

Cross-Interaction Constant and Intrinsic Reaction Barrier

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The cross second-derivative of the activation energy, ΔG^\ddagger , with respect to the two component thermodynamic barriers, ΔG_X^\ddagger and ΔG_Y^\ddagger , can be given in terms of a cross-interaction constant (CIC), β_{XY} (ρ_{XY}), and also in terms of the intrinsic barrier, ΔG_0^\ddagger , with a simple relationship between the two: $\beta_{XY} \approx -1/(6\Delta G_0^\ddagger)$. 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 $\beta_{XY} \approx 0$) 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.* Brønsted and Hammett equations, have provided considerable insights into reactivity theory. These equations are extended to include second-derivative parameters,¹ 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.² The cross-interaction constants (CICs), ρ_{XY} and β_{XY} , represent the intensity of interaction between the two interacting molecules, X (*e.g.*, a nucleophile) and Y (an electrophile) in the adduct which

$$\log(k_{XY}/k_{HH}) = \rho_X \sigma_X + \rho_Y \sigma_Y + \rho_{XY} \sigma_X \sigma_Y \quad (1)$$

$$\log(k_{XY}/k_{HH}) = \beta_X pK_X + \beta_Y pK_Y + \beta_{XY} pK_X \cdot pK_Y \quad (2)$$

may be a TS, an intermediate or a product.² The Hammett type constant ρ_{XY} can be converted, or normalized, to the Brønsted type constant β_{XY} simply by multiplying $1/\rho_X^e \rho_Y^e$ where $\rho^e = \Delta \log k / \Delta \sigma$.^{1de,2b,3} Since normally both ρ_X^e and ρ_Y^e are negative, the signs of β_{XY} and ρ_{XY} are the same but the magnitude of ρ_{XY} is *ca.* an order of magnitude larger so that ρ_{XY} is far more sensitive to variations in X and Y.^{2b} Some ρ^e values are -3.2 (trityl cations),⁴ -5.9 (pyridinium ions),⁵ -2.9 (anilinium ions),⁵ -1.1 (benzylammonium ions),⁵ -2.2 (phenols),⁵ -4.9 (solvolysis of α -methylbenzyl chlorides in 80% aqueous acetone),³ 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.^{4,6} Ritchie expressed this phenomenon by eq. 3a,^{4,6} 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

$$\log k_{XY} = N_+ + \log k_0 \quad (3a)$$

$$\rho_{XY} = \beta_{XY} = 0 \quad (3b)$$

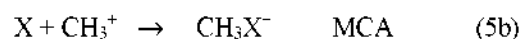
substrate (Y), an important corollary is that $\rho_{XY} = \beta_{XY} = 0$ (eq. 3b) for the reactions following the N_+ equation in accordance with the definition of cross-interaction constants,^{2b} eqs. 1 and 2. Originally, this condition of no interaction, *i.e.*, $\rho_{XY} = \beta_{XY} = 0$, was thought to be satisfied by a large distance between the two interacting molecules,^{2a-c} $r_{XY} \approx \infty$. In the bond forming processes, the sign of ρ_{XY} (β_{XY}) is negative and the magnitude (the intensity of interaction) decreases as the distance, r_{XY} , becomes longer.^{2a-c}

In this work we show that the CIC plays an important role as a link⁷ between the Ritchie N_+ and Marcus equation⁸ (eq. 4), in addition to a wide range of applications in the elucidation of organic reaction mechanisms.^{1,2} In eq. 4, ΔG_0^\ddagger

$$\Delta G^\ddagger = \Delta G_0^\ddagger + 1/2\Delta G^0 + (\Delta G^0)^2/(16\Delta G_0^\ddagger) \quad (4)$$

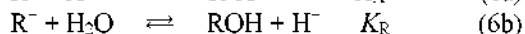
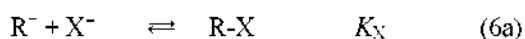
is the intrinsic reaction barrier *i.e.*, the barrier in the thermo-neutral reactions ($\Delta G^0=0$); an equivalent form may be given using the potential energy changes, ΔE^\ddagger , ΔE_0^\ddagger and ΔE^* .⁹

