

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

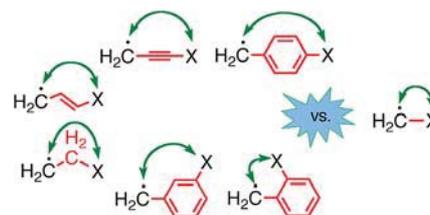
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Supporting Information

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 ($\bullet\text{CH}_2\text{-W-X}$). The connector groups include $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-p\text{-C}_6\text{H}_4-$, $-m\text{-C}_6\text{H}_4-$, and $-o\text{-C}_6\text{H}_4-$, and the substituents include H, CF_3 , CH_3 , $\text{CH}=\text{O}$, NH_2 , and $\text{CH}=\text{CH}_2$. Analysis of the results is facilitated by introducing two new quantities termed radical connector energies and molecule connector energies. We find that the $-\text{CH}_2-$ connector effectively turns off π -electron effects but allows the transmission of σ -electron effects, albeit at a reduced level. The effect of a substituent X attached to the $-\text{CH}=\text{CH}-$ and $-\text{C}\equiv\text{C}-$ connector groups is to represent a perturbation of the effect of the connector groups themselves (i.e., $\text{CH}=\text{CH}_2$ and $\text{C}\equiv\text{CH}$).



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 experimental^{6,7} and theoretical^{8,9} 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 ($\bullet\text{CH}_2\text{X}$), the RSE is given by the energy change for the hydrogen-transfer reaction:



The RSE measures the effect of X on the stability of the radical $\bullet\text{CH}_2\text{X}$ relative to its effect in the closed-shell parent (CH_3X), with CH_4 and $\bullet\text{CH}_3$ 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 CH_3X :

$$\text{RSE}(\bullet\text{CH}_2\text{X}) = \text{BDE}(\text{CH}_4) - \text{BDE}(\text{CH}_3\text{X}) \quad (2)$$

where $\text{BDE}(\text{CH}_3\text{X})$ is the energy change in the reaction



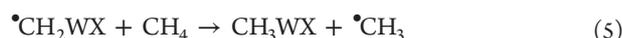
The effect of remote substituents on bond dissociation energies (BDEs) has also been a topic of interest in the chemical

literature. We note, for example, the experimental¹⁰ and theoretical^{11,12} studies of the effect of meta or para substituents (X) on benzylic ($\text{XC}_6\text{H}_4\text{CH}_2\text{-Y}$) C–Y BDEs. It was concluded that in the abstraction of Y from $p\text{-XC}_6\text{H}_4\text{CH}_2\text{-Y}$, the direction of the C–Y dipole is the major rate-determining factor, and that when $\text{Y} = \text{H}$, an electron-withdrawing X increases the C–H BDE whereas an electron-donating X decreases the C–H BDE. Additionally, Zavitsas et al.^{11a} investigated the effect of substituents (X) on the allylic C–F and C–H BDEs in $\text{XCH}=\text{CHCH}_2\text{-F}$ and $\text{XCH}=\text{CHCH}_2\text{-H}$. 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 CH_3WX :



and the RSEs for the associated radicals $\bullet\text{CH}_2\text{WX}$:



To assist in our analysis, it is convenient to define some additional quantities. First, we define the radical stabilization energy of $\bullet\text{CH}_2\text{WX}$ relative to that of $\bullet\text{CH}_2\text{WH}$ (designated RSE_W) as the energy change for the hydrogen-transfer reaction:



This can be formulated alternatively in terms of C–H bond dissociation energies as

$$\text{RSE}_W(\bullet\text{CH}_2\text{WX}) = \text{BDE}(\text{CH}_3\text{WH}) - \text{BDE}(\text{CH}_3\text{WX}) \quad (7)$$

or, equivalently

$$\text{RSE}_W(\bullet\text{CH}_2\text{WX}) = \text{RSE}(\bullet\text{CH}_2\text{WX}) - \text{RSE}(\bullet\text{CH}_2\text{WH}) \quad (8)$$

If there is no connector group (referred to subsequently as $W = \text{NIL}$), the RSE (in this case termed RSE_0) is given by

$$\text{RSE}_0(\bullet\text{CH}_2\text{X}) = \text{BDE}(\text{CH}_4) - \text{BDE}(\text{CH}_3\text{X}) \quad (9)$$

and is equal to the energy change for the reaction



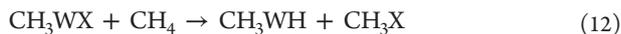
Thus, RSE_W carries over, in the limit of no connector group, to the conventional definitions of eqs 2 and 1, respectively.

