

Articles

Assessment of Nucleophilicity and Electrophilicity of Radicals, and of Polar and Enthalpy Effects on Radical Addition Reactions¹

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Principal component analysis (PCA) was performed on experimental rate constant and theoretical barrier height data of radical addition reactions involving various carbon- and sulfur-centered radicals and vinyl-type alkenes. Altogether six data sets were analyzed. In three cases the reactivity data were completed by certain descriptors, i.e., the electron affinity (EA) and negative ionization potential ($-IP$) of alkenes, as well as the exothermicity ($-\Delta H_r$) of reactions. It was found that in each case the first two principal components account for more than 93% of the total variance in the data. The scores of the first principal component correlate with EA and ($-\Delta H_r$), whereas those of the second principal component with ($-IP$). It is concluded that PCA is able to decompose both experimental and theoretical reactivity data into nucleophilic and electrophilic components, as well as into polar and enthalpy terms. In the plots of component loadings the radicals form significant groups depending on their character. Thus, PCA can classify radicals according to nucleophilicity and electrophilicity. The PCA results were validated by significant correlations of experimental and theoretical reactivity data with Hammett σ_p as well as with the descriptors EA, ($-\Delta H_r$), and ($-IP$). The hydroxymethyl radical is classified as strongly nucleophilic, the methyl radical as moderately nucleophilic, the *tert*-butoxycarbonylmethyl and cyanomethyl radicals as weakly nucleophilic, the phenylsulfonyl and tosyl radicals as moderately electrophilic, and the 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl radical as strongly electrophilic. It is concluded that the reactivities of *tert*-butoxycarbonylmethyl and cyanomethyl radicals are mainly governed by enthalpy effects. This conclusion is in agreement with the findings of Giese et al. [*Chem. Ber.* **1988**, *121*, 2063–2066] and Fischer et al. [*Helv. Chim. Acta* **1995**, *78*, 194–214]. A symmetry pattern of correlations is proposed: the reactivity correlates with EA for strongly nucleophilic radicals, with EA and ($-\Delta H_r$) for moderately nucleophilic radicals, with ($-\Delta H_r$) for weakly nucleophilic or weakly electrophilic radicals, with ($-\Delta H_r$) and ($-IP$) for moderately electrophilic radicals, and with ($-IP$) for strongly electrophilic radicals. On the basis of the symmetry pattern of correlations, it is concluded that the dominant factors influencing radical addition reactions are polar effects alone for strongly nucleophilic or strongly electrophilic radicals, polar and enthalpy effects for moderately nucleophilic or moderately electrophilic radicals, and enthalpy effects alone for weakly nucleophilic or weakly electrophilic radicals.

Introduction

A frequently raised question in the literature is what are the dominant factors influencing radical addition reactions? Experimental studies^{3–7} emphasize the im-

portance of polar effects, while theoretical calculations^{8–16} show a number of instances where enthalpy effects are more important or at least as important as polar effects.

Another important problem is the classification of radicals according to nucleophilicity and electrophilicity. Recently, Radom et al. published high-level ab initio quantum chemical calculations on radical addition reactions.^{8–11} They concluded that the reactivity of

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methyl radical is primarily governed by enthalpy effects, while the reactivities of hydroxymethyl and cyanomethyl radicals are strongly influenced by both polar and enthalpy effects. They stated that the methyl radical does not display general nucleophilic behavior, whereas the hydroxymethyl radical is generally nucleophilic and the cyanomethyl radical is generally electrophilic.

On the other hand, experimental studies led to the conclusion that the methyl radical is nucleophilic,¹⁷ whereas the cyanomethyl radical¹⁸ and the *tert*-butoxycarbonylmethyl radical¹⁹ are ambiphilic (borderline cases). Later, however, Fischer et al. suggested that the latter two radicals are weakly electrophilic.²⁰

A question may arise whether the cyanomethyl and *tert*-butoxycarbonylmethyl radicals are really electrophilic, i.e., whether the cyano group or the *tert*-butoxycarbonyl group have an electron-attracting character strong enough to change the methyl radical²¹ to electrophilic.

The most widespread method in the literature to classify radicals according to nucleophilicity and electrophilicity is a simple regression analysis of radical reactivity data as a function of certain descriptors (Hammett σ_p substituent constant, electron affinity, and ionization potential).^{3-11,17,19,20,22-34}

Recently, we showed^{1a} that principal component analysis (PCA) is able to separate polar and enthalpy effects on radical addition reactions, to decompose radical reactivity into nucleophilic and electrophilic components, and to classify radicals and alkenes according to reactivity and character. These results were qualitatively justified by theoretical models, i.e., the FMO model and Hammond's postulate.^{1a} The calculations^{1a} were performed on experimental rate constants of radical addition reactions involving 9 carbon-centered radicals and 15 vinyl-type alkenes. The radicals were classified as strongly, moderately, and weakly nucleophilic.