It is well established theoretically as well as experimentally that the Brønsted 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 $-\log K$ (Lewis basicity) vs. the *pK_a* values (Brønsted basicity) of the protonated amines.¹⁰ For the metal halides the slopes of the linear plots ranged from 0.6 to 1.3 with an average value of 0.9.¹⁰ It was also found that the proton affinity, PA (Brønsted basicity), is linearly related to the methyl cation affinity, MCA (Lewis basicity), eqs. 5, with a slope not far from unity.¹¹ For example, for 9 nucleophiles (F^- , Cl^- , Br^- , I^- , OH^- , NH_2^- , HF , H_2O , and NH_3) the slope was 0.92 ± 0.01 for both experimental and theoretical (at the G2 level) MCA vs. PA plots¹² with the correlation coefficients of $r \geq 0.999$.



This shows that $\Delta G_{HX}^0 (= 2.3RTpK_X = 1.36 \cdot pK_X \text{ kcal mol}^{-1}$ at 298 K) and ΔG_X^0 (the free energy of reaction for X in eq.

5b) can be interchangeable for most of the nucleophiles, X. In fact it was found that for the reactions of carbocations with "families" of nucleophiles, values of $-\log K_X$ (Lewis basicity, eq. 6a) are linearly related to pK_a 's of the conjugate acids of the nucleophiles (Brønsted basicity, pK_{HX}) with slopes close to unity.⁴ For such families, Brønsted slopes, $\beta_X = \delta\Delta G^\ddagger / \delta\Delta G_{HX}^\ddagger$, are nearly equal to the slopes of $\delta\Delta G^\ddagger$ vs $\delta\Delta G_X$ plots, eq. 7a, and can be interpreted to represent the



extents of bond formation at transition states. The traditional view that the Brønsted coefficient β_X is at least an approximate measure of the extent to which the nucleophilic addition has proceeded in the TS is based on this parallelism between the slope of the plot of ΔG^\ddagger vs ΔG_{HX}^\ddagger (proton or Brønsted basicity) and that of ΔG^\ddagger vs ΔG_X^\ddagger (carbon or Lewis basicity).¹³ The Marcus equation leads to eq. 7b, which indicates that the extent of bond formation, β_X , is dependent on both the intrinsic and thermodynamic barriers.

$$\beta_X = \delta\Delta G^\ddagger / \delta\Delta G_{HX}^\ddagger = \delta\Delta G^\ddagger / \delta\Delta G_X^\ddagger \quad (7a)$$

$$= 1/2 + \Delta G^\ddagger / (8\Delta G_0^\ddagger) \quad (7b)$$

Cross-interaction Constant (CIC) and Intrinsic Barrier

The thermodynamics of carbocation-carbanion bond formation is related closely to the pK_a and pK_R (eq. 6) of the carbanion and carbocation, respectively.⁴ Heats of formation, ΔH^\ddagger , for trimethyl- and triphenylcyclopropenium cations with a series of substituted arylmalononitrile anions in acetonitrile solution, and for triphenylmethyl cation with a series of 9-fluorenyl ions in benzonitrile solution gave a good single straight line plot against ($pK_a - pK_R$) with a slope of 1.18.¹⁴ On the other hand, Arnett *et al.*, have shown that the free energies of reaction, ΔG^\ddagger , are linearly related to the enthalpies, ΔH^\ddagger , for these reactions with a slope of 1.16.¹⁴ This means that eq. 8 holds since $1.16 \times 1.18 = 1.37 \approx 2.303RT$ at 298 K. Thus the changes in the free energy of reaction, $\delta\Delta G^\ddagger$, can be given as a sum of the changes in the component free energy terms, *i.e.*, those of the nucleophile

$$\Delta G^\ddagger = \Delta G_X^\ddagger - \Delta G_Y^\ddagger + \text{constant} \quad (8)$$

