0	11.5	13.4	nd	nd
ΔΔ*G*	6.1	4.2	1.8	-0.4		

[a] Energies in kcal/mol; nd = not determined.

The effect of lengthening a saturated hydrocarbon chain between the upe and trifluoroacetate is indicated by the results for structures **67a-c** (Table 7). Though heterolysis releasing the ethanyl radical-cation $(CH_2CH_2)^{\bullet+}$ was endergonic by 23.8 kcal/mol, significant enhancement ($\Delta\Delta G$ = 10.2 kcal/mol) was found. On lengthening the chain to the $(CH_2)_3$ and $(CH_2)_4$ units (**67b** and **67c**, Table 7) the optimized structures of the released cations were abnormal cyclic forms such that the free energies did not truly reflect the effect of additional CH_2 spacers.

The EPR spectrum of the bicyclo[1.1.1]pent-1-yl radical indicated that this cage structure transmitted spin density rather effectively;[27,28] so it was also tested as a spacer. However, introduction of this cage (structure **68**) led to endergonic heterolysis and inhibition relative to the non-radical model (Table 7). The bicyclo[1.1.1]pentanylmethyl radical **69** was unsuitable because it underwent such rapid rearrangement by opening of its cage. Ethyne spacers were known to be effective in radical enhanced proton release,[3] although mixed results were obtained here (Tables 1 and 2) for nucleophile releases. The ethynyl radical is a σ-radical orthogonal to the adjacent π-system and this prevents conjugation of the upe. To circumvent this problem the $^{\bullet}CH_2C{\equiv}C$ unit, where the upe resides in a p-orbital available for conjugation with its neighbor triple bond, was next investigated (Table 7, structures **70a-f**). Vinyl radicals and aryl radicals are also σ-types so, for the same reason, $^{\bullet}CH_2CH{=}CH_2$ and $^{\bullet}CH_2C_6H_4$ units were examined as spacers (Table 7, structures **72a-f** and **74a-d**).

For the ethynyl series **70a-f** heterolytic release of trifluoroacetate was endergonic for spacers ranging from 1 to 6 ethynyl units and ΔG^{*} varied by only a small amount over the whole set (Table 7). For the ethenyl set **72a-f**, the process went from endergonic for one ethenyl spacer to marginally exergonic for six spacers. By way of contrast, for the set of aryl spacers (**74a-d**) the endergonicity increased from 1.9 to 13.4 kcal/mol. The computed enhancements relative to the

models with the same number of spacers ($\Delta\Delta G$) are plotted against the number of spacer units in Figure 1.

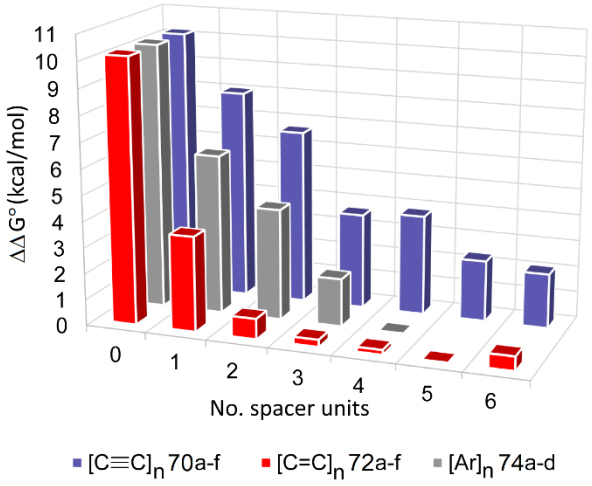


Figure 1. Plot of heterolysis enhancements ($\Delta\Delta G$) against the number of spacer units for radicals **70a-f**, **72a-f** and **74a-d**.

