Cross-Interaction Constant and Intrinsic Reaction Barrier

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Received April 13, 2001

The cross second-derivative of the activation energy, \( \Delta G^2 \), with respect to the two component thermodynamic barriers, \( \Delta G_X \) and \( \Delta G_Y \), can be given in terms of a cross-interaction constant (CIC), \( \beta_{XY} (\rho_{XY}) \), and also in terms of the intrinsic barrier, \( \Delta G^0_\infty \), with a simple relationship between the two: \( \beta_{XY} \equiv -1/(6\Delta G^0_\infty) \). This equation shows that the distance between the two reactants in the adduct (TS, intermediate, or product) is inversely related to the intrinsic barrier. An important corollary is that the Ritchie \( N \) equation holds (for which \( \beta_{XY} \equiv 0 \)) for the reactions with high intrinsic barrier. Various experimental and theoretical examples are presented to show the validity of the relationship, and the mechanistic implications are discussed.

Keywords: Cross-interaction constant, Intrinsic barrier, Ritchie \( N \) equation, Marcus equation.

Introduction

Linear free energy relationships, e.g. Brönsted and Hammett equations, have provided considerable insights into reactivity theory. These equations are extended to include second-derivative parameters, eqs. 1 and 2, and continue to contribute powerfully to elucidation of the organic reaction mechanisms by allowing more detailed prediction of the transition state (TS) structure. The cross-interaction constants (CICs), \( \rho_{XY} \) and \( \beta_{XY} \), represent the intensity of interaction between the two interacting molecules, \( X \) (e.g., a nucleophile) and \( Y \) (an electrophile) in the adduct which may be a TS, an intermediate or a product. The Hammett type constant \( \rho_{XY} \) can be converted, or normalized, to the Brönsted type constant \( \beta_{XY} \) simply by multiplying \( 1/\beta^c \), where \( \beta^c = \Delta \rho/\Delta \sigma_{10} \). Since normally both \( \rho_{XY} \) and \( \beta_{XY} \) are negative, the signs of \( \beta_{XY} \) and \( \rho_{XY} \) are the same but the magnitude of \( \rho_{XY} \) is an order of magnitude larger so that \( \rho_{XY} \) is far more sensitive to variations in \( X \) and \( Y \). Some \( \rho_{XY} \) values are -3.2 (trityl cations), -5.9 (pyridinium ions), -2.9 (anilinium ions), -1.1 (benzylammonium ions), -2.2 (phenols), -4.9 (solvolysis of \( \alpha \)-methylbenzyl chlorides in 80% aqueous acetone), etc. Thus, \( \beta_{XY} = c \rho_{XY} \) where \( c \) is a positive constant.

In the reactions between stable carbocations (or electrophiles; \( Y \)) and nucleophiles (\( X \)), the relative reactivities of the nucleophiles are found to be independent of the nature of the electrophilic carbocations. Ritchie expressed this phenomenon by eq. 3a, eq. 3 which does not contain any parameter characteristic of the substrate (\( Y \)). Since \( N \) is a function only of the nucleophile (\( X \)) and independent of the substrate (\( Y \)), an important corollary is that \( \rho_{XY} = \beta_{XY} \equiv 0 \) (eq. 3b) for the reactions following the \( N \) equation in accordance with the definition of cross-interaction constants, eqs. 1 and 2. Originally, this condition of no interaction, i.e., \( \rho_{XY} = \beta_{XY} \equiv 0 \), was thought to be satisfied by a large distance between the two interacting molecules, eqs. 3a-c \( r_{XY} = \infty \). In the bond forming processes, the sign of \( \beta_{XY} \) is negative and the magnitude (the intensity of interaction) decreases as the distance, \( r_{XY} \), becomes longer. eqs. 3a-c

In this work we show that the CIC plays an important role as a link between the Ritchie \( N \) and Marcus equation, eq. 4, in addition to a wide range of applications in the elucidation of organic reaction mechanisms. eqs. 1, 2

\[
\Delta G^2 = \Delta G^0_\infty + 1/2\Delta G^2 + (\Delta G^0)^2/(16\Delta G^0_\infty) \quad (4)
\]

is the intrinsic reaction barrier i.e., the barrier in the thermoneutral reactions (\( \Delta G^2=0 \)); an equivalent form may be given using the potential energy changes, \( \Delta E^0 \), \( \Delta E^0_\infty \), and \( \Delta E^0_\infty \).

