Influence of Connector Groups on the Interactions of Substituents with Carbon-Centered Radicals

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Supporting Information

Abstract: High-level G3X(MP2)-RAD calculations have been carried out to examine the effect of interposing a “connector” group (W) on the interaction between a substituent (X) and the radical center in carbon-centered radicals (°CH₃=W→X). The connector groups include -CH₃, -CH=CH-, -C≡C-, -p-C₆H₄Cl-, -m-C₆H₄Cl-, and -o-C₆H₄Cl-, and the substituents include H, CF₃, CH₃, CH=O, NH₂, and CH=CH₂. Analysis of the results is facilitated by introducing two new quantities termed radical connector energies and molecule connector energies. We find that the -CH₃-connector effectively turns off σ-electron effects but allows the transmission of π-electron effects, albeit at a reduced level. The effect of a substituent X attached to the -CH=CH- and -C≡C- connector groups is to represent a perturbation of the effect of the connector groups themselves (i.e., CH=CH₃ and C≡CH).

1. INTRODUCTION

A wide range of reactions in synthetic organic chemistry,1 polymer chemistry,2 biochemistry,3 and inorganic chemistry4 exploit the effect of substituents on the thermodynamic stabilization or destabilization of carbon-centered radicals. An understanding of the factors that influence their thermodynamic stability is therefore very important.5 There have been numerous experimental6,7 and theoretical8,9 studies to quantify how proximate substituents, i.e., substituents directly attached to the carbon radical center, affect free radical stabilities.

A common measure of the effect of a substituent X on the stability of a carbon-centered radical is the radical stabilization energy (RSE). For a monosubstituted radical (°CH₃X), the RSE is given by the energy change for the hydrogen-transfer reaction:

°CH₂X + CH₄ → CH₃X + °CH₃

(1)

The RSE measures the effect of X on the stability of the radical °CH₂X relative to its effect in the closed-shell parent (CH₃X), with CH₄ and °CH₃ being included as the reference (unsubstituted) species. Defined in this way, a positive value for the RSE implies a net stabilization of the substituted radical with respect to the reference radical, relative to the same effect in the parent closed-shell species, whereas a negative value implies a net destabilization.

The RSE of eq 1 can equivalently be regarded as the difference between the homolytic C–H bond dissociation energy (BDE) of methane and CH₃X:

RSE(°CH₂X) = BDE(CH₄) − BDE(CH₃X)

(2)

where BDE(CH₃X) is the energy change in the reaction

CH₃X → °CH₃X + °H

(3)

The effect of remote substituents on bond dissociation energies (BDEs) has also been a topic of interest in the chemical literature. We note, for example, the experimental10 and theoretical11,12 studies of the effect of meta or para substituents (X) on benzylic (XCH₂CH₃→Y) C–H BDEs. It was concluded that in the abstraction of Y from p-XCH₂CH₃→Y, the direction of the C–Y dipole is the major rate-determining factor, and that when Y = H, an electron-withdrawing X increases the C–H BDE whereas an electron-donating X decreases the C–H BDE. Additionally, Zavittas et al.11c investigated the effect of substituents (X) on the allylic C–F and C–H BDEs in XCH=CHCH₂→F and XCH=CHCH₂→H. They found that similar types of electronic effects are present in allylic and benzylic systems, but that the effects transmitted through one double bond in allylic systems are greater than those transmitted through the aromatic ring in para-substituted benzylic systems.

In the present study, we systematically examine the effect of interposing various connector groups (W) between the substituent X and the radical center, on C–H bond dissociation energies and on the stabilities of the resultant carbon-centered radicals. For this purpose, we examine the C–H BDEs for molecules CH₃WX:

CH₃WX → °CH₂WX + °H

(4)

and the RSEs for the associated radicals °CH₂WX:

°CH₂WX + CH₄ → CH₃WX + °CH₃

(5)

To assist in our analysis, it is convenient to define some additional quantities. First, we define the radical stabilization energy of °CH₃WX relative to that of °CH₃WH (designated RSE₢) as the energy change for the hydrogen-transfer reaction:

