

Super Radical Stabilizers

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ABSTRACT

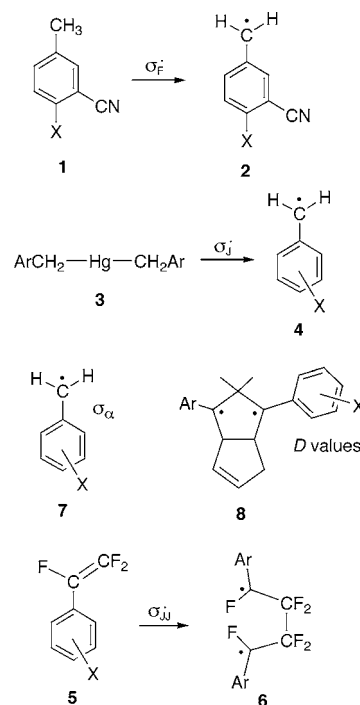
A comprehensive series of substituted 1,1-dimethyl-2-methylenecyclopropanes have been thermally rearranged. These rearrangements proceed via singlet biradical intermediates that can be stabilized by substituents. Rates are greatly enhanced by certain groups that are termed super radical stabilizers. Substituents included 4-pyridyl *N*-oxide, 2-(1,6-methano[10]annuleny), and a number of anion-substituted phenyl groups. Simple valence bond theory, as well as more sophisticated computational studies, gives insights into modes of radical stabilization.

Introduction

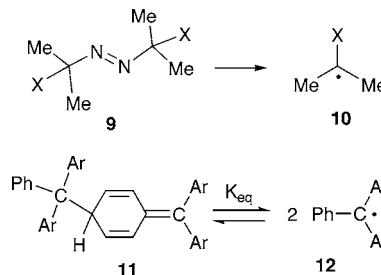
Carbon-centered free radicals have continued to hold the interest of chemists since Gomberg's discovery of the triphenylmethyl radical in 1900.¹ We and others have been interested in qualitative and quantitative abilities of various groups to stabilize radicals. A number of probes have been developed to evaluate radical-stabilizing effects on benzylic-type radicals, and various σ^* free radical substituent constant scales have been developed. These include the σ_F^* scale developed by Fisher² based on bromination rates of *m*-cyanotoluenes **1**, which attempts to minimize polar effects in the free radical bromination of toluene. Jackson³ has developed the σ_J^* scale based on rates of thermal decomposition of dibenzylmercurials **3**, which proceeds via benzylic radicals **4**. Jiang and Ji⁴ have developed the σ_{JJ}^* scale based on rates of cyclodimerization of trifluorostyrenes **5** where 1,4-biradicals **6** are intermediates. Scales that do not use kinetic data are the Arnold σ_α^* scale,⁵ based on benzyl radical hyperfine coupling constants in the electron spin resonance (ESR), and the Adam^{6,7} zero-field splitting parameter *D* of triplet biradicals **8**. All of these methods for evaluating radical stabilizing effects have their positive features as well as limitations.

In addition to these σ^* scales, methods for evaluating stabilization of radicals **10** by groups X, based on rates of pyrolysis of azoalkanes **9** and related substrates, have been developed.^{8–10} Measurement of the dissociation of **11** into substituted triphenylmethyl radicals **12** by ESR also allows evaluation of radical-stabilizing effects.¹¹ Increasingly

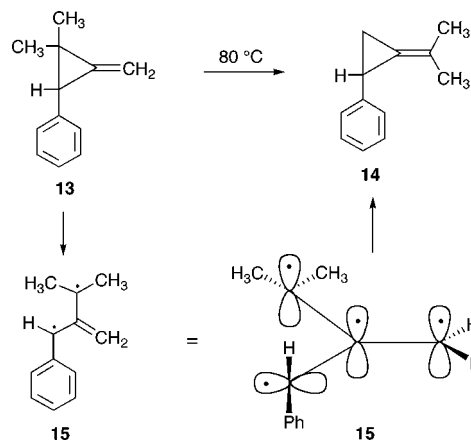
Xavier Creary is a native of Montclair, NJ, who received his B.S. from Seton Hall University in 1968 and his Ph.D. from The Ohio State University with Professor Paul Gassman in 1973. After postdoctoral studies in the laboratory of Professor Joseph Bunnett at the University of California, Santa Cruz, he joined the faculty at the University of Notre Dame in 1974. He is now the Charles L. Huisling Professor of Chemistry with research interests in the area of mechanistic organic chemistry and special interests in the chemistry of carbocations, free radicals, carbenes, and electron-transfer processes.



sophisticated theoretical calculations also allow an evaluation of radical-stabilizing effects.^{6a,9b,12}

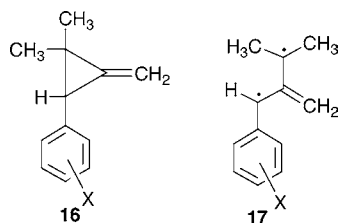


A number of years ago, we prepared the methylenecyclopropane **13** and found that it rearranged at a conve-



nient rate at 80 °C to give the isopropylidene-cyclopropane **14**.¹³ The general methylenecyclopropane rearrangement is an intriguing process that has been subject to numerous investigations.¹⁴ It is theoretically possible that this reaction is a concerted 1,3-sigmatropic rearrangement pro-

ceeding with inversion of stereochemistry at the migrating center.¹⁵ However the accepted mechanism involves a stepwise formation of a singlet biradical intermediate such as **15**, which can close to give the rearranged product **14**.¹⁶ With this mechanism in mind, we envisaged that the rate of this rearrangement should be dependent on the stability of the biradical **15**, that is, substituents on the ring that stabilize the benzylic radical should enhance the rearrangement rate. These substituent effects give a quantitative measure of radical-stabilizing abilities of various groups on carbon-centered free radicals. We have therefore used the rearrangement rate of substituted methylenecyclopropanes **16** as a quantitative measure of the



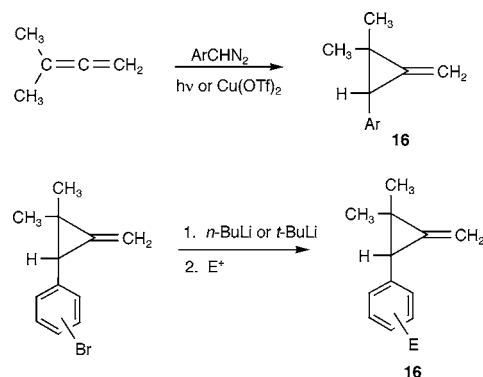
ability of substituents to stabilize the biradical **17**.^{17–26} This Account will summarize these radical-stabilizing effects that we have discovered and will discuss some of the most effective radical stabilizers, which we have termed “super radical stabilizers”.²⁴

Syntheses and Kinetic Studies

Our studies have led us to prepare and measure rearrangement rates of 103 different methylenecyclopropanes

described in this Account. The methodology used to prepare these substrates involved mainly addition of arylcarbenes to 1,1-dimethylallene, where the major product **16** is derived from addition of the most substituted double bond of the allene (Scheme 1).¹³ In the case of Ar

Scheme 1. Preparation of Substituted Methylenecyclopropanes



= *p*-BrC₆H₄, lithium–halogen exchange followed by reaction with electrophilic reagents gave additional methylenecyclopropanes.