It is well established theoretically as well as experimentally that the Brönsted basicity is linearly correlated with the Lewis basicity. For example, equilibrium constants \( K \) for the coordination of metal halides and metal ions with bases (anilines and benzamides) in solution gave linear plots of logK (Lewis basicity) vs. the pKa values (Brönsted basicity) of the protonated amines. For the metal halides the slopes of the linear plots ranged from 0.6 to 1.3 with an average value of 0.9. It was also found that the proton affinity, PA (Brönsted basicity), is linearly related to the methyl cation affinity, MCA (Lewis basicity), eq. 5, with a slope not far from unity. For example, for 9 nucleophiles (F, Cl, Br, I, OH, NH2, HF, H2O, and NH3) the slope was 0.92 ± 0.01 for both experimental and theoretical (at the G2 level) MCA vs. PA plots with the correlation coefficients of \( r \geq 0.999 \).
Cross-Interaction Constant and Intrinsic Reaction Barrier

The thermodynamics of carboxication-carbanion bond formation is related closely to the pK and pK values of the carbanion and carboxation, respectively. Heats of formation, $\Delta H^0$, for trimethyl- and triphenylcyclopentonium cations with a series of substituted arylmalononitrile anions in acetonitrile solution, and for triphenylmethyl cation with a series of 9-fluorenide ions in benzonitrile solution gave a good single straight line plot against (pK-pK) with a slope of 1.18. On the other hand, Arnett et al., have shown that the free energies of reaction, $\Delta G^0$, are linearly related to the enthalpies, $\Delta H^0$, for these reactions with a slope of 1.16. This means that eq. 8 holds since 1.16 x 1.18 = 1.37 = 2.303RT at 298 K. Thus the changes in the free energy of reaction, $\Delta G^0$, can be given as a sum of the changes in the component free energy terms, i.e., those of the nucleophile

$$\Delta G^0 = \Delta G^0_Y - \Delta G^0_X + \text{constant}$$

and the nucleophile (X) and substrate (or electrophile, Y), $\Delta G^0_X$ and $\Delta G^0_Y$ can be derived from the two pK, changes, $\delta pK^+_X$ and $\delta pK^+_Y$.

Equations 1 and 2 can now be transformed into the free energy forms based on the relation given by eq. 9. For example, eq. 2 becomes,

$$\Delta G^+ = \beta_X \Delta G^+_X + \beta_Y \Delta G^+_Y + \beta_{XY} \Delta G^+_X \Delta G^+_Y$$

and hence,

$$\delta^2 \Delta G^+ / (\partial \Delta G^+_X \cdot \partial \Delta G^+_Y) = \beta_{XY} = -\beta_{XY}/1.36$$

On the other hand, partial second-derivative of $\Delta G^+$ in the Marcus equation (eq. 4) with respect to $\Delta G^+_X$ and $\Delta G^+_Y$ leads to

$$\delta^2 \Delta G^+ / (\partial \Delta G^+_X \cdot \partial \Delta G^+_Y) = 1/(8 \Delta G^+_0)$$

From eqs. 11 and 12, we obtain

$$\beta_{XY} = -\beta_{XY}/1.36 = 1/(8 \Delta G^+_0)$$

Thus,

$$\beta_{XY} \equiv -1/(6 \Delta G^+_0)$$

This equation (eq. 14) can be derived by equating the first-derivatives of $\Delta G^+$ in eqs. 4 and 10 with respect to $\Delta G^+_0$. Thus,

$$1/2 + \Delta G^+_0 / (8 \Delta G^+_0) = \beta_X - (\beta_{XY}/1.36) \cdot \Delta G^+_0$$

Rearranging this,

$$\beta_X = 1/2 + [1/(8 \Delta G^+_0) + \beta_{XY}/1.36] \Delta G^+_0$$

For thermoneutral reactions, $\beta_X = 1/2$ (eq. 7b) so that $[A] = 0$ or $\Delta G^+_0 = 0$. The requirement $[A] = 0$ leads to eq. 14.