°CH₂WX + CH₃WH → CH₃WX + °CH₃WH

(6)
This can be formulated alternatively in terms of C–H bond dissociation energies as
\[ \text{RSE}_W(\cdot CH_2WX) = \text{BDE}(CH_2WH) - \text{BDE}(CH_2WX) \] (7)
or, equivalently
\[ \text{RSE}_W(\cdot CH_2WX) = \text{RSE}(\cdot CH_2WX) - \text{RSE}(\cdot CH_2WH) \] (8)
If there is no connector group (referred to subsequently as \( W = \text{NIL} \)), the RSE (in this case termed \( \text{RSE}_0 \)) is given by
\[ \text{RSE}_0(\cdot CH_2X) = \text{BDE}(CH_2) - \text{BDE}(CH_2X) \] (9)
and is equal to the energy change for the reaction
\[ \cdot CH_2X + CH_4 \rightarrow CH_3X + CH_3 \] (10)
Thus, \( \text{RSE}_W \) carries over, in the limit of no connector group, to the conventional definitions of eqs 2 and 1, respectively.

It is convenient to define also the radical connector energy (RCE) of \( \cdot CH_2WX \) as the energy change for the formal reaction:
\[ CH_2WX + \cdot CH_3 \rightarrow CH_2WH + \cdot CH_3X \] (11)
This measures how the connector group \( W \) affects the interaction between \( X \) and \( CH_3 \) relative to that between \( H \) and \( CH_2 \). A positive value of the RCE indicates that \( W \) enhances the interaction between \( X \) and \( CH_3 \) relative to that between \( H \) and \( CH_2 \).

In a similar manner, the molecule connector energy (MCE) is given by the energy change for the formal reaction:
\[ CH_2WX + CH_4 \rightarrow CH_2WH + CH_3X \] (12)
This measures how the connector group \( W \) affects the interaction between \( X \) and \( CH_3 \) compared with that between \( H \) and \( CH_2 \).

Finally, the effect of the connector group \( W \) on the RSE is given by the difference between \( \text{RSE}_W \) and \( \text{RSE}_0 \). It is easy to show that this is equal to the difference between the RCE and the MCE:
\[ \text{RSE}_W - \text{RSE}_0 = \text{RCE} - \text{MCE} \] (13)

The connector groups \( W \) that we have examined in the present study include \(-CH_2-, -CH=CH-, -C≡C-, -p-C_6H_4-, -m-C_6H_4-, and -o-C_6H_4-\). The substituents \( X \) that we examine include \( H, CF_3, CH_3, CH≡O, NH_2, \) and \( CH≡CH \).

2. THEORETICAL PROCEDURES

Standard ab initio molecular orbital theory10 and density functional theory14 (DFT) calculations were carried out with the Gaussian 03,15 Gaussian 09,16 and Molpro 2009.17 computer programs.

BDEs and RSEs were calculated with the high-level composite procedure G3X(MP2)-RAD,18 which approximates URCSSD(T)/G3X large energies computed at geometries optimized by the (U)B3-LYP/6-31G(2df,p) method (unrestricted version for open-shell species). This procedure has previously been found to represent a good compromise between accuracy and affordability for predicting the thermochemistry of monosubstituted and multiply substituted radicals.

Single-point energy calculations were also carried out with the restricted-open-shell (RO) version19 of Grimme’s B2-PLYP double-hybrid density functional theory procedure,20 in conjunction with the 6-311+G(3df,2p) basis set at (U)B3-LYP/6-31G(d) geometries. The ROB2-PLYP method has 59% HF exchange and 28% MP2 correlation. It has been found to slightly underestimate the BDEs, giving a mean deviation (MD) of \(-6.4 \text{ kJ mol}^{-1}\) and a mean absolute deviation (MAD) of \(6.4 \text{ kJ mol}^{-1}\) from values calculated with the high-level W1 method21 and \(-4.7 \text{ and } 4.9 \text{ kJ mol}^{-1}\), respectively, from available experimental BDEs.22 For RSEs, ROB2-PLYP yielded an MAD of \(1.5 \text{ kJ mol}^{-1}\) from W1 values and \(2.7 \text{ kJ mol}^{-1}\) from experimentally based RSEs.22 To obtain zero-point vibrational energies, the B3-LYP/6-31G(d) and B3-LYP/6-31G(2dfp) vibrational frequencies were scaled23 by 0.9806 and 0.9854, respectively. The calculated energies in the text correspond to G3X(MP2)-RAD values at 0 K, whereas corresponding ROB2-PLYP/6-311+G(3df,2p) values at 0 K are given in the Supporting Information (Table S1).