We have previously reported rearrangement rates of substrates **16** at 80 °C in C₆D₆ solvent. However, some of our earlier data¹⁷ were reported in isooctane solvent at 100 °C. We have now re-determined these rates in C₆D₆, which has become our standard solvent. The previous kinetic method involved measurement of integrated absorption intensities in the olefinic region of 300 MHz ¹H NMR spectra relative to intensities of an internal standard

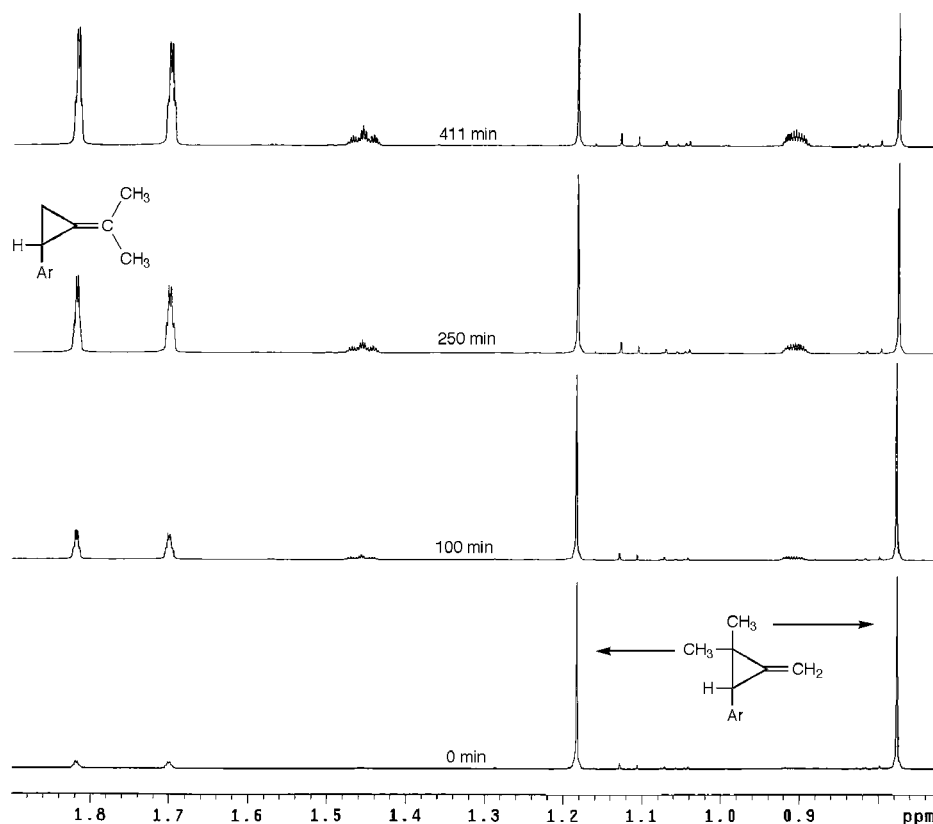


FIGURE 1. Evolving ¹H NMR spectra during rearrangement of **16** (Ar = *p*-F-C₆H₄) at 80 °C in C₆D₆.

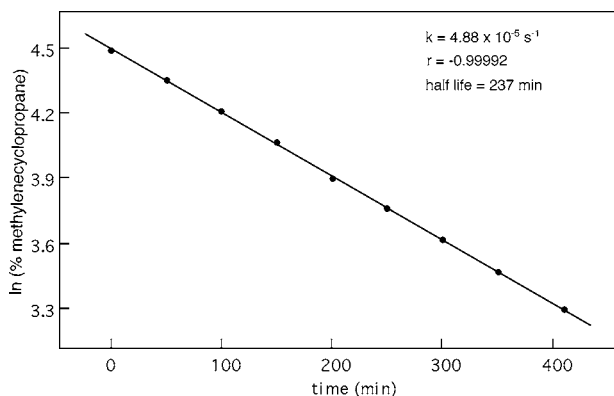


FIGURE 2. First-order kinetic plot for rearrangement of **16** (Ar = *p*-F-C₆H₄) at 80 °C in C₆D₆.

Table 1. Effect of *Para*-Substituents on Rearrangement Rate of **16** in C₆D₆ at 80.0 °C