As expected, $\Delta\Delta G$ decreased for the heterolyses of all three sets as the number of spacer units increased. For the ethenyl series (red, **72a-f**) enhancement was significant for one unit but died to essentially zero for 2 to 6 ethene units. For the aryl series (gray, **74a-d**) enhancement was observed for up to 3 phenyl ring spacers. It is rather extraordinary that the upe in **74c** which is 3 rings, that is 13 C–C bonds, removed from the site of developing positive charge exerts a measurable effect! (see however below). The ethynyl spacers were the most effective in terms of transmission of the enhancement. Remarkably, for this series (blue, **70a-f**) modest $\Delta\Delta G$ values remained measurable out to at least six ethyne spacers. Previous research had shown that polyethynyl spacers were also effective in transmitting RED-shift in deprotonation reactions although the effect was of much greater magnitude.[3]

CONCLUSIONS

Previous research had shown that radical centers, in molecules that dissociated to protons or carbo-cations, either enhanced the process or had negligible effect; inhibition was not observed for any structure. In contrast to this, in the present study of the inverse dissociation to nucleophiles, radical centers could either enhance or inhibit the process depending on the configuration. Spontaneous heterolytic dissociations, with release of O-centered nucleophiles, including carboxylates, carbonates, sulfonates and phosphates could readily be achieved when the co-released radical-cation possessed benzyl or greater conjugation. Facile dissociations to acetone enolate and ester enolates were more difficult but were achievable when linked with the cyclohepta-2,4,6-trienylmethyl structure. 1,3-Dicarbonyl type carbanions were released when linked to the fluorenylmethyl or cyclohepta-2,4,6-trienyl-7-methyl types of incipient radical-cations. Results for both ribose and deoxyribose nucleotide C4' radicals supported the understanding that they undergo spontaneous heterolytic fragmentation and that this is an important route to DNA and RNA strand breaks.

The most favorable precursor configurations had the upe centered on a C-atom, rather than on an O-atom, with the incipient positive charge (formally) on an adjacent atom. Enhanced heterolytic dissociation was still obtained in precursors with up to six ethyne spacer units between the radical center and the incipient positive charge. Up to two phenyl ring spacers could be employed, but only one vinyl unit, before enhancement became negligible.

If the *main* factor stimulating the heterolytic dissociations were some influence from the upe in the radical precursors, then the lengths of the bonds Z–A in the radical precursors $R_mZ^{\bullet}–AL_n$ would be expected to increase, relative to those of the models $HR_mZ–AL_n$, in line with the magnitude of the enhancement. The computed C–C bond lengths for the Meldrumate radical platforms are in the final column of Table 1 and the C–O bond lengths for the trifluoroacetate

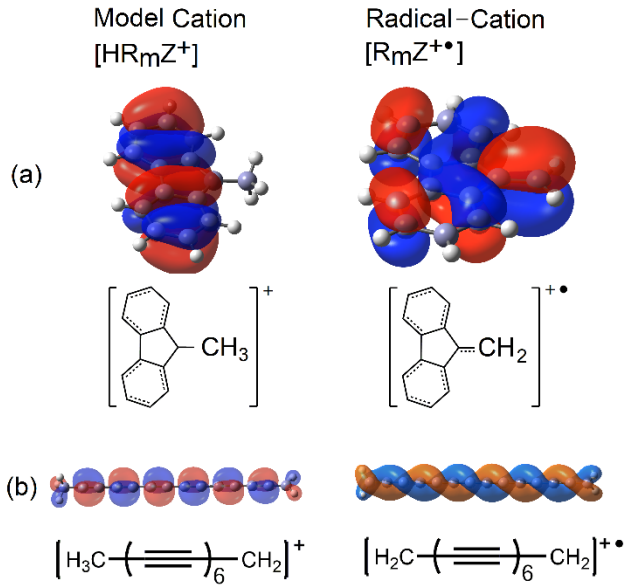
platforms are in Table 2. However, there was no correlation of r(C–C)/Å or of r(C–O)/Å with the ΔG^{*} values of the respective heterolyses. More significantly, the differences in the bond lengths of the radical and model [Δr(C–C)/Å] did not correlate with the $\Delta\Delta G$ enhancements for the Meldrumate series; nor was there a correlation for the corresponding Δr(C–O)/Å differences for the trifluoroacetate series (see Figure S1 of the Supporting Information). It appears, therefore, that the upe of the radical center in the precursors was not an important influence in promoting the heterolytic dissociations.