Equation 14 shows that: (i) The CIC, $\beta_{XY}$ (and hence $\rho_{XY}$), is a function only of the intrinsic barrier, and does not depend on the reaction energy, $\Delta G^+_0$, in contrast to $\beta_X$ (eq. 7b), a first-derivative selectivity parameter, which is a function of both $\Delta G^+_0$ and $\Delta G^+_0$. (ii) The CIC is a negative quantity whose magnitude is inversely related to the intrinsic barrier. The higher the intrinsic barrier, the smaller is the magnitude of $\beta_{XY}$ (or $\rho_{XY}$) and hence the longer is the distance ($\tau_{XY}$, Scheme 1) so that the two reactants are farther apart in the TS: higher intrinsic barrier $\rightarrow$ smaller size of CIC $\rightarrow$ lower extent of bond formation in the TS. (iii) An important consequence of the relation (eq. 14) is that the Ritchie $N_r$ equation (eqs. 3) holds for the reaction series with extremely high intrinsic reaction barrier, $\Delta G^+_0 = \infty$. This result has been
qualitatively predicted by Richard in his work on the application of the $N_t$ relation to quinone methides. He interpreted this as an insensitive variation of the rates ($k_{XY}$) with the change in the electrophile (Y) due to the high intrinsic barrier.

For endothermic and exothermic processes, $\beta_X > 1/2$ and $< 1/2$, respectively, (eq. 7b), so that $|A|$ in eq. 16 should be positive in the non-thermoneutral reactions. Thus, $\beta_X = -1/(6\Delta G_X^\alpha)$, indicating that the magnitude of the CIC ($\beta_X$) in the non-thermoneutral reactions is smaller than that in the corresponding thermoneutral reactions.

$$|\beta_X(\Delta G^\alpha \neq 0)| < |\beta_X(\Delta G^\alpha=0)|$$

(17)

**Experimental and Theoretical Examples**

Experimentally, it is difficult to show functional dependence of the degree of bond formation ($\delta_{XY}$) on the intrinsic barrier ($\Delta G_{XY}^\circ$). This is because the degree of bond formation is also dependent on the thermodynamic barrier (eq. 7b) since eq. 14 is strictly applicable only for thermoneutral reactions ($\Delta G^\circ = 0$). Since experimental results on such thermoneutral reactions are scarce, we can give only limited number of examples that are reported in the literature. However, there are sufficient theoretical results to substantiate the prediction of eq. 14, i.e., the higher the intrinsic barrier, the smaller is the magnitude of the CIC and hence the lower is the degree of bond formation, or the looser is the TS.

Experimental intrinsic barriers in gas-phase nucleophilic displacements have been reported by Pellerite and Brauman for methyl transfer reactions, eq. 18.

$$X^- + CH_3X \rightleftharpoons XCH_3 + X^-$$

(18)

The intrinsic barriers, $\Delta E_{o}^\alpha$, were found to be linearly correlated with the methyl cation affinities (MCA, eq. 5b) with a slope of ca. 0.5. This was interpreted to indicate a linear increase of charge separation in the trigonal-bipyramidal (TBP) TS of the exchange reaction with the intrinsic barrier, i.e., the higher the intrinsic barrier, the greater is the charge separation and hence the greater is the distance ($r_{XY}$) between the nucleophile, $X^-$, and the methyl (partial) cation in the TS. The slope of ca. 0.5 obtained for 8 nucleophiles ($X = Br, Cl, CH_2CO_2, CD_3S, F, t-BuO, CH_3O$, and HCC) is in agreement with that predicted by eq. 7b for the thermoneutral reactions ($\Delta G^\circ = 0$).

Lewis et al. have measured the barriers ($\Delta G_{o}^\alpha$) for the identity methyl transfers, eq. 18, with various nucleophiles, $X^-$, in solution. For $X=CH_3HSO_3^-$ and $CH_3HSe^-$ in sulfolane, the $\Delta G_{o}^\alpha$ values were 23.6 and 20 ± 3.5 kcal mol$^{-1}$, respectively. The charges on the $CH_3$ group in the TS were estimated to be +0.2 and −0.25, respectively, indicating that for the higher $\Delta G_{o}^\alpha$ ($C_6H_5SO_3^-$) the TS is looser with the smaller extent of bond formation than that for the lower $\Delta G_{o}^\alpha$ exchange of $C_6H_5Se^-$. Thus these limited experimental results are in good accord with the prediction of eq. 14.