(or carbanion, X) and electrophile (or carbocation, Y), eq. 9. They pointed out that the relative pK_a 's (hence $\delta\Delta G_X^\ddagger$'s) and

$$\delta\Delta G^\ddagger = \delta\Delta G_X^\ddagger + \delta\Delta G_Y^\ddagger \quad (9)$$

pK_R 's ($\delta\Delta G_Y^\ddagger$'s) are not sensitive to solvent so that the use of values measured in different solvents are justified.¹⁴ This type of relation, eq. 9, holds for the addition of resonance-stabilized carbocations and various nucleophiles including carbanions,⁴ and can be extended to other S_N2 reactions in which the relative free energy changes of the components, the nucleophile (X) and substrate (or electrophile, Y), $\delta\Delta G_X^\ddagger$

and $\delta\Delta G_Y^\ddagger$, can be derived from the two pK_a changes, δpK_X and δpK_Y .¹⁵

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,

$$\Delta G^\ddagger = \beta_X \Delta G_X^\ddagger + \beta_Y \Delta G_Y^\ddagger + \beta_{XY} \Delta G_X^\ddagger \Delta G_Y^\ddagger \quad (10)$$

and hence,

$$\partial^2 \Delta G^\ddagger / (\partial \Delta G_X^\ddagger \cdot \partial \Delta G_Y^\ddagger) = \beta_{XY} = -\beta_{XY} / 1.36 \quad (11)$$

On the other hand, partial second-derivative of ΔG^\ddagger in the Marcus equation (eq. 4) with respect to ΔG_X^\ddagger and ΔG_Y^\ddagger leads to

$$\partial^2 \Delta G^\ddagger / (\partial \Delta G_X^\ddagger \cdot \partial \Delta G_Y^\ddagger) = 1 / (8\Delta G_0^\ddagger) \quad (12)$$

From eqs. 11 and 12, we obtain

$$\beta_{XY} = -\beta_{XY} / 1.36 = 1 / (8\Delta G_0^\ddagger) \quad (13)$$

Thus,

$$\beta_{XY} \approx -1 / (6\Delta G_0^\ddagger) \quad (14)$$

This equation (eq. 14) can be derived by equating the first-derivatives of ΔG^\ddagger in eqs. 4 and 10 with respect to ΔG_X^\ddagger . Thus,

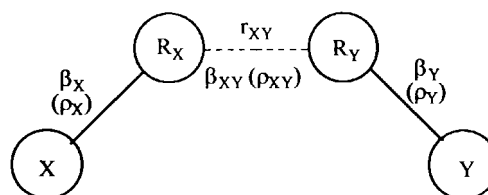
$$1/2 + \Delta G_Y^\ddagger / (8\Delta G_0^\ddagger) = \beta_X - (\beta_{XY} / 1.36) \cdot \Delta G_Y^\ddagger \quad (15)$$

Rearranging this,

$$\begin{aligned} \beta_X &= 1/2 + \{1 / (8\Delta G_0^\ddagger) + \beta_{XY} / 1.36\} \Delta G_Y^\ddagger \\ &= 1/2 + \{A\} \Delta G_Y^\ddagger \end{aligned} \quad (16)$$

For thermoneutral reactions, $\beta_X = 1/2$ (eq. 7b) so that $\{A\} = 0$ or $\Delta G_Y^\ddagger = 0$. The requirement $\{A\} = 0$ leads to eq. 14.

Equation 14 shows that: (i) The CIC, β_{XY} (and hence ρ_{XY}), is a function only of the intrinsic barrier, and does not depend on the reaction energy, ΔG^\ddagger , in contrast to β_X (eq. 7b), a first-derivative selectivity parameter, which is a function of both ΔG_0^\ddagger and ΔG^\ddagger . (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 β_{XY} (ρ_{XY}) and hence the longer is the distance (r_{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*-equation (eqs. 3) holds for the reaction series with extremely high intrinsic reaction barrier, $\Delta G_0^\ddagger \approx \infty$. This result has been



Scheme 1. Adduct (TS, intermediate or product) formation by *e.g.*, a nucleophile (X) and electrophile (Y); R's are reaction centers and X and Y are the parts causing structural changes *e.g.* by substituents. r_{XY} is the distance between the two reaction centers.

qualitatively predicted by Richard¹⁶ in his work on the application of the N_+ 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.