The energetics for dissociations of a set of nucleophiles all linked to the same dihydronaphthalene unit (released as $R_mZ^{+\bullet}$) are in Table 3. The Gibbs free energies of the dissociations of both models and radicals cover a range of more than 40 kcal/mol. It is noteworthy, however, that the $\Delta\Delta G$ enhancements were all 6.4±0.3 kcal/mol, irrespective of the anion released. Reference to Table 1 (structure **18**) and Table 5 (structures **43a-c**) indicates that $\Delta\Delta G$ was also in a narrow range 17±2 kcal/mol for release of other nucleophiles attached to the fluorenylmethyl unit. Examination of the $\Delta\Delta G$ values for release of nucleophiles attached to the dihydroanthacene unit (released as $R_mZ^{+\bullet}$) (see: Table 1; structure **17** and Table 2; structure **33**) shows they were also in the narrow range 11±2 kcal/mol irrespective of the anion released. The probable conclusion to be drawn from this is that the most important factor that promotes heterolytic dissociation is the greater resonance stabilization of the radical-cation $R_mZ^{+\bullet}$ released from the radical precursors when compared to the non-radical-cations HR_mZ^{+} released from the models.

Comparison of the frontier SOMOs of the radical-cations $R_mZ^{+\bullet}$ with the HOMOs of the model-derived cations HR_mZ^{+} lends support to this interpretation. To illustrate this point,

graphics of the frontier orbitals of two examples are displayed in Figure 2. The much greater π-conjugation of the upe in the SOMO of the fluorenylmethyl radical-cation (Figure 2(a) right) compared to the model cation (Figure 2(a) left) is apparent. The HOMO of the model tetradeca-2,4,6,8,10,12-hexayn-1-ylium cation (Figure 2(b), left) is a conventional extended π-system. In comparison to this the SOMO of the corresponding radical-cation (Figure 2(b), right) is a remarkable function. It consists of only positive and negative lobes forming a π-double helix extending over all 14 C-atoms of the tetradeca-2,4,6,8,10,12-hexayne chain. This extensive orbital has only one, helically disposed, node. The SOMOs of the radical-cations with fewer ethyne units, **70a-e**, also possess analogous but shorter double helical structures.

Figure 2. Frontier orbitals of fluorenylmethyl and hexaynylmethyl cations and radical-cations.



The extensive conjugation available in the SOMOs of the radical-cations will lead to greater thermodynamic stabilization of the radical-cations than the model cations. This is undoubtedly a key contributor to the enhancement of heterolytic dissociation.

EXPERIMENTAL SECTION

DFT calculations were implemented with the Gaussian 09 suite of programs.[29] A computational method, that would give reliable results for free radicals and would require modest computing resources was needed. A benchmarking study including second row elements had been carried out[30] in which results for 9 radical reaction types were compared with results from the high-level composite ab initio G4 method.[31] Twenty three different density functional theory (DFT) functionals (plus the MP2 ab initio method) were tested and the results indicated that M05,[32] PBE0 (PBE1PBE)[33] and LC-PBE[34] were the most accurate and that CAM-B3LYP[35] also gave very satisfactory results. The PBE0 functional was chosen for this research and optimizations were carried out with the PBE1PBE/6-311+G(2d,p) method. Solvent effects were modelled with radii and non-electrostatic terms from Truhlar and co-workers' SMD solvation model.[26] Vibrational frequency calculations enabled the status of GSs to be checked and free energies to be computed. Gas phase enthalpies and free energies $\Delta G°$ were adjusted for zero point and thermal corrections to 1 atm. and 298 K. For solution processes the standard state of an ideal gas at a concentration of 1 mol/L is more appropriate; Gibbs free energies are then denoted by ΔG^*. The relationship of these standard states is:[36] $\Delta G^* = \Delta G° - RT\ln(24.46) = \Delta G° - 1.89$ kcal/mol. The lowest energy structures of conformationally flexible molecules were, in most cases, estimated from related molecules computed previously.[2,3] In all cases the same conformation was employed for the model species as that for the radical species. Six-member ring conformations were shown previously to have only a small effect. Cartesian matrices for the optimized structures are in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Computational methods.Plot of bond lengths vs. enhancement factors. Cartesian coordinates and energies of optimized structures of precursors and products.