Potential energy scans or conformational searches were carried out for the molecules and radicals, wherever necessary, to try to ensure that all conformations correspond to global rather than merely local minimum energy structures. The B3-LYP/6-31G(d) and B3-LYP/6-31G(2dfp) optimized geometries are given in Tables S3 and S4 (Supporting Information), respectively.

3. RESULTS AND DISCUSSION

Bond dissociation energies (BDEs), radical stabilization energies (RSEs and RSEs), radical connector energies (RCEs), and molecule connector energies (MCEs) were calculated for 42 \( CH_2WX \) molecules and the related \( CH_2WX \) radicals, for all combinations of the connector groups \( W \) shown in red in Figure 1 and the substituents \( X \) listed in the caption to this figure.

![Figure 1](http://doc.rero.ch)

Figure 1. \( CH_2-W-X \) systems examined in the present study, highlighting the various connector groups \( W \) in red (\( X = H, CF_3, CH_3, CH≡O, NH_2, \) and \( CH≡CH \)).

Table 1 presents the BDEs, RSEs, RSEs, RCEs, and MCEs calculated at the G3X(MP2)-RAD level. Corresponding values obtained at the ROB2-PLYP/6-311+G(3df,2p) level show very similar qualitative trends, with a mean absolute deviation from the G3X(MP2)-RAD values of \(2.6 \text{ kJ mol}^{-1}\) for the current set of radicals (see Table S1, Supporting Information).

3.1. Radical Stabilization Energies for \( CH_2WX \) Radicals (RSEs)

Table 1 presents the BDEs, RSEs, RSEs, RCEs, and MCEs calculated at the G3X(MP2)-RAD level. Corresponding values obtained at the ROB2-PLYP/6-311+G(3df,2p) level show very similar qualitative trends, with a mean absolute deviation from the G3X(MP2)-RAD values of \(2.6 \text{ kJ mol}^{-1}\) for the current set of radicals (see Table S1, Supporting Information).

Table 1. Bond dissociation (BDEs), radical stabilization (RSEs and RSEs), radical connector (RCEs), and molecule connector (MCEs) energies for \( CH_2WX \) molecules.

<table>
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<tr>
<th>Substituent</th>
<th>BDE (kJ mol(^{-1}))</th>
<th>RSE (kJ mol(^{-1}))</th>
<th>RCE (kJ mol(^{-1}))</th>
<th>MCE (kJ mol(^{-1}))</th>
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<td>278.9</td>
<td>70.4</td>
<td>208.5</td>
<td>107.1</td>
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The RSE values for \( W = \text{NIL} \) in Table 1 confirm that carbon-centered radicals \( (\cdot CH_2X) \) in the absence of a connector group \( (\text{designated } W = \text{NIL}) \) have been extensively studied.3,5,9 The RSE values for \( W = \text{NIL} \) in Table 1 confirm that carbon-centered radicals can be stabilized by \( \pi \)-electron donors \((e.g., X = NH_2, RSE = 45.2 \text{ kJ mol}^{-1}\)\), \( \pi \)-electron acceptors \((e.g., X = CHO, RSE = 36.0 \text{ kJ mol}^{-1}\)\), and, more weakly, by hyperconjugative donors \((e.g., X = CH_3, RSE = 14.5 \text{ kJ mol}^{-1}\)\), whereas they are destabilized by strongly \( \pi \)-electron-withdrawing groups \((X = CF_3, RSE = -7.2 \text{ kJ mol}^{-1}\)\). A large positive RSE occurs when \( X = CH\equivCH \) \((RSE = 71.1 \text{ kJ mol}^{-1}\)\), which reflects the substantial resonance stabilization that the resultant alkyll radical enjoys.