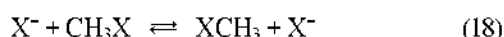
For endothermic and exothermic processes, $\beta_X > 1/2$ and $< 1/2$, respectively, (eq. 7b), so that $\{A\}$ in eq. 16 should be positive in the non-thermoneutral reactions. Thus, $\beta_{XY} > -1/(6\Delta G_0^\ddagger)$, indicating that the magnitude of the CIC (β_{XY}) in the non-thermoneutral reactions is smaller than that in the corresponding thermoneutral reactions.

$$|\beta_{XY}(\Delta G^\ddagger \neq 0)| < |\beta_{XY}(\Delta G^\ddagger = 0)| \quad (17)$$

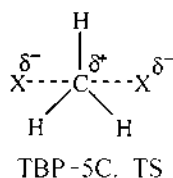
Experimental and Theoretical Examples

Experimentally, it is difficult to show functional dependence of the degree of bond formation (δr_{XY}) on the intrinsic barrier ($\delta\Delta G_0^\ddagger$). 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 ($\Delta G^\ddagger = 0$). 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 Brauman¹⁷ for methyl transfer reactions, eq. 18.



The intrinsic barriers, ΔE_0^\ddagger , 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-bipy-



ramidal (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}^\ddagger) between the nucleophile, X^- , and the methyl (partial) cation in the TS. The slope of *ca.* 0.5 obtained for 8 nucleophiles ($X = Br, Cl, CH_3CO_2, CD_3S, F, t-BuO, CH_3O,$ and HCC) is in agreement with that predicted by eq. 7b for the thermoneutral reactions ($\Delta G^\ddagger = 0$).

Lewis *et al.*¹⁸ have measured the barriers (ΔG_0^\ddagger) for the identity methyl transfers, eq. 18, with various nucleophiles, X^- , in solution. For $X = C_6H_5SO_3^-$ and $C_6H_5Se^-$ in sulfolane,

the ΔG_0^\ddagger 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 ΔG_0^\ddagger ($C_6H_5SO_3^-$) the TS is looser with the smaller extent of bond formation than that for the lower ΔG_0^\ddagger 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 coworker¹⁹ 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 ($DI = 100\Delta R/R$ where R is the C-X bond length: a larger DI corresponds to a looser or "exploded" TS) and the ΔE_0^\ddagger values. In terms of the degree of bond formation in the TS, expressed as percentage bond order change of the C-X bond (formation) in the TS ($\% \Delta n^\ddagger$)²⁰, the two *i.e.*, ΔE_0^\ddagger and $\% \Delta n^\ddagger$, are related as predicted by eq. 14 as shown in Table 1. Later higher level theoretical studies on the variations of the intrinsic barriers with the substrates and nucleophiles have also supported the predictions by eq. 14. For the identity chloride exchanges at the primary carbon center, R, the intrinsic barrier (at the MP2/6-31+G**//MP2/6-31+G* level)^{21a} was found to be higher for the looser TS with a lower degree of bond

Table 1. Intrinsic barriers (ΔE_0^\ddagger , in kcal mol⁻¹) and the extent of bond formation in the TS (as expressed in $\% \Delta n^\ddagger$) for the identity methyl transfer reactions, $X^- + CH_3X \rightleftharpoons XCH_3 + X^-$, at the RHF 4-31G level¹⁸

X	ΔE_0^\ddagger (kcal mol ⁻¹)	$\% \Delta n^\ddagger$ ¹⁹
CCH	50.4	33.3
CN	43.8	33.7
NC	28.5	38.6
OH	21.2	47.6
SH	15.6	46.3
F	11.7	54.3
Cl	5.5	49.8