substituent	k (s ⁻¹)	k_{rel}	σ_C^*
4-OTf	4.65×10^{-5}	0.83 ^a	-0.08
4-F	4.88×10^{-5}	0.88	-0.06
4-H	5.57×10^{-5}	1.00	0.00
4-OAc	6.25×10^{-5}	1.12 ^a	0.05
4-CF ₃	6.26×10^{-5}	1.12	0.05
4-Br	7.17×10^{-5}	1.29	0.11
4-Cl	7.19×10^{-5}	1.29	0.11
4-SnMe ₃	7.56×10^{-5}	1.36	0.13
4- <i>t</i> -Bu	8.00×10^{-5}	1.44	0.16
4-CH ₃	8.05×10^{-5}	1.45	0.16
4-I	8.18×10^{-5}	1.47	0.17
4-PO(OEt) ₂	8.24×10^{-5}	1.52	0.17
4-HgCl	8.27×10^{-5}	1.48	0.17
4-SO ₂ CH ₃	8.35×10^{-5}	1.50	0.18
4-SOCH ₃	8.47×10^{-5}	1.52	0.18
4-SiMe ₃	8.78×10^{-5}	1.58	0.20
4-CONMe ₂	9.23×10^{-5}	1.66 ^a	0.22
4-cyclopropyl	9.57×10^{-5}	1.72	0.24
4-OH	1.01×10^{-4}	1.81	0.26
4-OCH ₃	1.03×10^{-4}	1.85	0.27
4-OTBS	1.04×10^{-4}	1.86	0.27
4-CH ₂ SiMe ₃	1.04×10^{-4}	1.87	0.27
4-B[OCH ₂ CH ₂ O]	1.06×10^{-4}	1.90	0.28
4-PS(OEt) ₂	1.09×10^{-4}	1.96	0.29
4-N(O)=N-Bu- <i>t</i>	1.11×10^{-4}	2.00	0.30
4-NHAc	1.22×10^{-4}	2.19 ^a	0.34
4-boronic anhydride	1.23×10^{-4}	2.21	0.34
4-CO ₂ Et	1.32×10^{-4}	2.38	0.38
4-N ₃	1.40×10^{-4}	2.41	0.38
4-CSNMe ₂	1.35×10^{-4}	2.43	0.39
4-CO ₂ CH ₃	1.40×10^{-4}	2.52	0.40
4-CO- <i>t</i> -Bu	1.44×10^{-4}	2.59 ^a	0.41
4-SCH ₃	1.59×10^{-4}	2.85	0.45
4-CO ₂ H	1.59×10^{-4}	2.85 ^a	0.45
4-Ph	1.60×10^{-4}	2.87	0.46
4-CN	1.66×10^{-4}	2.98	0.47
4-COCH ₃	1.80×10^{-4}	3.23 ^a	0.51
4-COPh	1.87×10^{-4}	3.35 ^a	0.53
4-C(CH ₃)=CH ₂	1.90×10^{-4}	3.41	0.53
4-CCH	1.94×10^{-4}	3.49 ^a	0.54
4-NO ₂	2.09×10^{-4}	3.75	0.57
4-CCCH ₃	2.07×10^{-4}	3.71 ^a	0.57
4-CH=N-Bu- <i>t</i>	2.14×10^{-4}	3.97	0.60
4-CHO	2.43×10^{-4}	4.35 ^a	0.64
4-CH=CH ₂	2.60×10^{-4}	4.67	0.67
4-CH=N-OH	2.66×10^{-4}	4.78	0.68
4-N=N-Bu- <i>t</i>	2.70×10^{-4}	4.85	0.69
4-NH ₂	2.82×10^{-4}	5.06	0.70
4-CH=N-OCH ₃	2.86×10^{-4}	5.13	0.71
4-COCF ₃	3.64×10^{-4}	6.53 ^a	0.81
4-NMe ₂	4.39×10^{-4}	7.88	0.90
4-CH=N-NMe ₂	4.60×10^{-4}	8.27	0.92
4-N=N(O)-Bu- <i>t</i>	5.26×10^{-4}	9.45	0.98
4-N=N-Ph	7.00×10^{-4}	12.1	1.08
4-CH=N(O)-Bu- <i>t</i>	7.53×10^{-4}	13.5	1.13

^a Previously unreported.

Table 2. Effect of *Meta*-Substituents on Rearrangement Rate of **16** in C₆D₆ at 80.0 °C

substituent	k (s ⁻¹)	k_{rel}	σ_C^*
3-CN	4.16×10^{-5}	0.75	-0.13
3-PO(OEt) ₂	4.24×10^{-5}	0.78	-0.11
3-NO ₂	4.29×10^{-5}	0.77	-0.11
3-CF ₃	4.65×10^{-5}	0.84	-0.08
3-SO ₂ CH ₃	4.79×10^{-5}	0.86	-0.07
3-OTf	4.92×10^{-5}	0.88 ^a	-0.05
3-PS(OEt) ₂	4.93×10^{-5}	0.89	-0.05
3-Cl	5.15×10^{-5}	0.92	-0.03
3,5-di-Cl	5.24×10^{-5}	0.94	-0.03
3-F	5.30×10^{-5}	0.95	-0.02
3-OCH ₃	5.38×10^{-5}	0.97	-0.02
3-SCH ₃	5.50×10^{-5}	0.99	-0.01
3-SOCH ₃	5.55×10^{-5}	1.00	0.00
3-H	5.57×10^{-5}	1.00	0.00
3-CH ₃	6.03×10^{-5}	1.08	0.03
3-SiMe ₃	6.46×10^{-5}	1.16	0.06
3,5-di-CH ₃	6.46×10^{-5}	1.16	0.06

^a Previously unreported.

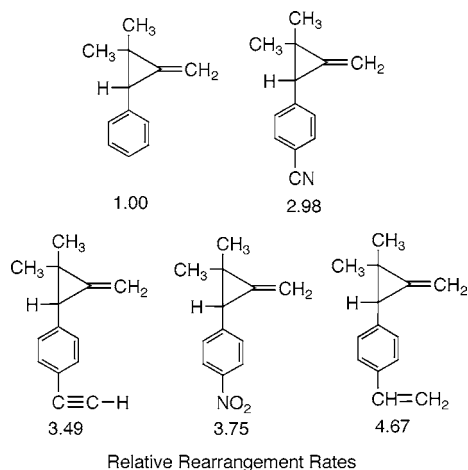
(dimethyl maleate). Our current method relies on 600 MHz ¹H NMR spectroscopy and measurement of relative areas of methyl hydrogens for starting material and product. Figure 1 shows typical data for **16** (Ar = *p*-F-C₆H₄) at 80.0 °C, while Figure 2 shows typical first-order kinetic behavior for this substrate.

Table 1 gives rate data for many previously determined *para*-substituted substrates, as well as data for a number of substituents not previously reported. Table 2 gives data for *meta*-substituents. The corresponding σ_C^* values, which are defined as $\sigma_C^* = \log(k_{\text{rel}})$, are also given.

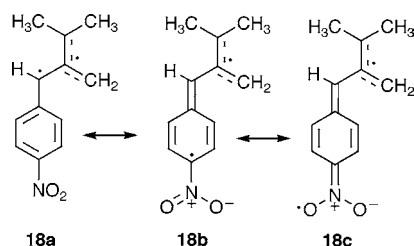
Substituent Effects on the Methylenecyclopropane Rearrangement.

Tables 1 and 2 illustrate the major advantage of the σ_C^* substituent constant scale, which is availability of data. Unlike many other scales where only a relatively small number of values are available, our scale has values for virtually all of the common substituents, as well as many less common substituents. The first thing that is apparent from data in Tables 1 and 2 is that substituent effects on the rate are generally small. Substituents in the *para*-position enhance the rate, with the sole exceptions being the strong inductively electron-withdrawing *p*-F and *p*-OSO₂CF₃ groups. Data in Table 2 show that electron-withdrawing groups in the *meta*-position also slow the rate slightly. These findings are consistent with ESR benzylic radical hyperfine coupling constant data,⁵ which also suggest that electron-withdrawing substituents in the *meta*-position results in less spin delocalization (and presumably slightly destabilized benzylic radicals).