Substituents \( W \) that are related to the connector groups themselves \( (W) \) play their own role in stabilizing or destabilizing the radical. For example, in \( CH_3WX \) radicals \((i.e., CH_3WX) \) with \( X = H, \) entries 8–14 in Table 1), a vinyl group \((W = CH\equivCH, RSE of alkyll radical is 71.1 \text{ kJ mol}^{-1})\), a phenyl group \((W = C_6H_5\)
Table 1. G3X(MP2)-RAD Bond Dissociation Energies (BDEs), Radical Stabilization Energies (RSEs and RSEs), Radical Connector Energies (RCEs), and Molecule Connector Energies (MCEs) in kJ mol⁻¹ at 0 K for Species Related to CH₃WX and CH₃WX

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<th>X</th>
<th>W</th>
<th>BDE (CH₃WX)</th>
<th>RSE (CH₃WX)</th>
<th>RSE₀ (CH₃WX)</th>
<th>RCE (CH₃WX)</th>
<th>MCE (CH₃WX)</th>
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</table>

RSE of benzyl radical is 59.2 kJ mol⁻¹) or an ethynyl group (W = −CH≡C−, RSE of propargyl radical is 52.9 kJ mol⁻¹) stabilize the radical center by conjugation, whereas the methyl group stabilizes the radical via hyperconjugation (W = −CH₃−). RSE of ethyl radical is 14.5 kJ mol⁻¹.

If we examine the RSEs of CH₃WX values listed in Table 1 more closely (Figure 2), we can see that they represent perturbations by X on the RSE of CH₃WX values noted above. For example, the RSEs when W is −CH≡CH− fall in the range 68.2−91.5 kJ mol⁻¹, with values of 68.2 (X = CF₃), 71.1 (X = H), 72.2 (X = CH₃), 75.8 (X = CH≡O), 79.6 (X = NH₂), and 91.5 (X = CH≡CH₂) kJ mol⁻¹. Likewise, when W is −≡C≡C−, the RSEs fall in the range 47.1−67.3 kJ mol⁻¹ (including 52.9 kJ mol⁻¹ when X = H), whereas when W is −p-C₆H₄−, the RSEs are in the range 52.3−63.9 kJ mol⁻¹ (including 59.2 kJ mol⁻¹ when X = H). For W = −CH₃−, the RSE for X = H is 14.5 kJ mol⁻¹, whereas it is in the range 7.6−12.2 kJ mol⁻¹ for the other substituents.

Figure 2 also indicates that the transmission of electronic effects by the −CH≡CH− and −≡C≡C− groups is such that the RSEs of CH₃WX follow the same trends as those for CH₃X. For example, the RSEs are generally the highest when X is −CH≡CH₂ and the lowest when X is CF₃ consistent with the trend seen in the absence of any connector groups (i.e., W = NIL). On the other hand, the −p-C₆H₄− connector is inferior to −CH≡CH− at transmitting the effect of X, whereas the −o-C₆H₄− and −m-C₆H₄− groups are relatively poor transmitters, in that the RSEs of CH₃WX in these cases are almost independent of the nature of X. Likewise, −CH₃− is a poor π-electron-transmitting group, and the RSEs here largely reflect the σ-electron effect of X.
For example, there is a lowering of the RSE for the CF₃ and other electron-withdrawing substituents (CH=O and NH₂) when W = -CH₂-.

The similar qualitative trends in the transmission of electronic effects when W = -CH=CH-, -C≡C-, and -p-C₆H₄- compared with *CH₃X, may be rationalized in terms of the resonance structures in Figure 3. Specifically, we can see that, in each case, there is a contributing resonance structure in which X is directly attached to the radical center. Thus the radical center enjoys the superimposed stabilizing effect of interposing an -p-C₆H₄- group not only acts largely as an insulating group between the radical center and the substituent X but also leads even to negative RSE₀ values (-2.3 to -6.9 kJ mol⁻¹). In several cases (e.g., CF₃, CH=O, and NH₂), this reflects a σ-withdrawing and thus radical destabilizing effect. In addition, recognizing that RSE₀ = RCE - MCE (eq 13), we note also that there are contributions to the negative RSE₀ values that arise in several cases from the positive MCE values (see section 3.3 below). Our results are consistent with the earlier finding of Zavitsas et al.¹¹ that the double bond of allyl is a better transmitter of electronic effects than the aromatic system of p-phenylene.