However, electrophilic radicals such as dicyanomethyl,⁵ phenylsulfonyl,²² *tert*-butoxyl,²³ phenylthiyl,²⁴ *p*-chlorophenylthiyl,²⁵ diethyl α -benzylmalonyl,²⁶ nitrate,²⁷ perfluoroalkyls,²⁸ tosyl,²⁹ methylmalononitrile,³⁰ perhaloalkylperoxyl,³¹ azidyl,³² and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl³³ can also be found in the literature. Unfortunately, a sufficient number of rate constants are available only for the reactions of phenylsulfonyl, tosyl, and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl radicals with the alkenes involved in our previous calculations.^{1a}

In addition to experimental rate constants, theoretical barrier height (activation energy) data are also available in the literature for some radical addition reactions.⁸⁻¹¹

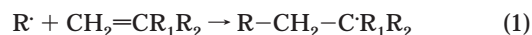
Our first aim in this paper was to investigate whether the method of analyzing radical reactivity data using PCA can be extended to further nucleophilic and *electrophilic* radicals and to *theoretical barrier height* data. Therefore, we assessed the nucleophilicity and electrophilicity of hydroxymethyl, cyanomethyl, methyl, phenylsulfonyl, tosyl, and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl radicals (in addition to the nine radicals involved in our previous study^{1a}), assessed the dominant factors influencing the addition reactions of these radicals, performed calculations on theoretical barrier height data, and compared the results with those obtained from experimental rate constant data.

The second aim was to justify the results *quantitatively*, i.e., to validate the method by means of the classical approach. Therefore, we investigated the reactivity of each radical as a function of the Hammett σ_p substituent constant, the electron affinity and negative ionization potential of alkenes, and the exothermicity (negative enthalpy) of reactions. In addition to simple regression analysis, we also used *multiple regression analysis* for the investigations.

Methods

We report here the results of calculations on radical addition reactions of various carbon- and sulfur-centered radicals and vinyl-type alkenes using principal component analysis,³⁵⁻³⁷ as well as simple and multiple regression analysis.³⁸ Both the PCA and the regression calculations were carried out using the DrugIdea program package³⁹ developed for the IBM PC and compatibles.

The scheme of the radical addition reactions investigated is as follows:



We analyzed the reactivities (logarithms of rate constants, log *k* values) of hydroxymethyl, cyanomethyl, methyl, phenylsulfonyl, tosyl and 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl (further on cyclic malonyl) radicals as well as of nine more-or-less nucleophilic radicals analyzed earlier^{1a} toward a set of vinyl-type alkenes. We also analyzed the reactivities (theoretical barrier height, i.e., activation energy data, E_a values) of hydroxymethyl, cyanomethyl, methyl, and *tert*-butyl radicals toward another set of vinyl-type alkenes.

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The rate constants and barrier height values used in the calculations were collected from the literature,^{1a,6,7,10,11,17,20,22,29,33,34} and they are given as Supporting Information. In addition to the radical reactivities, three descriptors were also considered as follows: electron affinity (EA) and negative ionization potential ($-IP$) of alkenes, as well as exothermicity ($-\Delta H_r$, negative enthalpy) of reactions between the alkenes and the methyl radical chosen as a model. The negative sign in ($-IP$) and ($-\Delta H_r$) was applied because these negative descriptors can be expected to have positive correlations with radical reactivities according to relevant theories (cf., the FMO model and the Evans–Polanyi relationship). The descriptor values were taken from the literature,^{1a,10,11,17} and they are also given as Supporting Information.

In the PCA calculations altogether six data sets were analyzed.

Data set 1 included experimental rate constant data for hydroxymethyl, cyanomethyl, methyl, and cyclic malonyl as well as 9 more-or-less nucleophilic radicals involved in our previous study.^{1a} Data set 1a (9 radicals \times 12 alkenes) included the following: {radicals} 2-hydroxyprop-2-yl, *tert*-butyl, hydroxymethyl, benzyl, methyl, 2-cyanoprop-2-yl, *tert*-butoxycarbonylmethyl, cyanomethyl, and cyclic malonyl; {alkenes} $CH_2=CR_1R_2$, where R_1 and R_2 are H and CN, Me and Ph, H and Ph, H and COOMe, Cl and Cl, H and SiMe₃, H and OCOMe, Me and Cl, Me and OCOMe, H and tBu, H and OEt, and Me and OMe, respectively. Data set 1b {(13 radicals + 3 descriptors) \times 7 alkenes} included the following: {radicals} the same radicals as in data set 1a and *p*-methoxybenzyl, *p*-fluorobenzyl, *p*-methylbenzyl, and *p*-cyanobenzyl; {alkenes} $CH_2=CR_1R_2$, where R_1 and R_2 are H and CN, H and Ph, H and COOMe, Cl and Cl, H and OCOMe, H and tBu, and H and OEt, respectively.

Data set 2 included experimental rate constant data for the same radicals as in data set 1b and phenylsulfonyl and tosyl radicals. Data set 2a (15 radicals \times 5 alkenes) included the following: {radicals} the same radicals as in data set 1b and phenylsulfonyl and tosyl; {alkenes} $CH_2=CR_1R_2$, where R_1 and R_2 are H and CN, H and Ph, H and COOMe, H and OCOMe, and H and tBu, respectively. Data set 2b {(15 radicals + 3 descriptors) \times 5 alkenes} included the same radicals and alkenes as those in data set 2a.

Data set 3 included theoretical barrier height data for hydroxymethyl, cyanomethyl, methyl, and *tert*-butyl radicals. Data set 3a (4 radicals \times 6 alkenes) included the following: {radicals} *tert*-butyl, hydroxymethyl, methyl, and cyanomethyl; {alkenes} $CH_2=CHR_1$, where R_1 is H, F, NH₂, Cl, CHO, and CN. Data set 3b {(4 radicals + 3 descriptors) \times 6 alkenes} included the same radicals and alkenes as those in data set 3a.

Each data set is essentially a data matrix containing the reactivity data ($\log k$ or E_a values) as well as the descriptor values. The radicals and the descriptors are taken as variables (columns of the matrix), and the alkenes are as mathematical–statistical cases (rows of the matrix).