It is convenient to define also the *radical connector energy* (RCE) of $(\bullet\text{CH}_2\text{WX})$ as the energy change for the formal reaction:



This measures how the connector group W affects the interaction between X and $\bullet\text{CH}_2$, relative to that between H and $\bullet\text{CH}_2$. A positive value of the RCE indicates that W enhances the interaction between X and $\bullet\text{CH}_2$ relative to that between H and $\bullet\text{CH}_2$.

In a similar manner, the *molecule connector energy* (MCE) is given by the energy change for the formal reaction:



This measures how the connector group W affects the interaction between X and CH_3 compared with that between H and CH_3 .

Finally, the effect of the connector group W on the RSE is given by the difference between RSE_W and RSE_0 . It is easy to show that this is equal to the difference between the RCE and the MCE:

$$\text{RSE}_W - \text{RSE}_0 = \text{RCE} - \text{MCE} \quad (13)$$

The connector groups (W) that we have examined in the present study include $-\text{CH}_2-$, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-p\text{-C}_6\text{H}_4-$, $-m\text{-C}_6\text{H}_4-$, and $-o\text{-C}_6\text{H}_4-$. The substituents (X) that we examine include H , CF_3 , CH_3 , $\text{CH}=\text{O}$, NH_2 , and $\text{CH}=\text{CH}_2$.

2. THEORETICAL PROCEDURES

Standard ab initio molecular orbital theory¹³ and density functional theory¹⁴ (DFT) calculations were carried out with the Gaussian 03,¹⁵ Gaussian 09,¹⁶ and Molpro 2009.1¹⁷ computer programs.

BDEs and RSEs were calculated with the high-level composite procedure G3X(MP2)-RAD,¹⁸ which approximates URCCSD(T)/G3XLarge 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^{18a-c} and multiply substituted⁹ 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 (but consistently) underestimate the BDEs, giving a mean

deviation (MD) of -6.4 kJ mol^{-1} and a mean absolute deviation (MAD) of 6.4 kJ mol^{-1} from values calculated with the high-level W1 method,²¹ and -4.7 and 4.9 kJ mol^{-1} , respectively, from available experimental BDEs.²² For RSEs, ROB2-PLYP yielded an MAD of 1.5 kJ mol^{-1} from W1 values and 2.7 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(2df,p) 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(2df,p) 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 $\text{RSE}_{w,s}$), radical connector energies (RCEs), and molecule connector energies (MCEs) were calculated for 42 CH_3WX molecules and the related $\bullet\text{CH}_2\text{WX}$ 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.

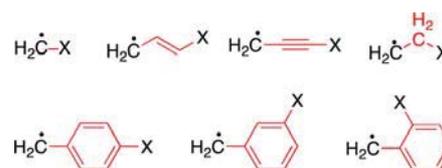


Figure 1. $\bullet\text{CH}_2\text{-W-X}$ systems examined in the present study, highlighting the various connector groups W in red ($X = \text{H}$, CF_3 , CH_3 , $\text{CH}=\text{O}$, NH_2 , and $\text{CH}=\text{CH}_2$).

Table 1 presents the BDEs, RSEs, $\text{RSE}_{w,s}$, 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 kJ mol^{-1} for the current set of radicals (see Table S1, Supporting Information).