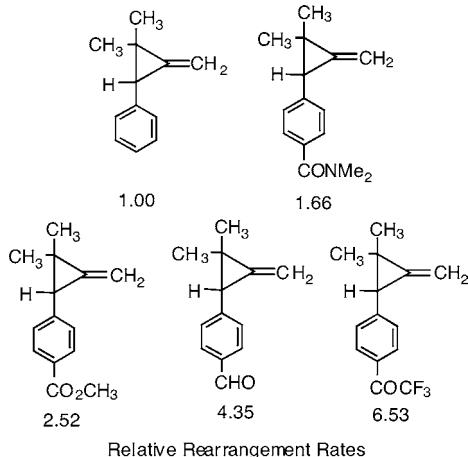
Immediately apparent is the effect of conjugation on the transition state leading to the biradical intermediate. Thus groups such as cyano, alkyne, nitro, and alkene in the *para*-position, which are capable of spin delocalization via conjugation as exemplified in **18a–18c**, enhance the rearrangement rate. Spin delocalization utilizing C=C, C=N, and N=N double bonds results in rate enhance-



ments that are considered “large” for the rearrangement of **16**.

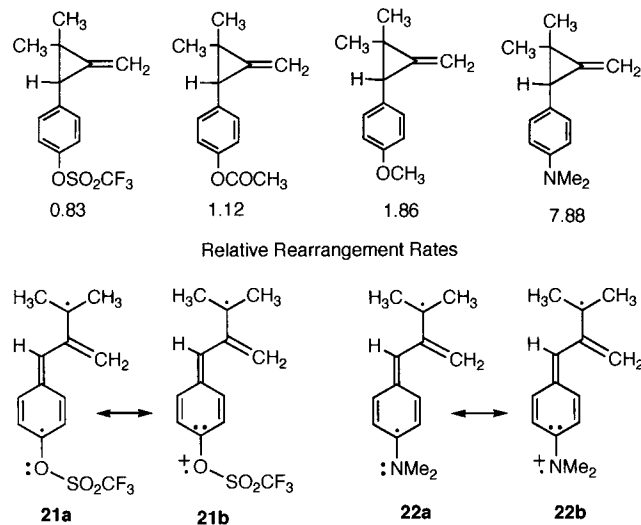


Carbonyl-containing substituents, which also stabilize the biradical intermediate via conjugation, exert a range of rate effects, which appear to depend on the availability of the carbonyl group for spin delocalization. Thus the amide, where the C=O is involved in competing amide resonance, is the least radical-stabilizing, while the COCF₃ group is the most stabilizing. B3LYP/6-31G* computa-



tional studies²⁷ show that the amide group in the benzylic radical **19** is twisted out of conjugation with the phenyl ring by 37°, presumably due to steric effects (Chart 1). Hence the spin density on the carbonyl oxygen of **19** (0.034) is decreased relative to the ester, aldehyde, and ketone analogues. Carbonyl groups with more double bond character, such as COCF₃ in radical **20**, appear to interact better with the developing spin at the *para*-position. This is reflected by increased spin density (0.110) on oxygen in radical **20**.

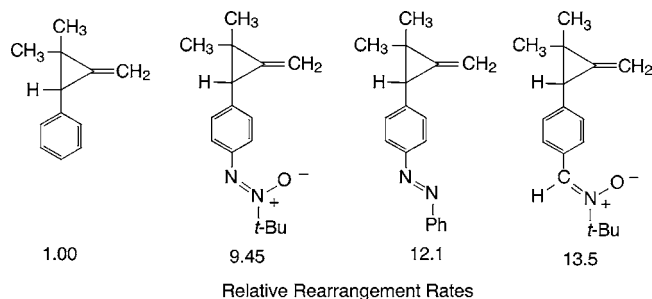
Resonance interactions involving nonbonding electron pairs is also an important radical-stabilizing feature. The increasing reaction rates in the series of substrates **16**, where X = *p*-OTf, *p*-OAc, *p*-OCH₃, and *p*-NMe₂, is a manifestation of the ability of the nonbonding electrons on oxygen to delocalize spin. Thus forms such as **21b** have



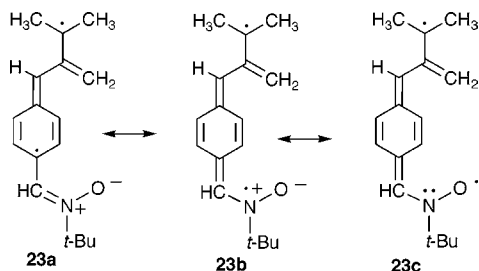
decreased importance, while forms such as **22b** assume increased importance.

Super Stabilizing Substituents.

While many other subtle effects of substituents in Tables 1 and 2 are of interest, the *p*-N=N(O)-*Bu-t*, *p*-N=N-Ph, and *p*-CH=N(O)-*Bu-t* groups stand out due to their large rate enhancements.²⁴ In fact, for many years, the largest rate enhancements that we had observed were around a factor of 5. However, these later three groups are especially effective at enhancing the rate of **16**, and Creary and Engel have arbitrarily called these groups “super radical stabilizers”.²⁴ They are extraordinarily effective at stabilizing the radical-like transition state. This stabilization in rearrangement of the nitronium system was attributed to spin delocalization utilizing forms such as **23b** and **23c**, which

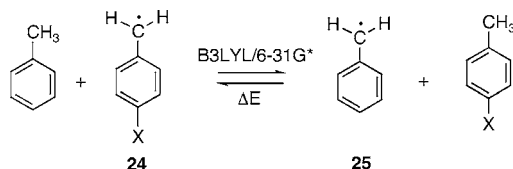


can be recognized as a nitroxyl radical. Nitroxyl radicals are well-known to possess special kinetic as well as thermodynamic stability.²⁸



While this simple valence bond approach offers reasonable explanations for many radical-stabilizing effects, additional insight can be derived from B3LYP/6-31G* computational data. The radical stabilization energy (ΔE) of various groups can be calculated from the isodesmic reaction of toluene with substituted benzyl radicals **24** (Scheme 2).²⁴ There is a good correlation (Figure 3) between rearrangement rate of **16** and calculated radical stabilization energies of analogous benzyl radicals. The slope of this line (0.7) suggests significant benzylic radical character in the transition state for the rearrangement of

Scheme 2. Isodesmic Reaction of Toluene with Substituted Benzyl Radicals



16. These computational data also show significant spin density on the nitrogen (0.166) and the oxygen (0.234) of the benzylic radical **26** (a computational analogue of biradical **23**). There is a corresponding reduction in the spin density at the benzylic carbon in **26** (0.637) relative to the benzyl radical **25** (0.792). Bond length data are also in accord with valence bond considerations which emphasize the importance of forms such as **26a** (Chart 2).

Super Stabilizing Aromatic Groups

We have also carried out kinetic studies on a number of substrates, which allow comparison of the radical stabilizing ability of benzene with that of other aromatic systems.²³ Rate data for thermal rearrangement of these substrates are summarized in Table 3, and relative rates have been converted to γ_C^* (group σ_C^* values). With an arbitrary rate enhancement factor of 10, the final five aromatic systems in Table 3 qualify as "super radical stabilizers".