In contrast to the paucity of the experimental kinetic results, the theoretical reports for the structural dependence of the TS on the intrinsic barrier are abundant. Early theoretical results on the identity methyl transfer reactions, eq 18, at relatively low level of theory (RHF/4-31G) by Wolfe and coworkers have indicated clearly that the higher the intrinsic barrier (with $X=Cl, F, HS, HO, HCC, NC$ and $H$), the looser is the TS. They showed that there exists a linear correlation between the Distortion Index (DI=$100r_{XY}$) and the percentage bond order change of the C-X bond (formation) in the TS. The slope of DI with a lower degree of bond formation, or the looser is the TS.

**Table 1. Intrinsic barriers ($\Delta E_{o}^\alpha$, in kcal mol$^{-1}$) and the extent of bond formation in the TS (as expressed in $\% \Delta n^o$) for the identity methyl transfer reactions, $X^- + CH_3X \rightleftharpoons XCH_3 + X^-$, at the RHF-4-31G level**

<table>
<thead>
<tr>
<th>$X$</th>
<th>$\Delta E_{o}^\alpha$ (kcal mol$^{-1}$)</th>
<th>$% \Delta n^o$ (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH</td>
<td>50.4</td>
<td>33.3</td>
</tr>
<tr>
<td>CN</td>
<td>43.8</td>
<td>33.7</td>
</tr>
<tr>
<td>NC</td>
<td>28.5</td>
<td>38.6</td>
</tr>
<tr>
<td>OH</td>
<td>21.2</td>
<td>47.6</td>
</tr>
<tr>
<td>SH</td>
<td>15.6</td>
<td>46.3</td>
</tr>
<tr>
<td>F</td>
<td>11.7</td>
<td>54.3</td>
</tr>
<tr>
<td>Cl</td>
<td>5.5</td>
<td>49.8</td>
</tr>
</tbody>
</table>

**Table 2. The intrinsic barriers ($\Delta E_{o}^\alpha$, in kcal mol$^{-1}$) and percentage bond order change (\% $\Delta n^o$) in the bond formation for Cl$^- + RCl \rightleftharpoons CIR + Cl^-$ reactions,²⁰ ²¹**

<table>
<thead>
<tr>
<th>$R$</th>
<th>$\Delta E_{o}^\alpha$</th>
<th>$% \Delta n^o$ (Ref.)</th>
<th>$\rho_{XY}$ ²²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_4$H$_2$</td>
<td>7.7</td>
<td>41</td>
<td>0.64</td>
</tr>
<tr>
<td>CH$_3$CH$_2$</td>
<td>11.2</td>
<td>38</td>
<td>0.68</td>
</tr>
<tr>
<td>CH$_2$CHCH$_3$</td>
<td>8.2</td>
<td>39</td>
<td>0.74</td>
</tr>
<tr>
<td>CHCCCH$_2$</td>
<td>6.9</td>
<td>40</td>
<td>0.80</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CH$_2$</td>
<td>18.0</td>
<td>35</td>
<td>0.58</td>
</tr>
<tr>
<td>(CH$_3$)$_3$CH$_2$</td>
<td>6.9</td>
<td>40</td>
<td>0.66</td>
</tr>
</tbody>
</table>

²²Calculated at the MP2/6-31+G+/MP2/6-31+G* level. ²¹These approximate values were estimated from the experimental $\rho_{XY}$ values for $HCN$ and $CsHSe$ assuming $\rho_{XY} = 1/2\rho_{YZ}$. The reactions are exothermic by −6−9 kcal mol$^{-1}$ at the AM1 level.
formation in the TS as presented in Table 2. For example, neopentyl (R=(CH₃)₃CCH₂) chloride has the highest intrinsic barrier (18.0 kcal mol⁻¹) and the TS is the earliest with the lowest degree of bond formation (%Δn° = 35). Since the neopentyl group is bulky, the TS is formed at a far away distance, r_{c-CI} = large. Similarly the bulky secondary carbon centers (R'R²CH⁻) lead to the higher intrinsic barrier and lower extent of bond formation in the TS for the identity chloride exchange reactions than the primary carbon centers (RCH₂⁻). Theoretical studies at the MP2/6-31+G* level have shown that the average intrinsic barriers were ΔE°₀=9.2 (for 6 R's) and 12.5 kcal mol⁻¹ (for 9 R'R²-sets) with the degree of bond formation %Δn°=39 (average C-Cl distance d_{C-Cl} = 4.67 ± 0.02 Å) and 34 (average d_{C-Cl} = 4.80 ± 0.02 Å) respectively.²¹ Experimentally the average CICs (ρ_{C2}) for the nucleophilic substitution reactions of primary alkyl arenesulfonates (RCH₂OSO₂C₆H₄Z for 9 R's) and secondary arenesulfonates (R²R³CHOSO₂C₆H₄Z for 10 sets) with anilines (XCH₃NH₂) were 0.33 ± 0.03 and 0.12 ± 0.01 respectively.²⁰ These results clearly show that the bulky secondary carbon centers form looser TSs than at the primary carbon centers. Similar results are also obtained with the identity fluoride exchanges.²¹ It is important to note here that this result of a lower degree of bond formation for the sterically hindered TS should apply only to the thermoneutral processes. Since the sterically hindered products in a non-thermoneutral process should result in an endothermic process (ΔG° > 0), the TS will be located on a later position (a larger value of %Δn°) along the reaction coordinate, which is exactly an opposite to that expected from a thermoneutral process. This is obvious from eq. 7b; for a positive ΔG°, the bond formation becomes greater than that with ΔG° ≤ 0.