3.1. Radical Stabilization Energies for $\bullet\text{CH}_2\text{WX}$ Radicals [RSE($\bullet\text{CH}_2\text{WX}$)]. The effect of substituents X on the stability of carbon-centered radicals ($\bullet\text{CH}_2\text{X}$), in the absence of a connector group (designated $W = \text{NIL}$), has been extensively studied.^{5,8,9} The RSE values for $W = \text{NIL}$ in Table 1 confirm that carbon-centered radicals can be stabilized by π -electron donors (e.g., $X = \text{NH}_2$, $\text{RSE} = 45.2 \text{ kJ mol}^{-1}$), π -electron acceptors (e.g., $X = \text{CHO}$, $\text{RSE} = 36.0 \text{ kJ mol}^{-1}$) and, more weakly, by hyperconjugative donors (e.g., $X = \text{CH}_3$, $\text{RSE} = 14.5 \text{ kJ mol}^{-1}$), whereas they are destabilized by strongly σ -electron-withdrawing groups ($X = \text{CF}_3$, $\text{RSE} = -7.2 \text{ kJ mol}^{-1}$). A large positive RSE occurs when X is $\text{CH}=\text{CH}_2$ ($\text{RSE} = 71.1 \text{ kJ mol}^{-1}$), which reflects the substantial resonance stabilization that the resultant allyl radical enjoys.

Substituents (WH) that are related to the connector groups themselves (W) play their own role in stabilizing or destabilizing the radical. For example, in $\bullet\text{CH}_2\text{WH}$ radicals (i.e., $\bullet\text{CH}_2\text{WX}$ with $X = \text{H}$, entries 8–14 in Table 1), a vinyl group ($W = -\text{CH}=\text{CH}-$, RSE of allyl radical is 71.1 kJ mol^{-1}), a phenyl group ($W = -\text{C}_6\text{H}_4-$,

Table 1. G3X(MP2)-RAD Bond Dissociation Energies (BDEs), Radical Stabilization Energies (RSEs and RSE_{w,s}), Radical Connector Energies (RCEs), and Molecule Connector Energies (MCEs) in kJ mol⁻¹ at 0 K for Species Related to CH₃WX and [•]CH₂WX

	X	W	BDE (CH ₃ WX)	RSE ([•] CH ₂ WX)	RSE _w ([•] CH ₂ WX)	RCE ([•] CH ₂ WX)	MCE (CH ₃ WX)
1	CF ₃	NIL	436.3	-7.2	-7.2	0.0	0.0
2	CF ₃	-CH=CH-	360.9	68.2	-2.9	12.3	7.9
3	CF ₃	-C≡C-	382.0	47.1	-5.9	-15.0	-16.4
4	CF ₃	- <i>p</i> -C ₆ H ₄ -	376.8	52.3	-7.0	9.1	8.8
5	CF ₃	- <i>o</i> -C ₆ H ₄ -	372.8	56.3	-3.0	9.6	5.3
6	CF ₃	- <i>m</i> -C ₆ H ₄ -	371.3	57.8	-1.5	14.1	8.4
7	CF ₃	-CH ₂ -	421.5	7.6	-6.9	14.5	14.2
8	H	NIL	429.1	0.0	0.0	0.0	0.0
9	H	-CH=CH-	358.0	71.1	0.0	0.0	0.0
10	H	-C≡C-	376.2	52.9	0.0	0.0	0.0
11	H	- <i>p</i> -C ₆ H ₄ -	369.8	59.2	0.0	0.0	0.0
12	H	- <i>o</i> -C ₆ H ₄ -	369.8	59.2	0.0	0.0	0.0
13	H	- <i>m</i> -C ₆ H ₄ -	369.8	59.2	0.0	0.0	0.0
14	H	-CH ₂ -	414.5	14.5	0.0	0.0	0.0
15	CH ₃	NIL	414.5	14.5	14.5	0.0	0.0
16	CH ₃	-CH=CH-	356.9	72.2	1.1	9.8	23.3
17	CH ₃	-C≡C-	373.5	55.6	2.6	19.4	31.3
18	CH ₃	- <i>p</i> -C ₆ H ₄ -	368.6	60.4	1.2	12.8	26.1
19	CH ₃	- <i>o</i> -C ₆ H ₄ -	369.1	60.0	0.7	12.3	26.1
20	CH ₃	- <i>m</i> -C ₆ H ₄ -	369.5	59.6	0.3	12.6	26.8
21	CH ₃	-CH ₂ -	417.8	11.2	-3.3	-5.3	12.5
22	CHO	NIL	393.1	36.0	36.0	0.0	0.0
23	CHO	-CH=CH-	353.3	75.8	4.7	3.0	34.4
24	CHO	-C≡C-	375.2	53.9	1.0	-21.1	13.9
25	CHO	- <i>p</i> -C ₆ H ₄ -	367.4	61.7	2.4	1.2	34.8
26	CHO	- <i>o</i> -C ₆ H ₄ -	371.5	57.6	-1.7	-11.8	25.8
27	CHO	- <i>m</i> -C ₆ H ₄ -	371.0	58.0	-1.2	-3.4	33.8
28	CHO	-CH ₂ -	421.3	7.8	-6.7	-28.8	14.0
29	NH ₂	NIL	383.9	45.2	45.2	0.0	0.0
30	NH ₂	-CH=CH-	349.5	79.6	8.5	7.0	43.7
31	NH ₂	-C≡C-	366.7	62.3	9.4	-7.8	28.0
32	NH ₂	- <i>p</i> -C ₆ H ₄ -	365.2	63.9	4.6	8.9	49.4
33	NH ₂	- <i>o</i> -C ₆ H ₄ -	368.9	60.2	0.9	9.1	53.2
34	NH ₂	- <i>m</i> -C ₆ H ₄ -	370.2	58.8	-0.4	6.0	51.6
35	NH ₂	-CH ₂ -	418.1	11.0	-3.6	-29.1	19.7
36	CH=CH ₂	NIL	358.0	71.1	71.1	0.0	0.0
37	CH=CH ₂	-CH=CH-	337.5	91.5	20.4	-12.5	38.2
38	CH=CH ₂	-C≡C-	361.8	67.3	14.3	-22.4	34.4
39	CH=CH ₂	- <i>p</i> -C ₆ H ₄ -	370.2	58.8	-0.4	-38.1	33.3
40	CH=CH ₂	- <i>o</i> -C ₆ H ₄ -	369.8	59.3	0.0	-41.6	29.4
41	CH=CH ₂	- <i>m</i> -C ₆ H ₄ -	370.1	59.0	-0.3	-37.9	33.4
42	CH=CH ₂	-CH ₂ -	416.9	12.2	-2.3	-61.8	11.7