Table 2. The intrinsic barriers (ΔE_0^\ddagger , in kcal mol⁻¹) and percentage bond order change ($\% \Delta n^\ddagger$) in the bond formation for $Cl^- + RCl \rightleftharpoons ClR + Cl^-$ reactions.²⁰

R	ΔE_0^\ddagger ^a	$\% \Delta n^\ddagger$ ¹⁹	ρ_{XY} ^b
CH ₃	7.7	41	-0.64
CH ₃ CH ₂	11.2	38	-0.68
CH ₂ =CHCH ₂	8.2	39	-0.74
CHCCH ₂	6.9	40	-0.80
(CH ₃) ₂ CCH ₂	18.0	35	-0.58
(CH ₃) ₃ SiCH ₂	6.9	40	-0.66

^aCalculated at the MP2/6-31-G**//MP2/6-31-G* level. ^bThese approximate values were estimated from the experimental ρ_{XZ} values for $XC_6H_4NH_2 + ROSO_2C_6H_4Z \rightleftharpoons C_6H_4NHR + HSO_2C_6H_4Z$ assuming $\rho_{XZ} \approx 1/2\rho_{XY}$. 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 ($R=(CH_3)_3CCH_2$) chloride has the highest intrinsic barrier ($18.0 \text{ kcal mol}^{-1}$) and the TS is the earliest with the lowest degree of bond formation ($\% \Delta n^\ddagger = 35$). Since the neopentyl group is bulky, the TS is formed at a far away distance, r_{C-Cl}^\ddagger is large. Similarly the bulky secondary carbon centers (R^1R^2CH-) 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 (RCH_2-). Theoretical studies at the MP2/6-31+G^{*} level have shown that the average intrinsic barriers were $\Delta E_0^\ddagger = 9.2$ (for 6 R's) and $12.5 \text{ kcal mol}^{-1}$ (for 9 R^1R^2 -sets) with the degree of bond formation $\% \Delta n^\ddagger = 39$ (average C-Cl distance $d_{C-Cl}^\ddagger = 4.67 \pm 0.02 \text{ \AA}$) and 34 (average $d_{C-Cl}^\ddagger = 4.80 \pm 0.02 \text{ \AA}$) respectively.²¹ Experimentally the average CICs (ρ_{XZ}) for the nucleophilic substitution reactions of primary alkyl arenesulfonates ($RCH_2OSO_2C_6H_4Z$ for 9 R's) and secondary arenesulfonates ($R^1R^2CHOSO_2C_6H_4Z$ for 10 sets) with anilines ($XC_6H_4NH_2$) 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.^{21a} 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 ($\Delta G^0 > 0$), the TS will be located on a later position (a larger value of $\% \Delta n^\ddagger$) 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^0 , β_X (the degree of bond formation) becomes greater than that with $\Delta G^0 \leq 0$.

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 CH_3CO), the higher intrinsic barrier ($\Delta E_0^\ddagger = 8.3$ and $8.6 \text{ kcal mol}^{-1}$ for Cl⁻ and Br⁻, respectively) was found to give lower degree of bond formation in the TS (61 and 58% with $R=HCO$).²² An interesting, yet important, example which shows clearly that application of eq. 14 should be limited to the thermoneutral

Table 3. The intrinsic barriers, ΔE_0^\ddagger in kcal mol^{-1} , and percentage bond order changes in the TS, $\% \Delta n^\ddagger$, for bond formation in the reaction of $X + CH_3X^+ \rightleftharpoons XCH_3 + X$ (for $X=NH_3, H_2O$ and HF) and $X^- + CH_3X \rightleftharpoons XCH_3 + X^-$ (for $X=NH_2^-, OH^-$ and F^-)¹²

X	ΔE_0^\ddagger ^a	$\% \Delta n^\ddagger$ ¹⁹
NH ₃	56	44
H ₂ O	-1	48
HF	-34	55
NH ₂ ⁻	118	41
OH ⁻	59	46
F ⁻	-6	52

^aAT the G2//MP2/6-31G^{**} level. Based on reactants level.