AUTHOR INFORMATION

Corresponding Author

* jcw@st-andrews.ac.uk

Tel: 44(0)1334 463864

ORCID

John C. Walton: 0000-0003-2746-6276.

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REFERENCES

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1 (a) Hayon, E.; Simic, M. Acid-base properties of free radicals in solution. *Acc. Chem. Res.* **1974**, *7*, 114–121. (b) Buehl, M.; DaBell, P.; Manley, D. W.; McCaughan, R. P.; Walton, J. C. Bicarbonate and alkyl carbonate radicals: structural integrity and reactions with lipid components. *J. Am. Chem. Soc.* **2015**, *137*, 16153–16162. (c) Walton, J. C. Microhydration and the enhanced acidity of free radicals. *Molecules*, **2018**, *23*, 423.

2 (a) Mayer, P. M.; Glukhovtsev, M. N.; Gauld, J. W.; Radom, L. The effects of protonation on the structure, stability, and thermochemistry of carbon-centered organic radicals. *J. Am. Chem.*

Soc. **1997**, *119*, 12889–12895; (b) Mayer, P. M.; Radom, L. Deprotonating molecules and free radicals to form carbon-centered anions: A G2 ab initio study of molecular and free radical acidity. *J*. *Phys*. *Chem*. *A*, **1998**, *102*, 4918–4924; (c) Walton, J. C. Radical-enhanced acidity: why bicarbonate, carboxyl, hydroperoxyl, and related radicals are so acidic. *J*. *Phys*. *Chem*. *A,* **2017**, *121*, 7761–7767.

3 Walton, J. C. Enhanced proton loss from neutral free radicals: towards carbon-centered superacids. *J*. *Phys*. *Chem*. *A,* **2018**, *122,* 1422–1431.

4 (a) Studer, A.; Curran, D. P. Organocatalysis and C-H activation meet radical- and electron-transfer reactions. *Angew*. *Chem*., *Int*. *Ed*. **2011**, *50*, 5018–5022; (b) Zhang, B.; Studer, A. Recent advances in the synthesis of nitrogen heterocycles via radical cascade reactions using isonitriles as radical acceptors, *Chem*. *Soc*. *Rev*. **2015**, *44*, 3505–3521.

5 (a) Buckel, W.; Keese, R. One-electron redox reactions of CoASH esters in anaerobic bacteria - a mechanistic proposal. *Angew*. *Chem*.,*Int*. *Ed*. *Engl*. **1995**, *34*, 1502–1506; (b) Smith, D. M.; Buckel, W.; Zipse, H. Deprotonation of enoxy radicals: theoretical validation of a 50-year-old mechanistic proposal. *Angew*. *Chem*., *Int*. *Ed*. **2003**, *42*, 1867–1870; (c) Kim, J.; Darley, D. J.; Buckel, W.; Pierik, A. J. An allylic ketyl radical intermediate in clostridial amino-acid fermentation. *Nature* **2008**, *452*, 239–242.

6. Walton, J. C. Reflex carbocation release from covalent molecules by endogenous free radicals, *ACS Omega*, **2018**, *3*, 13290-13297.

7. (a) Gilbert, B. C.; Larkin, J. P.; Norman, R. O. C. Electron spin resonance studies. XXXIII. Evidence for heterolytic and homolytic transformations of radicals from 1,2-diols and related

compounds. *J. Chem. Soc. Perkin Trans. 2* **1972**, 794-802; (b) Behrens, G.; Koltzenberg, G.; Schulte-Frohlinde, D. Model reactions for the degradation of DNA-4' radicals in aqueous solution. Fast hydrolysis of α-alkoxyalkyl radicals with a leaving group in β-position followed by radical rearrangement and elimination reactions. *Z. Naturforsch.* **1982**, *37c*, 1205-1227; (c) Behrens, G.; Bothe, E.; Koltzenburg, G.; Schulte-Frohlinde, D. Formation and structure of 1,1-dialkoxyalkene radical cations in aqueous solution. An in situ electron spin resonance and pulse conductivity study. *J. Chem. Soc. Perkin Trans. 2* **1980**, 883-839; (d) Lenz, R.; Giese, B. Studies on the mechanism of ribonucleotide reductases. *J. Am. Chem. Soc.* **1997**, *119*, 2784-2794; (e) Robins, M. J.; Guo, Z.; Wnuk, S. F. Elimination of chlorine (radical) or tosylate (anion) from C2' of nucleoside C3' free radicals as model reactions postulated to occur at the active site of ribonucleotide reductases. *J. Am. Chem. Soc.* **1997**, *119*, 3637-3638.