The columns of these data matrixes are intercorrelated, i.e., the data are redundant. The method of principal component analysis^{35–37} makes use of the intercorrelations by starting from the correlation matrix of the variables. It eliminates the redundancy from the data, i.e., it reduces the dimensionality of the data by revealing several underlying components.

The underlying components are represented by new variables called principal components. Their values are the component scores. The principal components are, in fact, linear combinations of the original variables and vice versa. The linear coefficients of the latter linear combinations are called the component loadings, i.e., the correlation coefficients between the original variables and the principal components.

The principal components are uncorrelated, and they account for the total variance of the original variables. The first principal component accounts for the maximum of the total variance, the second one is uncorrelated with the first and accounts for the maximum of the residual variance, and so on until the total variance is accounted for. For a practical

problem, it is sufficient to retain only a few components accounting for a large percentage of the total variance.

First, the correlation matrix of the original variables is computed (this matrix contains the correlation coefficients of each original variable with the others). Second, the component loadings are calculated from the eigenvectors and eigenvalues of the correlation matrix. Finally, the component scores are obtained from the component loadings and the original variables.

Results

The detailed results of principal component analyses (variances accounted for by the individual principal components, component loadings and component scores) are given as Supporting Information.

For data sets 1 and 2, PCA yields two principal components that account for 93–97% of the total variance depending on the data set analyzed.

Data Set 1a. We found that the C1 and C2 scores of the first and second principal components, respectively, correlate with EA, ($-\Delta H_r$), and ($-IP$):

$$C1 = (7.180 \times 10^{-3})EA + 0.02927(-\Delta H_r) - 2.599 \quad (2)$$

$$n = 12, R = 0.952, F = 43.4, s = 0.339$$

$$C2 = 0.01180(-IP) + 10.60 \quad (3)$$

$$n = 12, R = 0.855, F = 27.3, s = 0.543$$

where n is the number of data points included in the regression calculations, R is the (multiple) correlation coefficient, F is the overall Fisher test value, and s is the standard error of the estimate.

The first principal component, correlating with EA and ($-\Delta H_r$), describes the nucleophilic character of radicals and the enthalpy effects on radical addition reactions. On the other hand, the second principal component, correlating with ($-IP$), describes the electrophilic character of radicals, i.e., even nucleophilic radicals bear a definite electrophilic character. However, the electrophilic character of the radicals investigated is of minor importance as shown by the percentage variances accounted for by the first and second principal components. In fact, the first principal component accounts for 77% of the total variance in data set 1a, whereas the second principal component explains 16%.

Data Set 1b. A plot of component loadings (A2 vs A1) is shown in Figure 1 for data set 1b. Three groups of radicals can be seen in the figure: strongly and moderately nucleophilic radicals (2-hydroxyprop-2-yl, *tert*-butyl, hydroxymethyl, *p*-methoxybenzyl, *p*-fluorobenzyl, *p*-methylbenzyl, benzyl, methyl); weakly nucleophilic radicals (*p*-cyanobenzyl, 2-cyanoprop-2-yl, *tert*-butoxycarbonylmethyl, cyanomethyl); and an electrophilic radical (cyclic malonyl).

The strongly and moderately nucleophilic radicals (including the hydroxymethyl and methyl radicals) fall into the same group as electron affinity, whereas the weakly nucleophilic radicals (including the *tert*-butoxycarbonylmethyl and cyanomethyl radicals) are in the same group as exothermicity. The electrophilic cyclic malonyl radical lies close to negative ionization potential.

This means the rate constants for the hydroxymethyl and methyl radicals can be expected to correlate with electron affinity, whereas the rate constants for the *tert*-

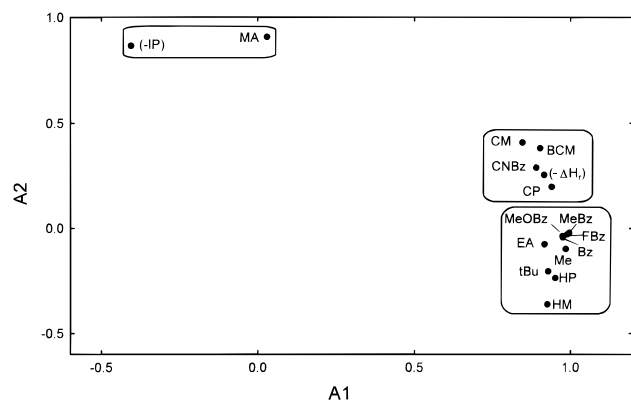


Figure 1. Plot of component loadings A2 vs A1 for data set 1b. The notations are: HP 2-hydroxyprop-2-yl, tBu *tert*-butyl, HM hydroxymethyl, MeOBz *p*-methoxybenzyl, FBz *p*-fluorobenzyl, MeBz *p*-methylbenzyl, Bz benzyl, Me methyl, CNBz *p*-cyanobenzyl, CP 2-cyanoprop-2-yl, BCM *tert*-butoxycarbonylmethyl, CM cyanomethyl, MA 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl. EA, (–IP), and (– ΔH_r) are the electron affinity of alkenes, the negative ionization potential of alkenes, and the negative enthalpy of reaction for the model methyl radical with alkenes, respectively.

butoxycarbonylmethyl and cyanomethyl radicals with exothermicity. This latter conclusion is in accordance with the findings of Fischer et al.²⁰ and Giese et al.¹⁸ who stated that enthalpy effects are of major importance for ester- and nitrile-substituted methyl radicals. Similarly, Figure 1 suggests that the rate constants for the cyclic malonyl radical correlate with negative ionization potential.