Table 4. The central barriers, (ΔE_c^\ddagger), well-depth ($\Delta E_c^\ddagger - \Delta E_m$), and percentage bond formation ($\% \Delta n^\ddagger$) in the transition state for identity thiocarbonyl transfers at the MP2/6-311+G^{**} level²²

X	ΔE_c^\ddagger (kcal mol^{-1})	Well-depth (kcal mol^{-1})	$\% \Delta n^\ddagger$	
			TS	Int
Cl	5.2	2.6	34	77
Br	6.2	0.2	44	67

processes for which the reaction barriers are the intrinsic barriers (ΔE_0^\ddagger or ΔG_0^\ddagger), is provided by the identity thiocarbonyl transfers, $X^- + RCSX \rightleftharpoons XCH_3 + X$, with $X = Cl$ and Br .²³ The potential energy changes are shown in Table 4. We note that central barrier height (ΔE_c^\ddagger) is lower with $X=Cl$ than Br . If this were the intrinsic barrier, ΔE_0^\ddagger , the extent of bond formation should have been greater for $X=Cl$. However, the $\% \Delta n^\ddagger$ 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, $\Delta E_c^\ddagger \neq \Delta E_0^\ddagger$. 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.*, $\% \Delta n^\ddagger$ 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, $\% \Delta n^\ddagger$, were in the reverse order F (44.8) > Br (36.8) > Cl (35.5). This sequence of ΔE_0^\ddagger (and $\% \Delta n^\ddagger$) 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 ($R=CH_3$) and ethyl ($R=C_2H_5$) carbons, eq. 19, at the MP3/6-31G^{**}//HF/3-21G level.²⁵ The



results show that higher intrinsic barrier at the ethyl ($\Delta E_0^\ddagger = 1.5$) than methyl carbon ($-0.8 \text{ kcal mol}^{-1}$, relative to the reactants) leads to a lower degree of bond formation in

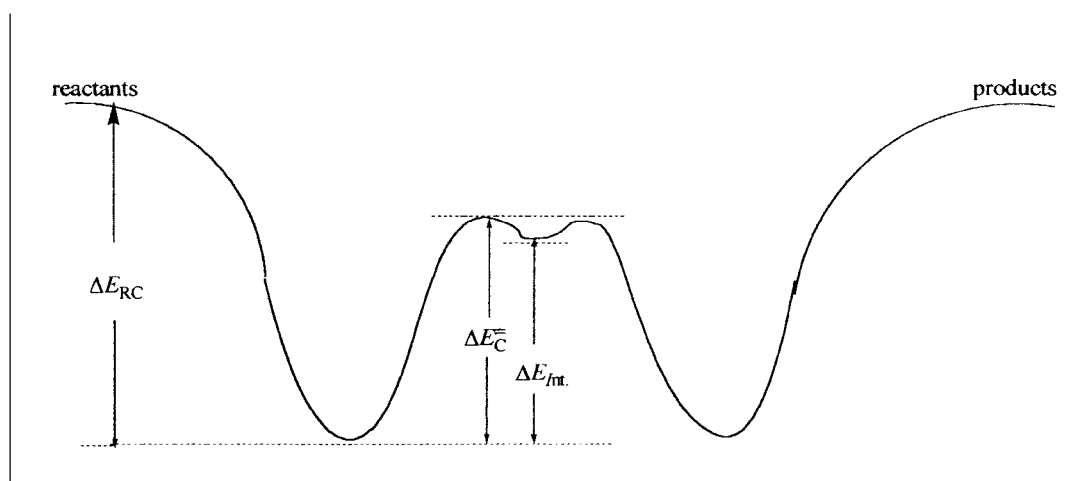


Figure 1. Potential energy surface for the gas-phase identity thiocarbonyl transfer reaction.

the TS (% $\Delta n^\ddagger = 48$ vs 51).