The pyridine *N*-oxide system is among the most interesting of the aromatic super stabilizers.^{22,23} The 4-pyridyl-*N*-oxide system **29** is enhanced by a factor of 75, while the 3-pyridyl-*N*-oxide is actually slower than the phenyl analogue **1**. The valence bond approach, as well as the computational approach, reveals the reasons for

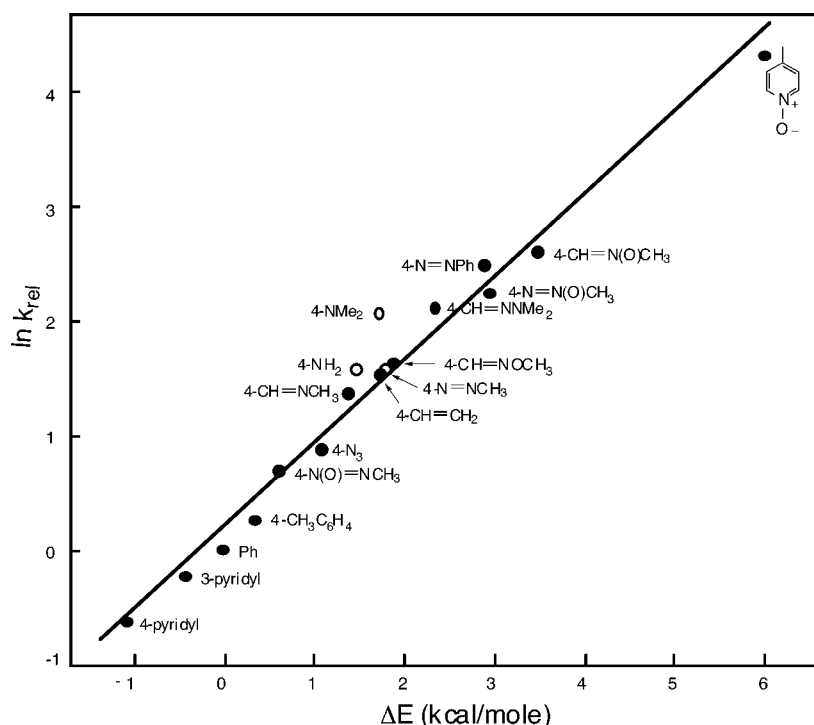
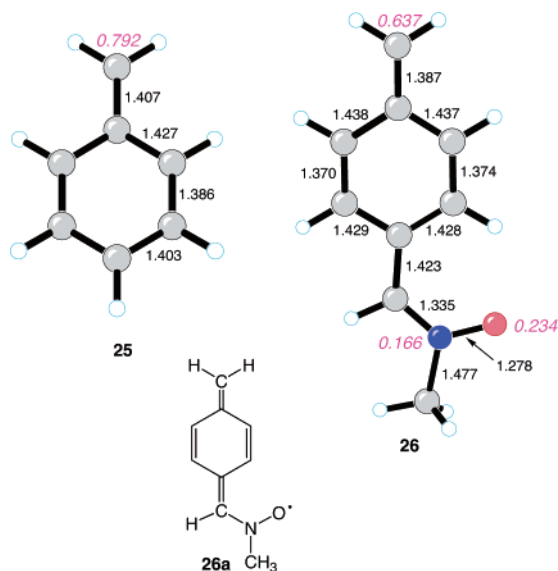
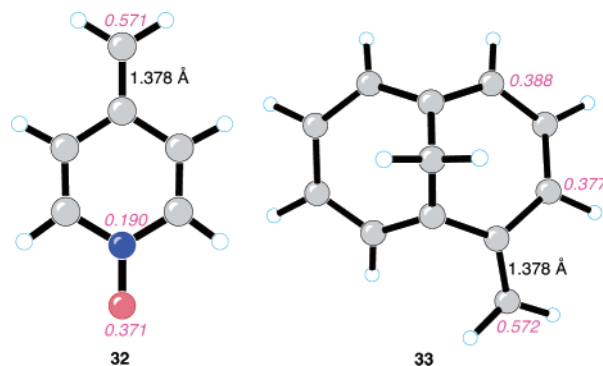


FIGURE 3. A plot of $\ln k_{rel}$ for rearrangement of **16** vs B3LYP/6-31G* radical stabilization energies of **24**.

Chart 2. B3LYP/6-31G* Structures of Benzyl Radical and *p*-CHNO(CH₃)-Substituted Benzyl RadicalChart 3. B3LYP/6-31G* Structures of Pyridine *N*-Oxide- and 1,6-Methano[10]annulene-Substituted Radicals

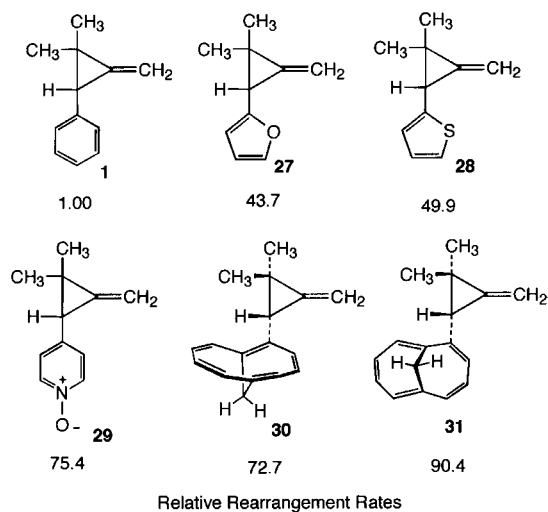
ture of **32** (Chart 3), which shows high spin density on both nitrogen and oxygen, as well as a shortened bond from the benzylic carbon to the ring. The radical **32** is stabilized by 6.0 kcal/mol relative to the unsubstituted benzyl radical **25**. These effects disappear in the 3-pyridyl-*N*-oxide system, where conjugation with the developing radical center cannot occur.

The 1,6-methano[10]annuleny group, an aromatic system first prepared by Vogel,²⁹ is a potent radical stabilizer. When attached to our methylenecyclopropane system, two separable diastereomers **30** and **31** result.²⁶ These systems are both highly reactive in the methylenecyclopropane rearrangement, rearranging 73 and 90 times faster than the parent system. Again, computational studies provide insight into the stabilization of radicals by the 1,6-methano[10]annuleny group. There is extensive spin delocalization in **33** as revealed by the relatively low-spin density (0.572) at the CH₂ position. However, this spin delocalization by the annulene ring necessarily results in disruption of aromaticity. The aromatic character of the 1,6-methano[10]annulene system,³⁰ which is not completely planar,³¹ is less than that of a benzene ring involved in delocalization. Hence the cost for disruption of aromaticity in radical **33** is less than must be paid for disruption of benzene aromaticity in **25**. The same principle accounts for the super radical stabilizing effect of furan and thiophene. Extensive spin delocalization into these ring systems does not require a large disruption of aromaticity.