RSE of benzyl radical is 59.2 kJ mol⁻¹) or an ethynyl group (W = -C≡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 = -CH₂-. RSE of ethyl radical is 14.5 kJ mol⁻¹).

If we examine the RSE([•]CH₂WX) values listed in Table 1 more closely (Figure 2), we can see that they represent perturbations by X on the RSE([•]CH₂WH) 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 = -CH₂-, 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 [•]CH₂WX follow the same trends as those for [•]CH₂X; e.g., 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 [•]CH₂WX in these cases are almost independent of the nature of X. Likewise, -CH₂- is a poor π -electron-transmitting group, and the RSEs here largely reflect the σ -electron effect of X.

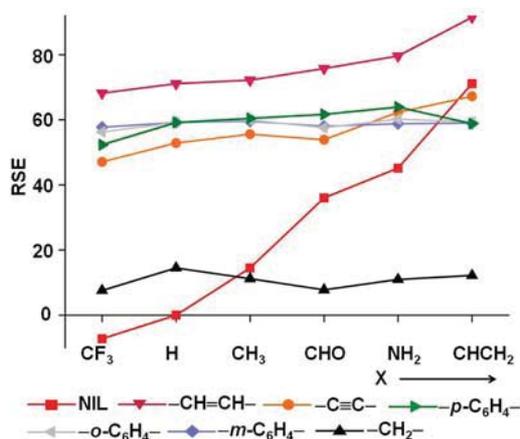


Figure 2. Variations with X of $RSE(^{\bullet}CH_2WX)$ values for various connector groups W (G3X(MP2)-RAD, kJ mol^{-1}).

For example, there is a lowering of the RSE for the CF_3 and other electron-withdrawing substituents ($CH=O$ and NH_2) when $W = -CH_2-$.

The similar qualitative trends in the transmission of electronic effects when $W = -CH=CH-$, $-C\equiv C-$, and $-p-C_6H_4-$ compared with $^{\bullet}CH_2X$, 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 effects of the group related to the connector (WX), as well as that of the substituent X. In the case of the $-m-C_6H_4-$ and $-CH_2-$ connector groups, this is not possible. An unexpected result is that the effect of interposing an $-o-C_6H_4-$ group is not comparable to that of an interposed $-p-C_6H_4-$ group, despite the fact that appropriate resonance structures can still be drawn in this case. This may be associated with unfavorable steric interactions.