Data Set 2a. PCA decomposes the radical reactivity into nucleophilic and electrophilic components just as for data set 1a. The C1 and C2 scores of the first and second principal components, respectively, correlate with EA, (– ΔH_r), and (–IP):

$$C1 = 0.01503EA + 1.123 \quad (4)$$

$$n = 5, R = 0.962, F = 37.4, s = 0.315$$

$$C1 = 0.04512(-\Delta H_r) - 5.423 \quad (5)$$

$$n = 5, R = 0.924, F = 17.6, s = 0.441$$

$$C2 = 0.01025(-IP) + 9.470 \quad (6)$$

$$n = 5, R = 0.908, F = 14.1, s = 0.483$$

It should be noted that the two-variable equation expressing C1 as a function of EA and (– ΔH_r) is not significant due to the low degrees of freedom.

In this case the electrophilic character of the radicals investigated is more significant as shown by the percentage variances accounted for by the first and second principal components. The first principal component describing the nucleophilic character of radicals and the enthalpy effects on radical addition reactions {correlation with EA and (– ΔH_r), respectively} accounts for 75% of the total variance in data set 2a, whereas the second principal component describing the electrophilic character of radicals {correlation with (–IP)} explains 21%.

Data Set 2b. A plot of component loadings (A2 vs A1) is shown in Figure 2 for data set 2b. Three groups of radicals can be seen in the figure: strongly and moderately nucleophilic radicals (2-hydroxyprop-2-yl, *tert*-butyl,

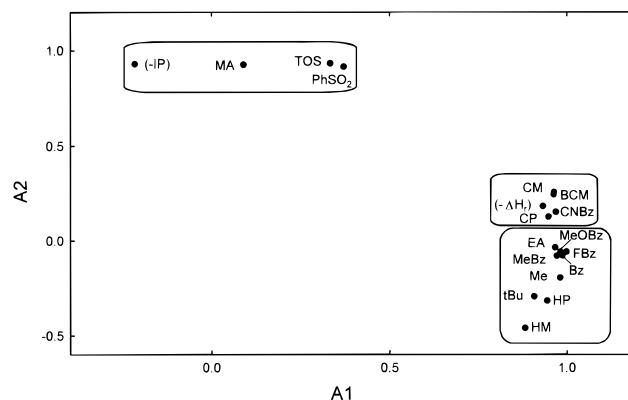


Figure 2. Plot of component loadings A2 vs A1 for data set 2b. The notations are the same as in Figure 1. In addition, PhSO₂ is phenylsulfonyl and TOS is tosyl.

hydroxymethyl, *p*-methoxybenzyl, *p*-fluorobenzyl, *p*-methylbenzyl, benzyl, methyl); weakly nucleophilic radicals (*p*-cyanobenzyl, 2-cyanoprop-2-yl, *tert*-butoxycarbonylmethyl, cyanomethyl); electrophilic radicals (phenylsulfonyl, tosyl, and cyclic malonyl).

Although data set 2b is based on two more (altogether 15) radicals and two fewer alkenes than data set 1b, the same conclusions can be drawn from Figure 2 as from Figure 1.

Data Set 3. In the case of data sets 3a and 3b, we investigated theoretical barrier height (E_a) data calculated by Radom et al.^{10,11} We applied (–EA), IP, and ΔH_r as descriptor variables rather than EA, (–IP), and (– ΔH_r), so that the results could be compared to those obtained for experimental log k values. Moreover, Radom et al.^{10,11} calculated reaction enthalpies for each “radical + alkene” reaction. We performed PCA calculations to reveal how the reaction enthalpies of different radicals correlate with each other and to find the underlying component(s) of reaction enthalpies. We found highly significant correlations. The first principal component explains 99.3% (!) of the total variance in reaction enthalpies. This fact indirectly justifies our earlier approach,^{1a} i.e., the reaction enthalpies of one particular radical can model those of other radicals appropriately. We then used the negative of this first principal component (– $\Delta H_{r,PCA}$) in the calculations rather than the reaction enthalpies for the individual radicals. The negative sign in (– $\Delta H_{r,PCA}$) was applied to obtain a positive reaction enthalpy descriptor since PCA calculates this principal component from the original reaction enthalpies using negative linear coefficients.

For data set 3a, PCA yields two principal components that account for 99.9% of the total variance. The above very high values (99.3% and 99.9%) of explained total variance can also be interpreted such that the theoretical data used in the calculations refer to the gas phase; therefore they do not contain any solvent effects. In addition, they do not contain any experimental error either.

Similarly to the case of experimental rate constant data, PCA is able to decompose theoretical barrier height data into nucleophilic and electrophilic components as well as into polar and enthalpy terms. This is shown by the following equations:

$$C1 = 1.027(-EA) - 1.178 \quad (7)$$

$$n = 6, R = 0.869, F = 12.3, s = 0.554$$

$$C1 = 0.9742(-\Delta H_{r,PCA}) + 0.000 \quad (8)$$

$$n = 6, R = 0.974, F = 74.5, s = 0.252$$

$$C2 = 0.9933IP - 9.983 \quad (9)$$

$$n = 6, R = 0.971, F = 65.4, s = 0.268$$

It should be noted that the two-variable equation expressing C1 as a function of $(-EA)$ and $(-\Delta H_{r,PCA})$ is not significant due to the low degrees of freedom.

For data set 3b including the descriptor variables PCA yields two principal components explaining 98% of the total variance in the data.