Table 3. Effect of Aryl Groups on the Rearrangement Rate of **16** in C₆D₆ at 80.0 °C

aryl group	k (s ⁻¹)	k_{rel}	γ_C^*
C ₆ H ₅ Cr(CO) ₃	1.82×10^{-5}	0.33	-0.49
2,6-di-CH ₃ -C ₆ H ₃	2.37×10^{-5}	0.43	-0.37
3-pyridyl- <i>N</i> -oxide	2.86×10^{-5}	0.51	-0.29
4-pyridyl	2.95×10^{-5}	0.53	-0.28
3-furanyl	4.31×10^{-5}	0.77	-0.11
3-pyridyl	4.39×10^{-5}	0.79	-0.10
phenyl	5.57×10^{-5}	1.00	0.00
3-thienyl	6.71×10^{-5}	1.21	0.08
ferrocenyl	8.90×10^{-5}	1.60	0.20
1-naphthyl	9.51×10^{-5}	1.71	0.23
2-naphthyl	1.74×10^{-4}	3.12	0.49
3-pyrenyl	5.27×10^{-4}	9.46	0.98
2-furanyl	2.43×10^{-3}	43.7	1.64
2-thienyl	2.78×10^{-3}	49.9	1.70
4-pyridyl- <i>N</i> -oxide	4.20×10^{-3}	75.4	1.88
methano[10]annuleny 30	4.06×10^{-3}	72.7	1.86
methano[10]annuleny 31	5.04×10^{-3}	90.4	1.96

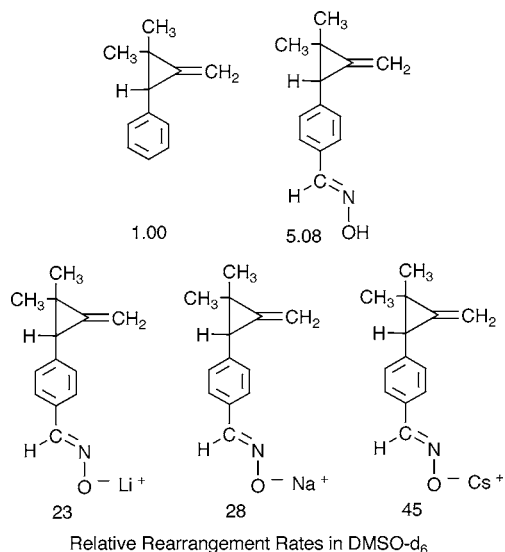
the large radical stabilizing effect of 4-pyridyl-*N*-oxide. As in the case of the nitronium, nitroxyl character in the transition state is the key stabilizing factor. This nitroxyl radical character is reflected in the B3LYP/6-31G* struc-



Anionic Groups.

In view of the relative effectiveness of the oxime substituent *p*-CH=NOH in enhancing the rearrangement rate of **16**, we next turned to the deprotonated analogue. Since these salts were not expected to be very soluble in C₆D₆, DMSO-*d*₆ was used as a convenient solvent. Rearrangement of **16** (X = *p*-CH=NO⁻ M⁺) occurred smoothly in this solvent, and rates of rearrangement of these and various other anionic derivatives of **16** in DMSO-*d*₆ are summarized in Table 4.²⁴

While the oxime substituent *p*-CH=NOH is classified as a good radical stabilizer, deprotonation leads to super radical stabilizers. There is a regular trend as counter-cation is varied from Li⁺ through Cs⁺, with the Cs⁺ salt



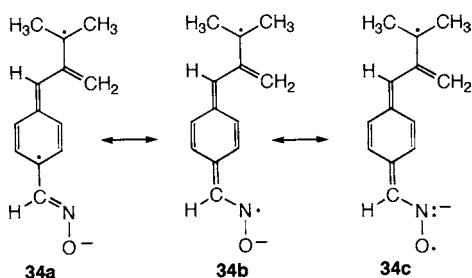
providing the most stabilization. This trend suggests that the “free anion” p -CH=NO⁻ is more capable of interacting

Table 4. Effect of Anionic Substituents on the Rearrangement Rate of 16 in DMSO- d_6

substituent	temp (°C)	k (s ⁻¹)	k_{rel}	σ_C^*
4-H	25.0	5.57×10^{-8}	1.00	0.00
4-H	80.0	7.90×10^{-5}	1.00	0.00
3-O ⁻ Na ⁺	80.0	1.11×10^{-4}	1.40	0.15
4-[C(O)NOCH ₃] ⁻ Na ⁺	25.0	9.67×10^{-8}	1.74 ^a	0.24
4-CO ₂ ⁻ Na ⁺	80.0	1.69×10^{-4}	2.14 ^a	0.33
4-CH=N-O ⁻ Li ⁺	80.0	1.83×10^{-3}	23	1.36
4-CH=N-O ⁻ Na ⁺	80.0	2.23×10^{-3}	28	1.45
4-CH=N-O ⁻ K ⁺	80.0	3.35×10^{-3}	42	1.62
4-CH=N-O ⁻ Cs ⁺	80.0	3.55×10^{-3}	45	1.65
4-S ⁻ Na ⁺	25.0	1.37×10^{-5}	246 ^a	2.39
4-(NCOCH ₃) ⁻ Na ⁺	25.0	2.86×10^{-6}	51 ^a	1.71
4-(CHNO ₂) ⁻ Na ⁺	25.0	3.70×10^{-6}	66 ^a	1.82
4-(CHCO- <i>t</i> -Bu) ⁻ Na ⁺	25.0	7.59×10^{-5}	1360 ^a	3.13
4-(NOCOCH ₃) ⁻ Cs ⁺	25.0	2.41×10^{-6}	43 ^a	1.63
4-O ⁻ Li ⁺	25.0	2.72×10^{-5}	490	2.69
4-O ⁻ Na ⁺	25.0	9.28×10^{-5}	1670	3.22
4-O ⁻ K ⁺	25.0	1.57×10^{-4}	2810	3.45
4-O ⁻ Cs ⁺	25.0	2.02×10^{-4}	3620	3.56

^a Previously unreported.