### 3.3. Decomposition into Radical Connector Energies (RCEs) and Molecule Connector Energies (MCEs)

The RSE₀ values indicate the extent to which the influence of X is attenuated by the interposition of various connector groups W. If X is directly connected to the radical center (i.e., W = NIL), then the resultant RSE (i.e., RSE₀) is the standard radical stabilization energy as defined by reaction 10. The differences between RSE₀ and RSEₚ can be quite substantial and it is of interest to try to understand their origin. This is best illustrated through a few examples.

If X = NH₂ and W = -C≡C- (entry 31 in Table 1), then RSEₚ is the energy change for the reaction

$$\text{CH}_2-\text{C≡C-}+\text{NH}_2 \rightarrow \text{CH}_2-\text{C≡C-}+\text{H}$$

which is 9.4 kJ mol⁻¹. This is substantially less than RSE₀ the energy of the reaction in the absence of the ethynyl connector group (RSE₀ for entry 29 in Table 1):

$$\text{CH}_2-\text{NH}_2 + \text{CH}_4 \rightarrow \text{CH}_3-\text{NH}_2 + \text{CH}_3$$

Figure 2. Variations with X of RSE(*CH₃WX) values for various connector groups W (G3X(MP2)-RAD, kJ mol⁻¹).

Figure 3. Resonance structures showing direct interaction of X with the radical center.

Figure 4. Variations with X of RSE₀ values for *CH₃WX for various connector groups W (G3X(MP2)-RAD, kJ mol⁻¹).
whose large magnitude (45.2 kJ mol$^{-1}$) reflects the large stabilizing effect of the amino group at a carbon radical center.

As noted earlier (eq 13), the difference between RSE$_W$ and RSE$_0$ (−35.8 kJ mol$^{-1}$) is also given by the difference between the radical stabilizing energy (RCE = −7.8 kJ mol$^{-1}$), in this case the energy of the reaction

$$
^*\text{CH}_2-\text{C}≡\text{C}=\text{NH}_2 + ^*\text{CH}_3
\rightarrow ^*\text{CH}_2-\text{C}≡\text{C}=\text{H} + ^*\text{CH}_2-\text{NH}_2
$$

(16)

and the molecule stabilizing energy (MCE = +28.0 kJ mol$^{-1}$), i.e., the energy of the reaction

$$
\text{CH}_3-\text{C}≡\text{C}=\text{NH}_2 + \text{CH}_4
\rightarrow \text{CH}_3-\text{C}≡\text{C}=\text{H} + \text{CH}_3-\text{NH}_2
$$

(17)

Our results indicate that the reduction in RSE in going from RSE$_0$ to RSE$_W$ is partly due to the unfavorable (negative) RCE but mainly to the favorable (positive) MCE. The negative MCE (eq 16) indicates that the sum of the stabilizing effects of individual ethynyl and amino groups at the radical center is greater than the effect of an aminoethynyl group, which seems reasonable. On the other hand, the strong positive MCE (eq 17) largely reflects the favorable donation of the lone pair of the amino group into the π* orbital of the triple bond in CH$_3$C≡CNH$_2$.