Figure 3 shows a plot of component loadings (A2 vs A1) for data set 3b. The *tert*-butyl, hydroxymethyl, and methyl radicals are in the same group as $(-EA)$ and $(-\Delta H_{r,PCA})$.

This can be interpreted in terms of the nucleophilicity of these radicals. However, they are closer to $(-\Delta H_{r,PCA})$ than to $(-EA)$, just as if their reactivities were governed by exothermicity, i.e., as if they were weakly nucleophilic. On the contrary, experimental facts show that the *tert*-butyl and hydroxymethyl radicals are strongly nucleophilic.^{4,7} Also, Figure 3 suggests a close similarity between the *tert*-butyl and methyl radicals which is in conflict with well-substantiated empirical findings, e.g., the large difference in their ionization potentials.^{7,17} The discrepancies above suggest that even high-level *ab initio* calculations overestimate the role of enthalpy effects in radical addition reactions.

As for the cyanomethyl radical, Figure 3 shows that it is far from $(-EA)$ and $(-\Delta H_{r,PCA})$, but even farther from IP. It can be concluded that cyanomethyl is not an electrophilic radical.

Validation of Results

The above results obtained using PCA can be justified by means of the classical approach to determine the dominant factors influencing radical addition reactions and to assess the nucleophilicity and electrophilicity of radicals. Therefore, we performed simple and multiple regression analyses to investigate the reactivity of each radical as a function of the Hammett σ_p substituent constant⁴⁰ and the EA, $(-\Delta H_r)$, and $(-IP)$ descriptor variables, respectively.

Validation for Experimental Reactivity Data.

The regression equations with σ_p are Hammett equations where the regression coefficient of σ_p is the ρ reaction constant. The regression equations obtained are summarized in Table 1.

The magnitude and sign of the ρ values show that 12 of the 15 radicals investigated are nucleophilic in the following decreasing order: 2-hydroxyprop-2-yl > *tert*-butyl > hydroxymethyl > *p*-methoxybenzyl > *p*-fluorobenzyl > *p*-methylbenzyl > benzyl > methyl > *p*-cyanobenzyl > 2-cyanoprop-2-yl > *tert*-butoxycarbonylmethyl > cyanomethyl.

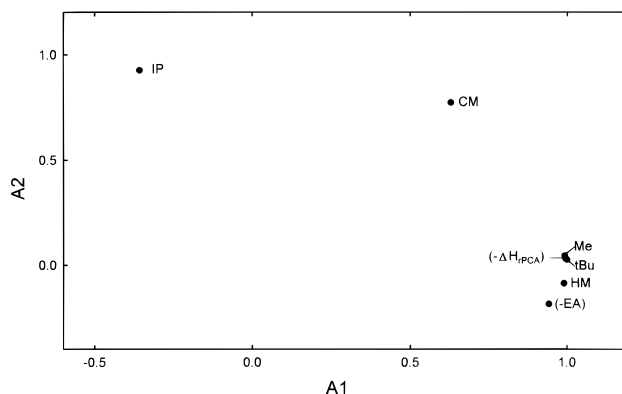


Figure 3. Plot of component loadings A2 vs A1 for data set 3b. The notations are the same as in Figure 1. In addition, $(-\Delta H_{r,PCA})$ is the negative of the first principal component obtained from theoretical reaction enthalpy data.

Table 1. Regression Equations^a Obtained for Experimental Radical Reactivities as a Function of Hammett σ_p [$\log k = \rho\sigma_p + \log k_0$]

radical ^b	ρ	$\log k_0$	n^c	r^d	F^e	s^f
HP	4.30	4.06	13	0.869	33.8	0.826
tBu	3.61	3.62	13	0.896	44.9	0.602
HM	3.41	3.21	10	0.849	20.7	0.799
MeOBz	2.66	1.58	7	0.902	21.7	0.492
FBz	2.57	1.54	7	0.858	13.9	0.594
MeBz	2.17	1.71	7	0.768	7.21	0.698
Bz	1.71	1.56	13	0.724	12.1	0.549
Me	1.59	4.40	10	0.798	14.0	0.453
CNBz	1.35	1.92	7	0.556	2.24 ^g	0.775
CP	1.10	2.07	13	0.730	12.6	0.348
BCM	0.642	5.03	13	0.566	5.18	0.315
CM	0.504	4.44	10	0.481	2.41 ^g	0.346
TOS	-0.090	-0.60	5	0.088	0.023 ^g	0.407
PhSO ₂	-0.55	-1.82	4	0.882	6.98 ^g	0.131
MA	-0.22	5.51	10	0.284	0.70 ^g	0.282

^a The two resonance-stabilized styrene molecules were omitted from the regression equations. ^b For the notations, see Figures 1 and 2. ^c Number of data points. ^d Correlation coefficient. ^e Fisher's test value. ^f Standard error of the estimate. ^g Not significant at the 5% level.

The sign of the ρ values shows that the remaining radicals (phenylsulfonyl, tosyl, and cyclic malonyl) are electrophilic.

The magnitude of the ρ values arranges the nucleophilic radicals into the same groups as seen in Figures 1 and 2. The sign of the ρ values is in accordance with the nucleophilic and electrophilic character of the radicals as predicted by PCA. Therefore, the σ_p regressions justify the results of PCA.