8. (a) Behrens, G.; Koltzenburg, G.; Ritter, A.; Schulte-Frohlinde, D. The influence of protonation or alkylation of the phosphate group on the ESR spectra and the rate of phosphate elimination from 2-methoxyethyl phosphate 2-yl radicals. *Int. J. Rad. Biol.* **1978**, *33*, 163-171; (b) Müller, S. N.; Batra, R.; Senn, M.; Giese, B.; Kisel, M.; Shadyro, O. Chemistry of C-2 glyceryl radicals: indications for a new mechanism of lipid damage. *J. Am. Chem. Soc.* **1997**, *119*, 2795-2803.

9. (a) Giese, B.; Burger, J.; Kang, T. W.; Kesselheim, C.; Wittmer, T. Model studies on the radical induced DNA-strand cleavage. *J. Am. Chem. Soc.* **1992**, *114*, 7322-7324; (b) Giese, B.; Dussy, A.; Elie, C.; Erdmann, P.; Schwitter, U. Synthesis and selective radical cleavage of C-4'-modified oligonucleotides, *Angew.Chem.* **1994**, *106*, 1941-1946; (c) Giese, B.; Beyrich-Graf, X.; Erdmann, P.; Petretta, M.; Schwitter, U. The chemistry of single-stranded 4'-DNA radicals:

influence of the radical precursor on anaerobic and aerobic strand cleavage, *Chem. Biol.* **1995**, *2*, 367-375; (d) Crich, D.; Mo, X.-S. Nucleotide C3',4'-radical cations and the effect of a 2'-oxygen substituent. The DNA/RNA paradox, *J. Am. Chem. Soc.* **1997**, *119*, 249-250.

10. Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. Chemistry of β-(acyloxy)alkyl and β-(phosphatoxy)alkyl radicals and related species: radical and radical ionic migrations and fragmentations of carbon-oxygen bonds, *Chem. Rev.* **1997**, *97*, 3273-3312.

11 McNab, H. Meldrum's acid, *Chem. Soc. Rev.* **1978**, *7*, 345–358.

12. Dumas, A. M.; Fillion, E. Meldrum's acids and 5-alkylidene Meldrum's acids in catalytic carbon-carbon bond-forming processes, *Acc. Chem. Res.* **2010**, *43*, 440–454.

13. Surzur, J.-M.; Teissier, P. Radical addition to unsaturated alcohols. III. Addition to unsaturated acetates: 1,2-radical migration of the acetoxy group, *Bull. Soc. Chim. Fr.* **1970**, 3060-3070.

14. Tanner, D. D.; Law, F. C. P. Free-radical acetoxy group migration, *J. Am. Chem. Soc.* **1969**, *91*, 7535-7537.

15. (a) Beckwith, A. L. J.; Tindal, P. L. Free radical acetoxy group migration. EPR spectral study, *Aust. J. Chem.* **1971**, *24*, 2099-2116; (b) Beckwith, A. L. J.; Duggan, P. J. The mechanism of the β-(acyloxy)alkyl radical rearrangement: kinetic and oxygen-18 labeling studies, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1777-1783.

16. (a) Giese, B.; Groeninger, K. S.; Witzel, T.; Korth, H.-G.; Sustmann, R. Synthesis of 2-desoxy sugars, *Angew. Chem.* **1987**, *99*, 246-247; (b) Giese, B.; Gilges, S.; Groninger, K. S.; Lamberth, C.; Witzel, T. Synthesis of 2-deoxysugars *Liebigs Ann. Chem.* **1988**, 615-617.