As another example, if X is CH$_2=CH$ and W is −CH$_2$− (entry 42 in Table 1), there is a very large reduction from RSE$_0$ (−71.1 kJ mol$^{-1}$, entry 36) to RSE$_W$ (−2.3 kJ mol$^{-1}$) associated with the interposition of the −CH$_2$− connecting group in $^*\text{CH}_2\cdot\text{CH}=\text{CH}_2$. This reduction is largely attributable to the large negative RCE (−61.8 kJ mol$^{-1}$), i.e., the energy of the reaction

$$
^*\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}_2 + ^*\text{CH}_3
\rightarrow ^*\text{CH}_2-\text{CH}_3 + ^*\text{CH}_3-\text{CH}=\text{CH}_2
$$

(18)

in addition to a small positive MCE (11.7 kJ mol$^{-1}$), i.e., the energy of the reaction

$$
\text{CH}_3-\text{CH}_2-\text{CH}=\text{CH}_2 + \text{CH}_4
\rightarrow \text{CH}_3-\text{CH}_3 + \text{CH}_3-\text{CH}=\text{CH}_2
$$

(19)

It is of course not surprising that the −CH$_2$− connector disrupts the favorable interaction between the vinyl group and the radical center, leading to a large loss of stabilization in the radical (eq 18), and that the effect in the precursor molecule is much smaller (eq 19). Indeed, large negative MCEs are observed also for the CH=O (−28.8 kJ mol$^{-1}$) and NH$_2$ (−29.1 kJ mol$^{-1}$) substituents (X) when the connecting group (W) is −CH$_2$−.

An overview of the trends in MCE and RCE values is displayed in Figure 5. We can see that, with only one exception (when the connecter is −C≡C− and X = CF$_3$), the MCE values are all positive. This indicates that the connecter and X generally prefer to be in the same molecule (CH$_3$WX) than in separate molecules (CH$_3$WH and CH$_4$X). On the other hand, the RCE values are sometimes positive and sometimes negative. Because the difference between RSE$_W$ and RSE$_0$ is given by the difference between the RCE and MCE, the largest values of RSE$_W$ − RSE$_0$ appear when RCE and MCE have opposite signs. This is particularly the case when X = CH=CH$_2$.

Figure 5. Calculated molecule connector energies (MCEs, red) and radical connector energies (RCEs, gray) (G3X(MP2)-RAD, kJ mol$^{-1}$).

4. CONCLUSIONS

(1) Among the connector groups (W) examined for radicals of the type $^*\text{CH}_3\text{WX}$, the effectiveness in transmission of the electronic effects of remote substituents (X) to the radical center ($^*\text{CH}_3$) decreases in the order $^*\text{CH}_2\cdot\text{CH}=\text{CH}_2 > ^*\text{CH}_2\cdot\text{NH}_2 > ^*\text{CH}2\cdot\text{CH}=\text{CH}_2 > ^*\text{CH}_2\cdot\text{H}_2$.

(2) In the case of the connector groups $-\text{CH}=\text{CH}_2$, −C≡C−, and −CH$_2$−, the effect of substituents is to represent a perturbation of the radical stabilization associated with the connector groups themselves (i.e., CH$_2$WH, CH$_2$NH$_2$, CH$_2$H). For example, when X = CF$_3$, there is a destabilizing perturbation, whereas when X = CH$_3$, there is a stabilizing perturbation. These may be measured using radical stabilization energies calculated relative to $^*\text{CH}_3\cdot\text{CH}_2$, designated RSE$_W$.

(3) Analysis of the effect of interposing a connector group between the substituent and the radical center is facilitated by introducing additional quantities related to the effect in the radical (the radical connector energy (RCE)) and the effect in the precursor molecule (the molecule connector energy (MCE)).

ASSOCIATED CONTENT

Supporting Information

Full citations are given for refs 15–17. Bond dissociation energies (BDEs), radical stabilization energies (RSEs and RSEW), radical connector energies (RCEs), and molecule connector energies (MCEs) for species related to CH$_3$WX and CH$_2$WX and calculated at the ROB2-PLYP/6-311+G(3df,2p)/UB3-LYP/6-31G(d) level (Table S1). Total energies of substituted methanes CH$_3$WX and substituted methyl radicals CH$_2$WX, calculated at the G3X(MP2)-RAD and ROB2-PLYP/6-311+G(3df,2p) levels (Table S2). B3-LYP/6-31G(d) and B3-LYP/6-31G(2df,p) optimized geometries (Tables S3 and S4). This material is available free of charge via the Internet: http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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