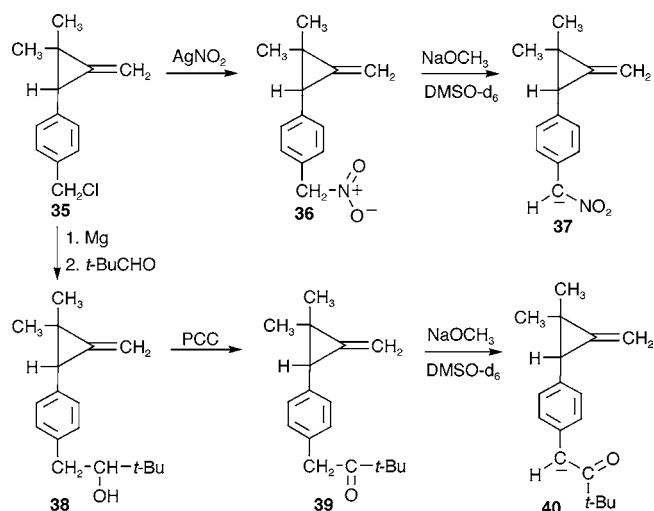
with the developing radical center. A valence-bond rationalization of this super stabilization involves spin delocalized forms such as **34**. The further implication is that



anions adjacent to a radical center, as suggested by **34b**, will have a stabilizing effect on the radical.

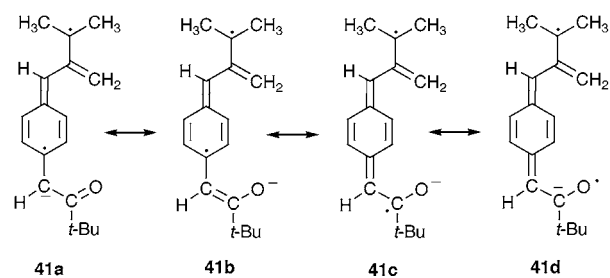
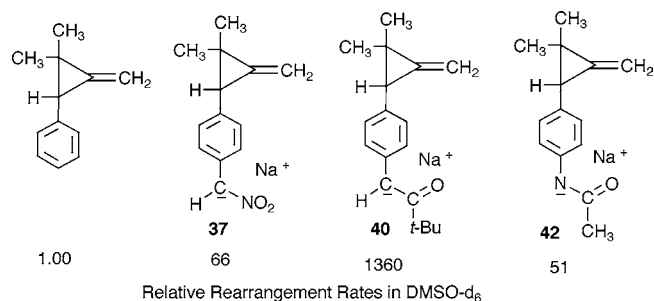
With this suggestion in mind, attention was turned to carbanion stabilization of radicals. The nitronate anion **37** and the enolate anion **40** were prepared as shown in Scheme 3 from the benzylic chloride **35**. These sodium salts were rearranged in DMSO- d_6 and rate data are given

Scheme 3. Preparation of Anionic-Substituted Methylene-cyclopropanes



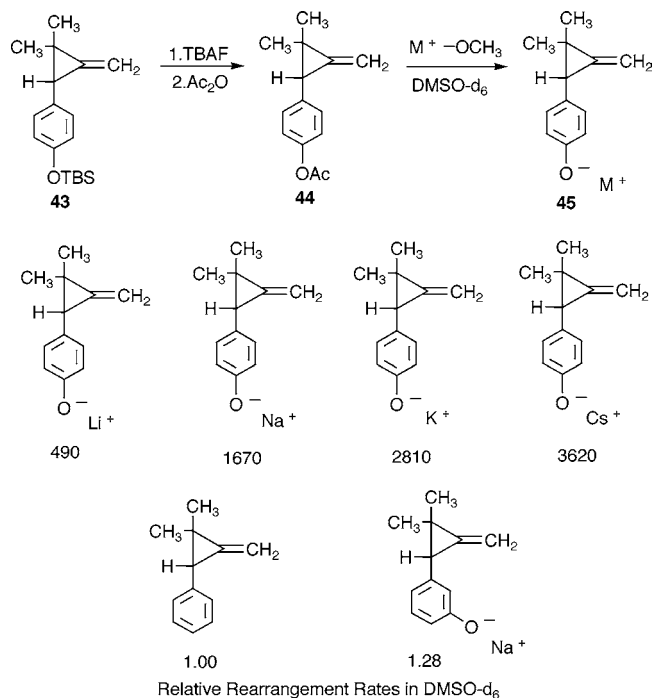
in Table 4. Much of these data are reported at 25.0 °C since it is more convenient to measure some of these faster rates at this lower temperature.

It is immediately apparent that the anionic substituents in **37** and **40** are super radical stabilizers. The enolate anion is especially effective as a radical stabilizer, and **40** rearranges with a half-life of only 2.53 h at 25 °C. Forms such as **41a–41d** undoubtedly contribute to stability of



the biradical intermediate. Forms **41c** and **41d** are recognizable as ketyl radical anions, which have substantial spin density on the oxygen atom. The amidate anion, ⁻NCOCH₃, in **42** is also a super stabilizer, although not as effective as enolate.

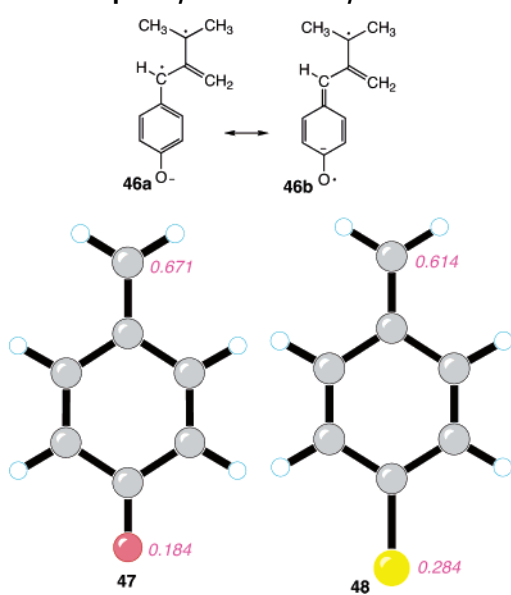
Which anionic groups are the best radical stabilizers? Taking a cue from the enolate **40**, the phenoxides **45** were examined. Since the free phenol (**16**; X = p -OH) was readily oxidized to a peroxide by atmospheric oxygen,²⁵ a new sequence was used to generate phenoxide anions that avoided isolation of the phenol. The acetate **44**, which



could be prepared from the silylated derivative **43**, was cleaved to the appropriate phenoxide by metal methoxides in DMSO-*d*₆. Kinetic studies were carried out on the resulting solutions of phenoxide anions **45** in DMSO-*d*₆, and data are given in Table 4.

Rearrangement of these phenoxides is extraordinarily rapid, with the cesium salt being the fastest rearranging substrate studied to date. An element effect is also observed and again implies that “free” anions interact best with developing radical centers. The rate enhancement is a conjugation effect since phenoxide in the *meta*-position has a negligible effect. Valence bond theory (ketyl radical character as in **46b**) as well as the B3LYP/6-311+G** structure of the benzylic radical **47** (Chart 4) offer insight into the mode of radical stabilization. The

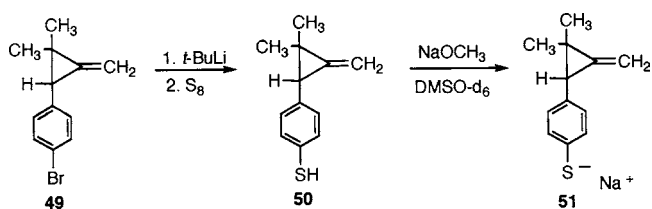
Chart 4. B3LYP/6-311+G** Structures of Phenoxy- and Thiophenoxy-Substituted Benzyl Radicals



calculated stabilization energy of **47** is 9.7 kcal/mol relative to the unsubstituted benzyl radical. The calculated spin density at the benzylic carbon of **47** (0.671) is substantially reduced relative to benzyl radical (0.813). The spin density on oxygen is significant (0.184) and attests to the ketyl character of **47**.