17. Crich, D.; Yao, Q. The β-(phosphonooxy)alkyl radical rearrangement, *J. Am. Chem. Soc.* **1993**, *115*, 1165-1166.

18. Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. Radical rearrangement of 2-O-(diphenylphosphoryl)glycosyl bromides. A new synthesis for 2-deoxy disaccharides and 2-deoxy ribonucleosides, *J. Org. Chem.* **1993**, *58*, 1083-1089.

19. Giese, B.; Erdmann, P.; Giraud, L.; Gobel, T.; Petretta, M.; Schafer, T.; von Raumer, M. Heterolytic C,O-bond cleavage of 4'-nucleotide radicals, *Tetrahedron Lett.* **1994**, *35*, 2683-2686.

20. Mohamed, R. K.; Peterson, P. W.; Alabugin, I. V. Concerted reactions that produce diradicals and zwitterions: electronic, steric, conformational, and kinetic control of cycloaromatization processes, *Chem. Rev.* **2013**, *113*, 7089-7129.

21. (a) Dedon, P. C.; Goldberg, I. H. Free-radical mechanisms involved in the formation of sequence-dependent bistranded DNA lesions by the antitumor antibiotics bleomycin, neocarzinostatin, and calicheamicin, *Chem. Res. Toxicol.* **1992**, *5*, 311-332; (b) Nicolaou, K. C.; Smith, A. L. Molecular design, chemical synthesis, and biological action of enediynes, *Acc. Chem. Res.* **1992**, *25*, 497-503; (c) Lee, M. D.; Ellestad, G. A.; Borders, D. B. Calicheamicins: discovery, structure, chemistry, and interaction with DNA, *Acc. Chem. Res.* **1991**, *24*, 235-243; (d) Kappen, L. S.; Goldberg, I. H.; Frank, B. L.; Worth, L.; Christner, D. F.; Kozarich, J. W.; Stubbe, J. Neocarzinostatin-induced hydrogen atom abstraction from C-4' and C-5' of the T

residue at a d(GT) step in oligonucleotides: shuttling between deoxyribose attack sites based on isotope selection effects, *Biochemistry* **1991**, *30*, 2034-2042; (e) Hangeland, J. J.; De Voss, J. J.; Heath, J. A.; Townsend, C. A.; Ding. W. D. Ashcroft, J. S.; Ellestad, G. A. Specific abstraction of the 5'S- and 4'-deoxyribosyl hydrogen atoms from DNA by calicheamicin γ1I, *J. Am. Chem. Soc*. **1992**, *114*, 9200-9202; (f) Christner, D. F.; Frank, B. L.; Kozarich, J. W.; Stubbe, J.; Golik, J.; Doyle, T. W.; Rosenberg, I. E.; Krishnan, B. Unmasking the chemistry of DNA cleavage by the esperamicins: modulation of 4'-hydrogen abstraction and bistranded damage by the fucose-anthranilate moiety, *J. Am. Chem. Soc*. **1992**, *114*, 8763-8767.

22. (a) Greenberg, M. M.; Barvian, M. R.; Cook, G. P.; Goodman, B. K.; Matray, T. J.; Tronche, C.; Venkatesan, H. DNA damage induced via 5,6-dihydrothymid-5-yl in single-stranded oligonucleotides, *J. Am. Chem. Soc*. **1997**, *119*, 1828-1839; (b) Barvian, M. R.; Greenberg, M. M. Independent generation of 5,6-dihydrothymid-5-yl in single-stranded polythymidylate. O2 is necessary for strand scission, *J. Am. Chem. Soc*. **1995**, *117*, 8291-1892; (c) Sugiyama, H.; Fujimoto, K.; Saito, I.; Kawashima, E.; Sekine, T.; Ishido, Y. Evidence for intra-strand C2' hydrogen abstraction in photo- irradiation of 5-halouracil-containing oligodeoxyribonucleotides by using stereospecifically C2'-deuterated deoxyadenosine, *Tetrahedron Lett*. **1996**, *37*, 1805-1808.

23. (a) Taverna Porro, M. L.; Greenberg, M. M. DNA double strand cleavage via interstrand hydrogen atom abstraction, *J. Am. Chem. Soc*. **2013**, *135*, 16368-16371; (b) Zhou, C.; Greenberg, M. M. DNA damage by histone radicals in nucleosome core particles, *J Am. Chem. Soc*. **2014**, *136*, 6562-6565.