The regression calculations with the EA, $(-\Delta H_r)$, and $(-IP)$ descriptor variables result in significant regression equations (Table 2) with EA for the strongly nucleophilic 2-hydroxyprop-2-yl, *tert*-butyl, and hydroxymethyl radicals, with EA and $(-\Delta H_r)$ for the moderately nucleophilic *p*-methoxybenzyl, *p*-fluorobenzyl, *p*-methylbenzyl, benzyl, and methyl radicals, with $(-\Delta H_r)$ for the weakly nucleophilic *p*-cyanobenzyl, 2-cyanoprop-2-yl, *tert*-butoxycarbonylmethyl, and cyanomethyl radicals, with $(-\Delta H_r)$ and $(-IP)$ for the moderately electrophilic tosyl and phenylsulfonyl radicals, and with $(-IP)$ for the strongly electrophilic cyclic malonyl radical.

The results are in accordance with the conclusions drawn from Figures 1 and 2, and, therefore, justify the results of PCA.

(40) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

Table 2. Regression Equations Obtained for Experimental Radical Reactivities as a Function of EA, ($-\Delta H_r$), and ($-\text{IP}$) [$\log k = a\text{EA} + b(-\Delta H_r) + c(-\text{IP}) + d$]

radical ^a	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>n</i> ^b	<i>R</i> ^c	<i>F</i> ^d	<i>s</i> ^e
HP	0.02495			7.754	12	0.918	53.3	0.849
tBu	0.01663			5.954	12	0.902	43.5	0.627
HM	0.01534			5.416	12	0.865	29.7	0.700
MeOBz	0.01362			3.695	7	0.945	41.8	0.386
FBz	0.01268	0.05050		-3.554	7	0.822	10.4	0.673
				3.624	7	0.936	35.2	0.392
MeBz	0.01113	0.05220		-3.736	7	0.904	22.3	0.475
				3.546	7	0.889	18.8	0.471
		0.04622		-2.962	7	0.866	14.9	0.514
Me	0.008405			5.647	12	0.869	30.8	0.377
		0.03470		0.7066	12	0.797	17.4	0.459
Bz	0.005513	0.02643		-0.4265	12	0.960	53.1	0.255
CNBz		0.04135		-2.318	7	0.916	26.1	0.348
CP		0.03664		-1.846	12	0.932	65.9	0.249
BCM		0.03101		1.786	12	0.854	27.0	0.330
CM		0.03161		1.038	12	0.909	47.5	0.253
TOS		0.02191	0.007452	4.099	5	0.989	42.9	0.162
PhSO ₂		0.03037	0.009599	3.671	6	0.987	58.7	0.240
MA			0.003192	8.452	12	0.671	8.18	0.268

^a For the notations, see Figures 1 and 2. ^b Number of data points. ^c (Multiple) correlation coefficient. ^d Fisher's test value. ^e Standard error of the estimate.

Validation for Theoretical Reactivity Data. The regression calculations⁴¹ with σ_p show that all radicals are nucleophilic. On the basis of the value of the reaction constant ρ , their nucleophilicity decreases in the following order: hydroxymethyl > *tert*-butyl > methyl > cyanomethyl. This is in accordance with the conclusions drawn from experimental data (see Tables 1 and 2).

The regression calculations⁴¹ with the ($-\text{EA}$), ($-\Delta H_{r,\text{PCA}}$), and IP descriptor variables resulted in highly significant regression equations with ($-\Delta H_{r,\text{PCA}}$), or, alternatively, slightly less significant regression equations with ($-\text{EA}$). This shows that all radicals are nucleophilic and that enthalpy effects are the most important factors in influencing radical addition reactions. Comparing these results with those obtained from experimental data, it appears that the theoretical calculations overemphasize the role of enthalpy effects.

Discussion

In the above calculations the polar and enthalpy effects were found to be the dominant factors influencing radical addition reactions. In addition to polar and enthalpy effects, however, steric and solvent effects may also influence these reactions.^{3,29,44,45} The α -steric effects were minimized by choosing vinyl-type alkenes for the investigations. Our analysis revealed no β -steric and solvent effects. The reason may be that these factors are negligible in the reactions investigated and in the solvents involved since they fall into the range of experimental error.^{3,44,45}

In the PCA results the first principal component describes the nucleophilic character of radicals, whereas the second principal component describes their electrophilic character. This is because the majority of radicals are nucleophilic. Of course, if the majority of radicals were electrophilic, the first principal component would

reflect electrophilicity. Moreover, if the radicals to be analyzed were very similar, i.e., the radical reactivity variables were highly correlated, PCA would find one principal component only.

A question could be raised on how the error in the experimental data sets influences the PCA results. Malinowski³⁶ pointed out a favorable feature of principal component analysis, i.e., that the principal components accounting for a large percentage of the variance in the original data reflect the most characteristic underlying factors, whereas the remaining principal components comprise the experimental error only.

Two advantageous features of principal component analysis should be mentioned here:

(1) According to experimental observations,³ benzyl radicals and styrenes should be treated separately from other radicals and alkenes since an increased radical-stabilizing phenyl effect and a decreased polar effect can be expected in their reactions. This is the reason we omitted styrenes from the σ_p regression calculations (see Table 1). However, the method of PCA does not require the separation of benzyl radicals and styrenes. Instead, their difference from other radicals and alkenes are shown by the results of PCA since this method can classify the radicals and alkenes according to similarity in reactivity and character.^{1a}

(2) For conventional methods, corrections should be made for the different frequency factors of different radicals. This is not required by PCA because the average frequency factors of radicals constitute constant terms in radical reactivities. The constant terms, even if they differ from each other for the different radicals, do not influence the correlations of radical reactivities; therefore, they have no influence on the PCA results either.