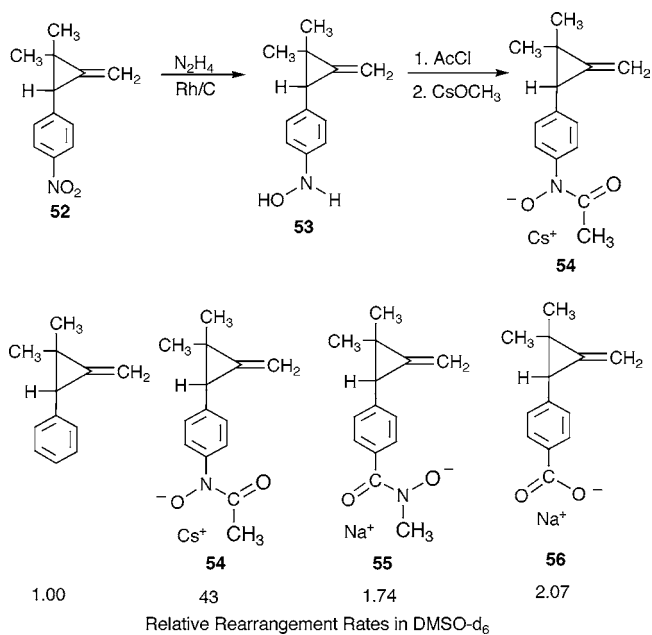
In view of the remarkable super radical-stabilizing ability of the phenoxide group, attention was next turned to the thiophenoxide analogue. A computational comparison at the B3LYP/6-311+G** level of radical **48**²⁷ with the phenoxide analogue **47** showed even less spin density at the benzylic carbon of **48**. This was compensated for by an increase in spin density at sulfur of **48** relative to oxygen in **47**. These factors point to even greater thiophenoxide stabilization of radicals. However, when the methylenecyclopropane **51** (Scheme 4) was rearranged, the rate

Scheme 4. Preparation of Thiolate-Substituted Methylenecyclopropane

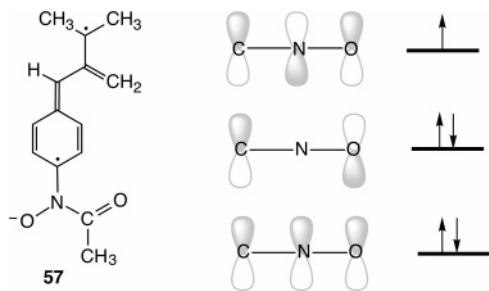


acceleration was *only* a factor of 256. Thiophenoxide appears to stabilize the transition state for the methylenecyclopropane rearrangement to a lesser degree than phenoxide despite the computational prediction. This is the first major discrepancy in this area between theory and experiment that we have observed. The reasons remain unclear, although the gas phase nature of the calculations versus the solution phase nature of the experiment may offer an explanation. The extent of weakening of the fragmenting cyclopropane bond in **45** by the anionic phenoxide (a ground-state effect) is also uncertain.

Scheme 5. Preparation and Rearrangement Rates of Hydroxamate-Substituted Methylenecyclopropanes



The final anionic super radical stabilizer that will be discussed is the hydroxamate derivative **54** (Scheme 5). This substrate was prepared by selective reduction of the nitro derivative **52** with hydrazine followed by acetylation and deprotonation of the neutral hydroxamic acid by CsOCH₃ in DMSO-*d*₆. Unlike the *p*-NHCOCH₃ derivative or the isomeric hydroxamate **55**, the hydroxamate group in **54** is classified as a super radical stabilizer. We rationalize this stabilization as a result of the arrangement of atoms in the biradical intermediate **57**, which allows spin



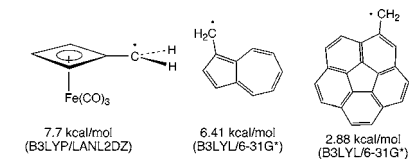
to be delocalized onto the anionic oxygen atom. Just as a nitroxyl radical can be viewed as a two-atom, three- π -electron system with spin delocalized between nitrogen and oxygen atoms, **57** can be viewed as a three-atom, five- π -electron system with spin delocalized onto all three atoms. By way of contrast, the hydroxamate group in **55** appears to possess no special radical stabilizing features. It behaves in fashion similar to the neutral amide *p*-CONMe₂, which is only a mild stabilizer.

Concluding Remarks

Some final thoughts on our σ^* radical substituent constant scale are appropriate. One of the major features of our σ_C^* scale that this Account emphasizes is its breadth. Unlike most other scales, σ_C^* constants are now available for virtually any common substituent, as well as for numerous uncommon groups of special interest. One of the limitations of our kinetically based σ^* scale is the inability to account for ground-state effects. How much of our rate enhancements are due to weakening of the fragmenting cyclopropane bond of the reactant, and how much is due to true radical stabilizing effects? While kinetic studies alone cannot sort out these factors, our computational studies reveal extensive spin delocalization in super stabilized radicals and suggest that our kinetic rate enhancements are due in large part to radical stabilization phenomena as opposed to ground-state effects.

While substituent effects on the rate of rearrangement of **16** were initially thought to be "small", comprehensive studies have led to the discovery of rate enhancements of up to a factor of 3600. How large can rate-enhancing effects become in the rearrangement of **16**? With the realization that certain anionic substituents are super stabilizers, a question remains as to the effect of cationic substituents, as well as substituents containing unpaired electrons. What are the effects of transition metal substituents as well as other aromatic systems? Computa-

tional studies can give some insight. The prediction is that the aromatic cyclobutadieneiron tricarbonyl system,³² as well as the azulene system²⁷ will be super radical stabilizers and therefore greatly enhance the methylenecyclopropane rearrangement rate. The corannulene system is



Calculated Radical Stabilization Energies Relative to Benzyl Radical

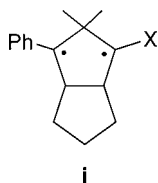
also another aromatic nucleus of much interest. However theory predicts only modest radical stabilizing ability²⁷ despite the availability of numerous resonance contributors. These computational predictions will await experimental verification.

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