24. (a) Dizdaroglu, M.; Von Sonntag, C.; Schulte-Frohlinde, D. Strand breaks and sugar release by γ-irradiation of DNA in aqueous solution, *J. Am. Chem. Soc.* **1975**, *97*, 2277-2778; (b) Giese, B. Long-distance charge transport in DNA: the hopping mechanism, *Acc. Chem. Res.* **2000**, *33*, 631-636.

25. (a) Hecht, S. M. RNA degradation by bleomycin, a naturally occurring bioconjugate, *Bionconjugate Chem.* **1994**, *5*, 513-526; (b) Holmes, C. E.; Hecht, S. M. Iron-bleomycin cleaves a transfer RNA precursor and its "transfer DNA" analog at the same major site, *J. Biol. Chem.* **1993**, *268*, 25909-25913.

26. (a) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal solvation model based on solute electron density and a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions, *J. Phys. Chem. B*, **2009**, *113*, 6378-6396; (b) Barone, V.; Cossi, M. Quantum calculation of molecular energies and energy gradients in solution by a conductor solvent model, *J. Phys. Chem. A*, **1998**, *102*, 1995-2001.

27. Maillard, B.; Walton, J. C. An ESR study of bicyclo[1.1.1]pent-1-yl radicals. *J. Chem.* Soc. *Chem. Commun.* **1983**, 900-901.

28. Adcock, W.; Binmore, G. T.; Krstic, A. R.; Walton, J. C.; Wilkie, J. Cross cage interactions in substituted bicyclo[1.1.1]pent-1-yl radicals. Dissociation to [1.1.1]propellane. *J. Am. Chem. Soc.*, **1995**, *117*, 2758-2766.

29. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov,

A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Mont-gomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian 09, Revision D.01; Gaussian, Inc.: Wallingford CT, 2016.

30. Francis, T. The bisulfite radical - what is its lifecycle in living systems? MChem Dissertation, University of St. Andrews, 2018.

31. Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. Gaussian-4 theory. *J. Chem. Phys.* **2007**, *126*, 84108-84119.

32. Zhao, Y.; Schultz, N. E.; Truhlar, D. G. Exchange-correlation functional with broad accuracy for metallic and nonmetallic compounds, kinetics, and noncovalent inter-actions *J. Chem. Phys.* **2005**, *123*, 161103(1)–161103(4).

33. (a) Adamo, C.; Barone, V. Toward reliable density functional methods without adjustable parameters: the PBE0 model *J. Chem. Phys.* **1999**, *110*, 6158–6170. (b) Ernzerhof, M.; Scuseria, G. E. Assessment of the Perdew-Burke-Ernzerhof exchange-correlation functional *J. Chem. Phys.* **1999**, *110*, 5029–5036.

34. (a) Vydrov, O. A.; Scuseria, G. E.; Perdew, J. P. Tests of functionals for systems with fractional electron number *J. Chem. Phys.* **2007**, *126*, 154109–154117. (b) Vydrov, O. A.; Heyd, J.; Krukau, A. V.; Scuseria, G. E. Importance of short-range versus long-range Hartree-Fock exchange for the performance of hybrid density functionals *J. Chem. Phys.* **2006**, *125*, 74106 – 74114. (c) Vydrov, O. A.; Scuseria, G. E. Assessment of a long-range corrected hybrid functional *J. Chem. Phys.* **2006**, *125*, 234109–234117.

35. Yanai, T.; Tew, D. P.; Handy, N. C. A new hybrid exchange-correlation functional using the coulomb-attenuating method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, *393*, 51-57.

36. (a) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. Aqueous solvation free energies of ions and ion-water clusters based on an accurate value for the absolute aqueous solvation free energy of the proton. *J. Phys. Chem. B* **2006**, *110*, 16066-16081; (b) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. Single-ion solvation free energies and the normal hydrogen electrode potential in methanol, acetonitrile, and dimethyl sulfoxide, *J. Phys. Chem. B* **2007**, *111*, 408-422.

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