Recently, it was found that polar effects in radical reactions can be better described by ionic σ scales than by specific radical σ^* scales that characterize radical stabilization (enthalpy effects).⁴² Therefore, we employed Hammett σ_p , the most common ionic σ scale to investigate the nucleophilicity and electrophilicity of radicals, i.e., to validate the PCA results.

The σ regression approach, although generally applicable, was criticized by Zavitsas and Pinto.⁴³ They

(41) Vinylamine was omitted from the calculations since it is an outlier due to an overlap between the vinyl π -system and the nitrogen lone pair, as Radom et al. pointed out.^{10,11}

(42) Héberger, K. *J. Phys. Org. Chem.* **1994**, 7, 244–250.

(43) Zavitsas, A. A.; Pinto, J. A. *J. Am. Chem. Soc.* **1972**, 94, 7390–7396.

(44) Salikhov, A.; Fischer, H. *Appl. Magn. Reson.* **1993**, 5, 445–455.

(45) Giese, B.; Kretzschmar, G. *Chem. Ber.* **1984**, 117, 3160–3164.

pointed out that the electron-donating and -withdrawing characteristics of a substituent determine the bond strengths of the C–H bond in hydrogen abstraction reactions. The analogy is obvious here: the bond energy of the double bond of alkenes depends on the electron acceptor and donor properties of the R_1 and R_2 substituents in eq 1. Therefore, it appears that Hammett σ_p measures both the polar and the enthalpy effects influencing radical addition reactions. On the other hand, our regression equations in Table 1 show a trend in the magnitude and sign of the ρ values that is in full accordance with the PCA results. That means the two independent methods, the PCA approach and the σ_p regression approach support each other.

It should be noted that the EA and $(-\Delta H_f)$ variables are intercorrelated, i.e. $r(\text{EA}, -\Delta H_f) = 0.723$ ($n = 12$). This intercorrelation seems to weaken the validity of the regression results. However, again, our regression equations in Table 2 show a trend (as to which descriptor variable correlates with which radical reactivity variable) that is in entire agreement with the PCA results. This means the two independent methods, the PCA approach and the multiple regression approach, support each other.

We concluded that the reactivities of *tert*-butoxycarbonylmethyl and cyanomethyl radicals are mainly governed by enthalpy effects. This conclusion is in agreement with the findings of Giese et al.¹⁸ and Fischer et al.²⁰ However, there are certain discrepancies in the conclusions on the nucleophilicity or electrophilicity of these two radicals. In fact, Giese et al.¹⁸ found that ester- and nitrile-substituted methyl radicals are on the borderline between nucleophilic and electrophilic behavior, and Fischer et al.²⁰ found that the *tert*-butoxycarbonylmethyl and cyanomethyl radicals are weakly electrophilic, whereas we found that these two radicals are weakly nucleophilic. As for the cyanomethyl radical, Radom et al.¹⁰ reached the same conclusions as those of Fischer et al.²⁰

This difference in the classification of *tert*-butoxycarbonylmethyl and cyanomethyl radicals might reflect that the transition from nucleophilic to electrophilic character is not very sharp. Nevertheless, another reason for this difference may be that one can find two, sometimes contradictory, definitions in the literature for nucleophilicity (electrophilicity):

(1) The experimentalist's definition says that nucleophilic (electrophilic) radicals react faster with more electron-deficient (more electron-rich) alkenes.

(2) The theoretician's definition says that for nucleophilic (electrophilic) radicals there is an electron transfer in the transition state from the radical (from the alkene) to the alkene (to the radical).

Our calculations are based on radical reactivities (logarithms of reaction rates, barrier heights); therefore, our approach involves the experimentalist's definition. On the other hand, the calculations of Radom et al.^{8–11} make use of the theoretician's definition. The two kinds of definitions may lead to different conclusions as shown by Tables 3 and 5 in the article of Radom et al.¹⁰

Their Table 3¹⁰ shows that the methyl, hydroxymethyl, and cyanomethyl radicals are nucleophilic since they react faster with more electron-deficient alkenes such as vinyl chloride, acrolein, and acrylonitrile.

Their Table 5¹⁰ shows that the cyanomethyl radical is electrophilic since there is an electron transfer in the transition state from the alkene to the radical (for each alkene).

A further reason for the difference in the classification of *tert*-butoxycarbonylmethyl and cyanomethyl radicals by Fischer et al.²⁰ and by the present authors may be the different approach. In fact, Fischer et al.²⁰ drew their conclusions from inspecting some deviations from $\log k$ vs $(-\Delta H_f)$ plots. On the contrary, our approach considers the reactivities of all radicals toward all alkenes simultaneously, i.e., it starts from a complete data matrix of radical reactivities instead of some individual radical reactivities. One advantage of this approach is that it can provide complete reactivity trends of radicals as a function of alkenes as well as those of alkenes as a function of radicals. In addition, the experimental error of individual radical reactivity data has a smaller influence on the reactivity trends obtained from complete data matrixes of radical reactivities than on the conclusions drawn from such individual data points. On the other hand, a disadvantage of our approach is that a complete data matrix of radical reactivities is not always available.