3.2. Radical Stabilization Energies for $^{\bullet}CH_2WX$ Radicals Relative to $^{\bullet}CH_2WH$. The effects shown in Figure 2 are perhaps more clearly indicated by the RSE_W values, included in Table 1 and displayed in Figure 4. The RSE_W s are the energy changes for reaction 6 and correspond to the values of $RSE(^{\bullet}CH_2WX)$ relative to $RSE(^{\bullet}CH_2WH)$. The RSE_W s also indicate the extent to which the influence of X is attenuated by the interposition of various connector groups. Figure 4 shows that the transmission of interactions is largest when $W = -CH=CH-$ and smallest when $W = -CH_2-$. It also shows that a triple bond ($-C\equiv C-$) is not always as effective in this respect as a double bond ($-CH=CH-$), but usually better than p -phenylene ($-p-C_6H_4-$). The very small RSE_W values for the o - and m -phenylene groups indicate that these groups hardly transmit the effect of X. The

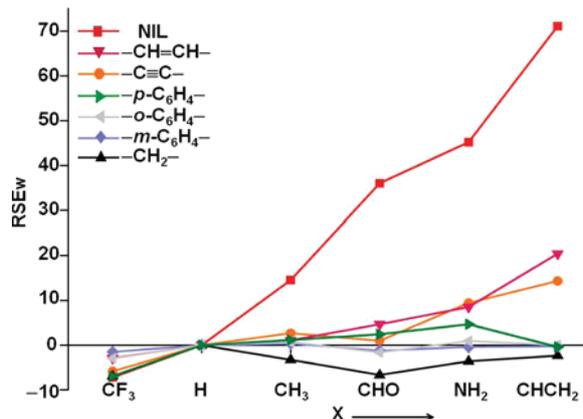
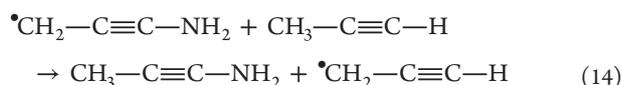


Figure 4. Variations with X of RSE_W values for $^{\bullet}CH_2WX$ for various connector groups W (G3X(MP2)-RAD, kJ mol^{-1}).

methylene ($-CH_2-$) group not only acts largely as an insulating group between the radical center and the substituent X but also leads even to *negative* RSE_W values (-2.3 to -6.9 kJ mol^{-1}). In several cases (e.g., CF_3 , $CH=O$, and NH_2), this reflects a σ -withdrawing and thus radical destabilizing effect. In addition, recognizing that $RSE_W - RSE_0 = RCE - MCE$ (eq 13), we note also that there are contributions to the negative RSE_W 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.^{11a} 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 RSE_W 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., $W = \text{NIL}$), then the resultant RSE (i.e., RSE_0) is the standard radical stabilization energy as defined by reaction 10. The differences between RSE_W and RSE_0 can be quite substantial and it is of interest to try to understand their origin. This is best illustrated through a few examples.

If $X = NH_2$ and $W = -C\equiv C-$ (entry 31 in Table 1), then RSE_W is the energy change for the reaction



which is 9.4 kJ mol^{-1} . This is substantially less than RSE_0 , the energy of the reaction in the absence of the ethynyl connector group (RSE_W for entry 29 in Table 1):

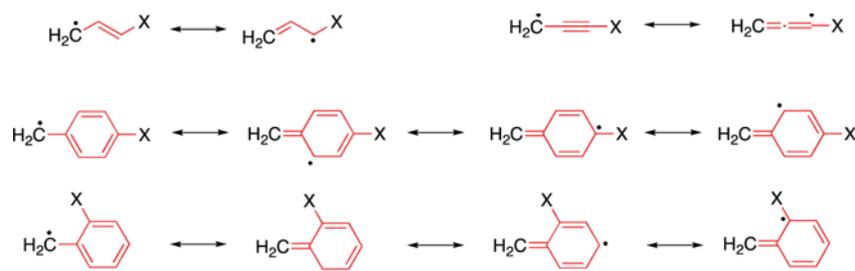
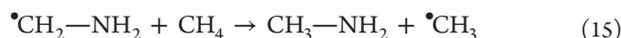


Figure 3. Resonance structures showing direct interaction of X with the radical center.

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