Table 3 shows that for neutral and anion nucleophiles the higher the intrinsic barrier, the lower is the extent of bond formation in the TS for the identity methyl transfer reactions at the G2//MP2/6-31G** level.¹² Similarly in the identity carbonyl transfers (R=HCO and CH₂CO), the higher intrinsic barrier (ΔE°₀ = 8.3 and 8.6 kcal mol⁻¹ for Cl⁻ and Br⁻, respectively) was found to give lower degree of bond formation in the TS (61 and 58% with R=HCO). An interesting, yet important, example which shows clearly that application of eq. 14 should be limited to the thermoneutral processes for which the reaction barriers are the intrinsic barriers (ΔE°₀ or ΔG°₀), is provided by the identity thiocarbonyl transfers, X⁻ + RCSX ↔, with X = Cl and Br.²³ The potential energy changes are shown in Table 4. We note that central barrier height (ΔE°₀) is lower with X=Cl than Br. If this were the intrinsic barrier, ΔE°₀, the extent of bond formation should have been greater for X=Cl. However, the %Δn° values are 34 (Cl) and 44 (Br), respectively, and hence the lower barrier gave the smaller degree of bond formation in apparent contradiction to that expected from eq. 14. On closer examination of Figure 1, one can understand why this is so: the central barrier is not actually the intrinsic barrier, ΔE°₀ ≠ ΔE°₀, The presence of the intermediate leads to an endothermic type process.

For X=Br, the barrier is higher but the well-depth is shallower so that the endothermicity is greater. This means that the TS becomes later (eq. 7b), i.e., %Δn° is greater, so that the greater extent of bond formation obtained for X=Br is simply due to the thermodynamic effect. However if we look at the extent of bond making in the intermediate, which is thermoneutral, we verify that the lower barrier (for X=Cl) leads indeed to a greater degree of bond formation with 77 (Cl) vs 67% (Br).

Another interesting case is the identity methyl transfer studies (eq. 18) by Vetter and Zulicke²⁴ at a relatively high level of theory, Cl(SD) with double zeta double polarization function (DZDP) and Davidson correction. They have shown that the intrinsic barriers for the identity halide exchanges are not in the simple sequence F-Cl-Br decreasing nucleophilicity and increasing leaving ability, but are in the order Cl (7.2) > Br (2.5) > F (2.2 kcal mol⁻¹). Accordingly the degree of bond formation in the TS, %Δn°, were in the reverse order F (44.8) > Br (36.8) > Cl (35.5). This sequence of ΔE°₀ (and %Δn°) is however in contrast to that obtained (F > Cl) at the lower level (4-31G) by Wolfe et al.¹⁹ (Table 1). Another example is the theoretical studies of water exchanges at methyl (R=CH₃) and ethyl (R=C₂H₅) carbons, eq. 19, at the MP3/6-31+G**/HF/3-21G level.²⁵ The

\[
H₂O + ROH⁺ := H₂OR⁺ + OH₂
\]

results show that higher intrinsic barrier at the ethyl (ΔE°₀=1.5) than methyl carbon (-0.8 kcal mol⁻¹, relative to the reactants) leads to a lower degree of bond formation in