Mechanistic Implications

Analyses of the data by Ritchie⁴ have shown that the reaction families that follow the N -equation are all intrinsic-barrier controlled reactions with relatively large and constant intrinsic barriers within a family. For the reactions $R^+ + H_2O \rightleftharpoons ROH + H^+$ with R = triarylmethyl (a), tropylium (b) and xanthylium (c) cations, a linear relation was found between ΔG^\ddagger and ΔG^0 with a constant ΔG_0^\ddagger for each family, eqs. 20.

$$\Delta G^\ddagger = 0.67 \pm 0.04 \cdot \Delta G^0 + 16.22 \pm 0.27 : r=0.986, n=12. \quad (20a)$$

$$\Delta G^\ddagger = 0.45 \pm 0.06 \cdot \Delta G^0 + 14.57 \pm 0.39 : r=0.958, n=7. \quad (20b)$$

$$\Delta G^\ddagger = 0.56 \pm 0.18 \cdot \Delta G^0 + 12.92 \pm 0.98 : r=0.839, n=6. \quad (20c)$$

These equations indicate that the effect of thermodynamic barrier on the rate (ΔG_0^\ddagger) is small relative to that of the constant ΔG_0^\ddagger values (13-16 kcal mol⁻¹ neglecting the second order term in eq. 4) since ΔG^0 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 -equation, the intrinsic barrier was found to vary linearly with ΔG^0 *i.e.*, ΔG_0^\ddagger was not a constant value but the overall activation barrier (ΔG^\ddagger) was constant. For example, the solvolysis reactions of α -R¹, R²-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 ($\Delta G_0^\ddagger = 14-27$ kcal mol⁻¹) and the two have compensatory relation so that the overall barriers (ΔG^\ddagger) are relatively constant at *ca.* 8 kcal mol⁻¹, eq. 21.²⁶ This means that the overall barrier, ΔG^\ddagger , is dependent on both ΔG_0^\ddagger and ΔG^0 since eq. 21 is approximately equal to eq. 4 with neglect of the second order term.

$$\Delta G_0^\ddagger = -0.46 \pm 0.05 \cdot \Delta G^0 + 8.49 \pm 1.21 (r=0.958, n=11) \quad (21)$$

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

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 ΔG_0^\ddagger a larger magnitude of β_{NY} (ρ_{NY}) is obtained. This is however exactly opposite to that expected from thermodynamically based rate-energy relations, *e.g.*, Bell-Evans-Polanyi (BEP) principle.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 β_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.^{16,28} 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 ($\delta\Delta G_0^\ddagger$). 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 β_X (eq. 7b) is reflected on the thermodynamic line (R \rightarrow P), whereas the magnitude of β_{NY} (ρ_{NY}) 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