Our results showed that the first principal component represents the nucleophilicity of radicals, whereas the second principal component represents the electrophilicity of radicals. At the same time the loading plots in Figures 1 and 2 show that the point of EA lies close to $A1 = 1$ with its $A2$ value being insignificant, whereas the point of $(-IP)$ lies close to $A2 = 1$ with its $A1$ value being insignificant. This shows the self-consistency of our results, if one recalls that the loading values are the correlation coefficients between the original variables and the principal components. This also confirms that only the phenylsulfonyl, tosyl, and cyclic malonyl radicals are electrophilic since they lie close to $A2 = 1$ and to $(-IP)$, whereas the *tert*-butoxycarbonylmethyl and cyanomethyl radicals are not electrophilic since they lie far from $A2 = 1$ and from $(-IP)$.

With regard to the electrophilicity of the phenylsulfonyl, tosyl, and cyclic malonyl radicals, it appears that the first two of them are moderately electrophilic, whereas the third one is strongly electrophilic. This is suggested by the following: (1) the regression equations in Table 2, i.e., that the reactivities of the phenylsulfonyl and tosyl radicals correlate with $(-\Delta H_f)$ and $(-IP)$ rather than with $(-\Delta H_f)$ or $(-IP)$ alone, whereas the reactivities of the cyclic malonyl radical correlate with $(-IP)$ alone and (2) the component loading plot in Figure 2, i.e., that, although the phenylsulfonyl and tosyl radicals are much closer to $(-IP)$ than the nucleophilic radicals, they are located about equal distance from $(-\Delta H_f)$ and $(-IP)$, whereas the cyclic malonyl radical is even closer to $(-IP)$, much closer than to $(-\Delta H_f)$.

Radical reactivity can be expected to correlate with the following descriptor variables when going from strongly nucleophilic toward strongly electrophilic character of radicals: EA for strongly nucleophilic radicals, EA and $(-\Delta H_f)$ for moderately nucleophilic radicals, $(-\Delta H_f)$ for weakly nucleophilic or weakly electrophilic radicals, $(-\Delta H_f)$ and $(-IP)$ for moderately electrophilic radicals, and $(-IP)$ for strongly electrophilic radicals.

This symmetry pattern of correlations, illustrated in Figure 4, can be seen in our results (see Figures 1 and 2, as well as Table 2).

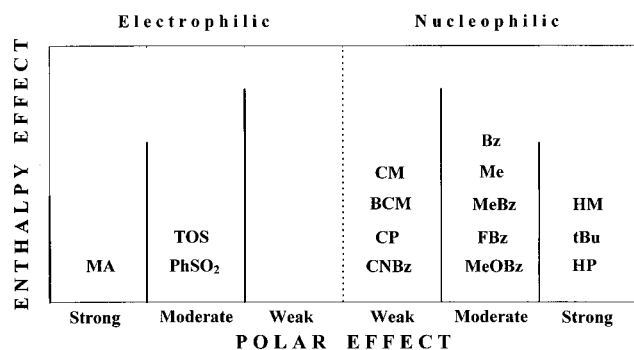


Figure 4. Schematic representation of the dominant factors influencing radical addition reactions.

One might argue that the symmetry pattern of correlations cannot be correct since $(-\Delta H_r)$ is usually correlated with EA and uncorrelated with $(-IP)$. It would follow that the reactivity would correlate with both EA and $(-\Delta H_r)$ for all nucleophilic radicals and would correlate with $(-IP)$ alone for all electrophilic radicals.

However, this is not the case. In fact, using different methods {PCA of experimental rate constant data and theoretical barrier height data, simple linear regression with σ_p , as well as multiple linear regression with EA, $(-\Delta H_r)$ and $(-IP)$ }, we found several examples of the reactivity correlations for strongly nucleophilic, moderately nucleophilic, weakly nucleophilic, moderately electrophilic, and strongly electrophilic radicals. Starting from these findings, the above symmetry pattern of correlations seems to be a reasonable extrapolation.

In our previous work^{1a} we pointed out that the reactivities of more nucleophilic radicals are described by the FMO model whereas those of the less nucleophilic radicals by Hammond's postulate. Now, this qualitative picture can be extended as follows.

The FMO model can describe the reactivities of strongly nucleophilic and strongly electrophilic radicals, Hammond's postulate is adequate for describing the reactivities of weakly nucleophilic and weakly electrophilic radicals, and both theories are relevant in the case of moderately nucleophilic and moderately electrophilic radicals.

Conclusions

The hydroxymethyl radical is strongly nucleophilic, whereas the *tert*-butoxycarbonylmethyl and cyanomethyl radicals are weakly nucleophilic. The methyl radical is moderately nucleophilic, and polar effects cannot be neglected in the case of this radical. The phenylsulfonyl and tosyl radicals are moderately electrophilic, whereas the cyclic malonyl radical is strongly electrophilic.

A symmetry pattern of correlations is proposed: the reactivity correlates with EA for strongly nucleophilic radicals, with EA and $(-\Delta H_r)$ for moderately nucleophilic radicals, with $(-\Delta H_r)$ for weakly nucleophilic or weakly electrophilic radicals, with $(-\Delta H_r)$ and $(-IP)$ for moderately electrophilic radicals, and with $(-IP)$ for strongly electrophilic radicals.

On the basis of the symmetry pattern of correlations, it is concluded that the dominant factors influencing radical addition reactions are polar effects alone for strongly nucleophilic or strongly electrophilic radicals, polar and enthalpy effects for moderately nucleophilic or moderately electrophilic radicals, and enthalpy effects alone for weakly nucleophilic or weakly electrophilic radicals.

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Supporting Information Available: Experimental rate constants, theoretical barrier heights, electron affinity and ionization potential values of alkenes, exothermicity values of radical addition reactions, results of principal component analysis (variances accounted for by the individual principal components, component loadings, component scores) (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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