<table>
<thead>
<tr>
<th>X</th>
<th>ΔE°₀ (kcal mol⁻¹)</th>
<th>Well-depth (kcal mol⁻¹)</th>
<th>%Δn°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>5.2</td>
<td>2.6</td>
<td>34</td>
</tr>
<tr>
<td>Br</td>
<td>6.2</td>
<td>0.2</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 4. The central barriers, (ΔE°₀), well-depth (ΔE°₀-ΔE₀), and percentage bond formation (%Δn°) in the transition state for identity thiocarbonyl transfers at the MP2/6-31+G** level²²
Mechanistic Implications

Analyses of the data by Ritchie have shown that the reaction families that follow the $N_c$ equation are all intrinsic-barrier controlled reactions with relatively large and constant intrinsic barriers within a family. For the reactions $R^+ + H_2O \leftrightarrow ROH + H^+$ with R = triarylmethyl (a), tropylium (b) and xanthylum (c) cations, a linear relation was found between $\Delta G^*$ and $\Delta G^0$ with a constant $\Delta G_0^*$ for each family, eqs. 20.

$$\Delta G^* = 0.67 \pm 0.04 \cdot \Delta G^0 + 16.22 \pm 0.27 : r = 0.986, n = 12.$$  

$$\Delta G^* = 0.45 \pm 0.06 \cdot \Delta G^0 + 14.57 \pm 0.39 : r = 0.958, n = 7.$$  

$$\Delta G^* = 0.56 \pm 0.18 \cdot \Delta G^0 + 12.92 \pm 0.98 : r = 0.839, n = 6.$$  

These equations indicate that the effect of thermodynamic barrier on the rate ($\Delta G_0^*$) is small relative to that of the constant $\Delta G_0^*$ values (13-16 kcal mol$^{-1}$ neglecting the second order term in eq. 4) since $\Delta G^*$ values were small with the average of ca. 6 kcal mol$^{-1}$ (the effect should be ca. 3 kcal mol$^{-1}$ considering the approximately 1/2 coefficients in eqs. 20). By contrast in the reaction series that does not follow the $N_c$ equation, the intrinsic barrier was found to vary linearly with $\Delta G^0$, i.e., $\Delta G_0^*$ was not a constant value but the overall activation barrier ($\Delta G^*$) was constant. For example, in the solvolysis reactions of $\alpha$-R$^1$, $R^2$-disubstituted $p$-methoxybenzyl cations have large changes in the thermodynamic driving force ($\Delta G^0 = -13 \sim -36$ kcal mol$^{-1}$) as well as in the intrinsic barrier ($\Delta G_0^* = 14 \sim 27$ kcal mol$^{-1}$) and the two have compensatory relation so that the overall barriers ($\Delta G^*$) are relatively constant at ca. 8 kcal mol$^{-1}$, eq. 21.\textsuperscript{26} This means that the overall barrier, $\Delta G^*$, is dependent on both $\Delta G_0^*$ and $\Delta G^0$ since eq. 21 is approximately equal to eq. 4 with neglect of the second order term.

$$\Delta G_0^* = -0.46 \pm 0.05 \cdot \Delta G^0 + 8.49 \pm 1.21 (r = 0.958, n = 11)$$  

These analyses suggest that the $N_c$ equation applies to the reaction series that are intrinsic-barrier controlled with a large constant intrinsic barrier leading to a negligible CIC, $\beta_{XY} (= \rho_{XY}) \approx 0$.