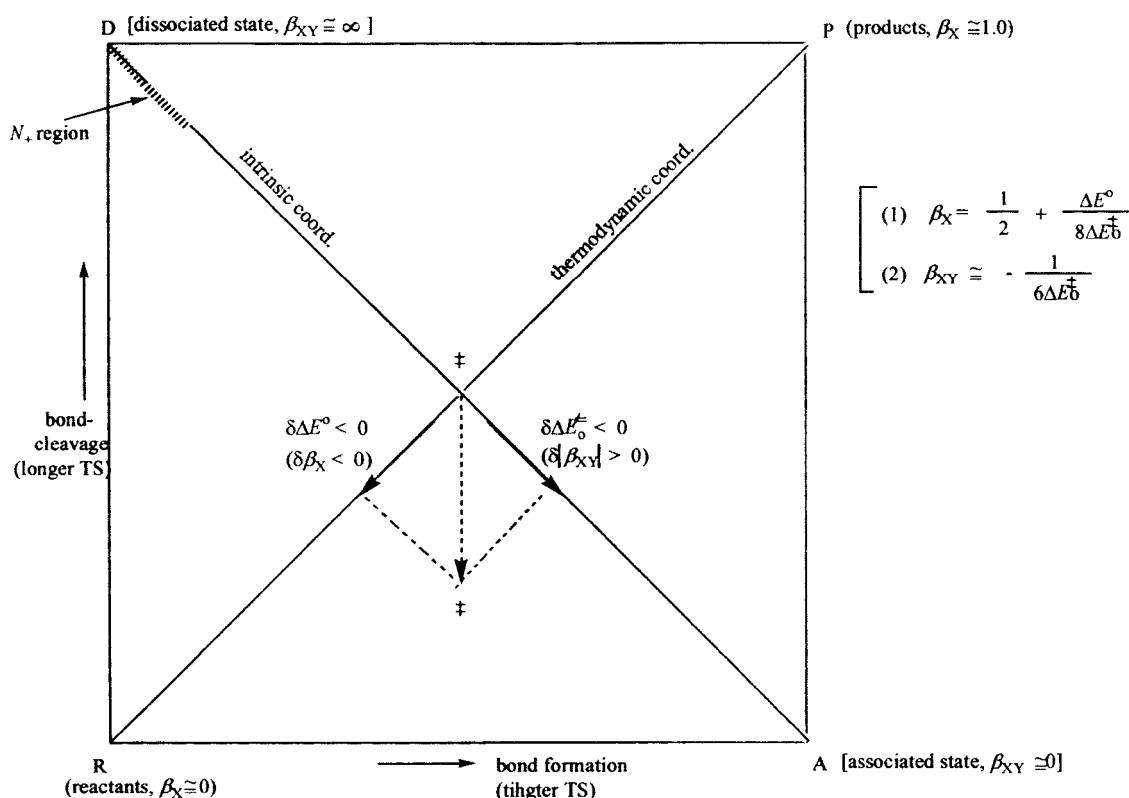


Figure 2. More O'Ferrall-Jencks Diagram. A stronger nucleophile depresses both the thermodynamic ($\delta\Delta E^0 < 0$) and intrinsic barriers ($\delta\Delta E_0^\ddagger < 0$), which leads to decrease ($\delta\beta_X < 0$) and increase ($\delta|\beta_{XY}| > 0$) in bond formation, respectively. The resultant vector sum represents the overall TS shift, as required by the Marcus equation, $\Delta E^* \approx \Delta E_0^* + 1/2\Delta E^0$.

equation, eq. 4, requires. The Ritchie N_+ equation holds on the intrinsic line close to D. It should be emphasized that the N_- equation and eq. 14 apply strictly to the intrinsic-barrier controlled reaction series.

For the N_- type reactions, two mechanisms are proposed. One involves desolvation of the ions.²⁹ 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 $\beta_{XY} \approx 0$ is satisfied. The other invokes the intervention of an electron-transfer (ET) mechanism.³⁰ Since in the ET reactions an electron (charge) is transferred ($D^+ + A^-$) but the covalent link ($D^- - A^-$) is not formed in the TS,³¹ i.e., an outer-sphere charge transfer occurs, the electrophile-nucleophile interaction should be feeble and may become negligible^{31c} so that the magnitude of the CIC (β_{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 β_X ($\beta_{\text{nucl}} = 0.67 - 0.29$)³² obtained, the latter ET mechanism is more likely to

apply for the N_+ type reactions.

Summary and Conclusion

The cross second-derivative of the activation energy, ΔG^* , with respect to the two component thermodynamic barriers, ΔG_X^\ddagger and ΔG_Y^\ddagger , has been shown to give two different forms: One in terms of the cross-interaction constant (CIC), β_{XY} (ρ_{XY}), and the other in terms of the intrinsic barrier, ΔG_0^\ddagger , with a very simple relationship between the two.

$$\beta_{XY} \approx -1/(6\Delta G_0^\ddagger). \quad (14)$$

One important corollary of this relationship is that the Ritchie N_+ 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 magnitude of the CIC, and hence 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_- 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.

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