The important relation, eq. 14, tells us that a stronger nucleophile with a lower intrinsic, or kinetic, barrier leads to a greater extent of bond making in the TS, since for a smaller $\Delta G_0^*$ a larger magnitude of $\beta_{XY} (\rho_{XY})$ is obtained. This is however exactly opposite to that expected from thermodynamically based rate-energy relations, e.g., Bell-Evans-Polanyi principle.\textsuperscript{27} For example, eq. 7b predicts an earlier TS with a lower degree of bond making in the TS since for a stronger nucleophile a less endothermic or a more exothermic reaction ($\delta \Delta G^0 < 0$) is expected with a smaller value of $\beta_X$. Thus it is clear that a stronger nucleophile (and nucleofuge) leads to a later TS with a greater degree of bond formation (and bond breaking) in the intrinsic-controlled reactions, whereas it leads to an earlier TS with a lower extent of bond formation (and bond breaking) in the thermodynamic-controlled reactions. These two opposing effects can be conveniently illustrated with a More O’Ferrall-Jencks type two dimensional potential energy diagram.\textsuperscript{1e,28} Figure 2. The diagonal line from reactants (corner, R) to products (corner, P) represents thermodynamic effect ($\delta \Delta G^0$), while that from dissociated (corner, D) to associated (corner, A) states intrinsic effect ($\delta \Delta G_0^*$). A stronger nucleophile depresses the corners P and A shifting the TS toward the corners R and A respectively, i.e., toward an earlier and a tighter TS, respectively. For a reaction with a greater thermodynamic driving force ($\delta \Delta G^0 < 0$) the TS shifts toward R but for a reaction with a lower intrinsic barrier the TS shifts toward A. And hence the magnitude of $\beta_X$ (eq. 7b) is reflected on the thermodynamic line ($R \rightarrow P$), whereas the magnitude of $\beta_{XY} (\rho_{XY})$ is reflected on the intrinsic line ($D \rightarrow A$), (eq. 14). Overall, the shift of the TS can be predicted by a vector sum of the two effects as the Marcus
equation, eq. 4, requires. The Ritchie $N_e$ equation holds on the intrinsic line close to D. It should be emphasized that the $N_e$ equation and eq. 14 apply strictly to the intrinsic-barrier controlled reaction series.

For the $N_e$ type reactions, two mechanisms are proposed: One involves desolvation of the ions. For example in a cation-anion combination, the solvated ions first form the solvent-separated ion pair, in which the anion (nucleophile) is partially desolvated. This ion pair is transformed in the rate-determining step into contact ion pair where partial desolvation of the cation (electrophile) has also taken place. This is followed by the formation of a neutral covalently bonded adduct. In this mechanism the cation-anion is not covalently bonded in the TS but the partially desolvated ion pair formation takes place so that the interaction between the two should be small in the TS and the condition $\beta_{XY}$ = 0 is satisfied. The other invokes the intervention of an electron-transfer (ET) mechanism. Since in the ET reactions an electron (charge) is transferred (D’+A’) but the covalent link (D’-A’) is not formed in the TS, i.e., an outer-sphere charge transfer occurs, the electrophile-nucleophile interaction should be feeble and may become negligible so that the magnitude of the CIC ($\beta_{XY}$) may become insignificantly small. However in view of the substantial charge transfer observed in the reactions of triarylmethyl cations with primary amines, as evidenced by a large $\beta_k$ ($\beta_{sec} = 0.67 - 0.29$), the latter ET mechanism is more likely to apply for the $N_e$ type reactions.

**Summary and Conclusion**

The cross second-derivative of the activation energy, $\Delta G^*_{XY}$, with respect to the two component thermodynamic barriers, $\Delta G^*_X$ and $\Delta G^*_Y$, has been shown to give two different forms: One in terms of the cross-interaction constant (CIC), $\beta_{XY}$ ($\rho_{XY}$), and the other in terms of the intrinsic barrier, $\Delta G^*_e$, with a very simple relationship between the two,

$$\beta_{XY} \equiv -1/(6\Delta G^*_e).$$

One important corollary of this relationship is that the Ritchie $N_e$ equation holds only for intrinsic-barrier controlled reaction series with high intrinsic barriers. This relationship also shows that the lower the intrinsic barrier, the greater is the extent of bond making in the TS. Conclusions reached are: A stronger nucleophile leads to a greater degree of bond formation in the TS for the intrinsic barrier controlled reaction series (as those for which the $N_e$ equation is applicable), whereas the contrary is true for the thermodynamically controlled reactions. The former is a consequence of eq. 14, a second-derivative parameter, while the latter results from eq. 7b, a first-derivative parameter.

**Acknowledgment.** We thank Inha University for support of this work. This work was also supported by grant No.
1999-2-123-0003-5 from the Basic Research Program of the Korea Science and Engineering Foundation, and from The Korea Research Foundation for the 21 Century.

References


5. Page, M. I.; Williams, A. Organic and Bio-organic Mechanisms; Longman: Harlow, 1997; Appendix A. The signs of ɵ in this Table should be reversed to negative for pKa vs ɵ plots.


15. Ref. 10, p 58.


20. This is defined as

$$\Delta n = \frac{[\text{exp}(-r^a) - \text{exp}(-r^a)]}{[\text{exp}(-r^b) - \text{exp}(-r^a)]} \times 100$$


