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Review Commentary

The principle of nonperfect synchronization: how does it apply to aromatic systems?†

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ABSTRACT: According to the Principle of Nonperfect Synchronization (PNS), a product-stabilizing factor, the development of which at the transition state lags behind bond changes, increases the intrinsic barrier of a reaction, but lowers it if it develops ahead of bond changes. Because of the generality of this principle, details of transition state structures can be deduced from comparisons of intrinsic barriers within classes of reactions. A major conclusion that has emerged from such comparisons is that reactions that lead to charge delocalization/resonance stabilized products have transition states in which the development of charge delocalization/resonance stabilization lags behind bond changes and, hence, have relatively high intrinsic barriers. This paper deals with reactions that lead to aromatic molecules or ions. The question we are asking is whether or not aromaticity follows the pattern of common resonance effects and lags behind bond changes at the transition state. Evidence based on experimentally determined intrinsic barriers of proton transfers from rhenium carbene complexes in solution, as well as that based on *ab initio* calculations of proton transfers in the gas phase, suggests that aromaticity development at the transition state may actually be *ahead* of bond changes. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: aromaticity; transition state imbalance; kinetics; proton transfer; *ab initio* calculations; PNS

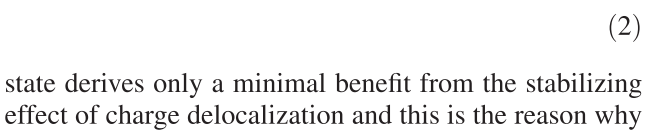
INTRODUCTION

The relationship between structure and reactivity is a central theme of physical organic chemistry. One notion that defines the term ‘reactivity’ more precisely is the concept of the intrinsic barrier,[1] which is the barrier when $\Delta G^{o} = 0$; it removes thermodynamic contributions to the barrier and allows a more meaningful comparison of reactivities between systems.

Ideally one would always want to determine intrinsic barriers when dealing with reactivity. However, this requires a determination of rate *and* equilibrium constants, which is not always feasible. One class of reactions that allows such measurements are proton transfers from carbon acids activated by π-acceptors, Eqn (1). These reactions are not only of interest beacuse of their ubiquity and fundamental nature, but they can also serve as a model for most polar reactions since they include all the important features of such reactions, for example, bond changes, charge transfer, resonance development/charge delocalization, and solvation/desolvation effects. Hence, understanding the factors that affect intrinsic barriers of such proton transfers helps one understand how these factors affect reactivity in general.

$$\mathrm{B^{\nu} + H{-}\overset{|}{\underset{|}{C}}{-}Y \rightleftharpoons BH^{\nu+1} + {>}C{=}Y^{-}} \qquad (1)$$

Research from various laboratories, including ours, has demonstrated that the π-acceptor strength of the Y group has a dominant effect on the intrinsic barriers of proton transfers, i.e. the stronger the π-acceptor, the higher the intrinsic barrier.[2] Representative examples are listed in Table 1. This π-acceptor effect is the result of a transition state imbalance whereby the charge delocalization into the π-acceptor group lags behind proton transfer, as shown in exaggerated form in Eqn (2)[2] (for a more nuanced representation see below). Because of this lag, the transition state derives only a minimal benefit from the stabilizing effect of charge delocalization and this is the reason why



$$\mathrm{B^{\nu} + H{-}\overset{|}{\underset{|}{C}}{-}Y \rightleftharpoons \left(\overset{\nu+\delta}{B}\cdots H\cdots \overset{\delta-}{\underset{|}{C}}{-}Y\right)^{\ddagger} \rightleftharpoons BH^{+} + {>}C{=}Y^{-}} \qquad (2)$$

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Table 1. Intrinsic barriers and intrinsic rate constants for proton transfer to secondary alicyclic amines[a]

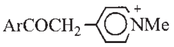
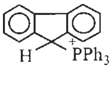
Carbon acid	Solvent[b]	$\Delta G_o^\ddagger$ kcal mol^{-1}	logk_o[c] (1 kcal = 4.184 kJ)
HCN	H_2O	ca. 5.6	ca. 8.6
$CH_2(CN)_2$	H_2O	ca. 7.8	ca. 7.0
9-Cyanofluorene	50% DMSO	10.9	4.58
Meldrum's acid	50% DMSO	11.9	3.90
$C_5H_2Cl_4$[d]	50% DMSO	12.3	3.59
1,3-Indandione	50% DMSO	12.9	3.13
9-Carbomethoxyfluorene	50% DMSO	13.3	2.84
Acetylacetone	50% DMSO	13.4	2.75
$(CO)_5Cr{=}C(OMe)$-CH_2Ph[e]	50% MeCN	14.6	1.86
CH_3NO_2	50% DMSO	16.1	0.73
$PhCH_2NO_2$	50% DMSO	17.4	−0.25

[a] Taken from Ref. 2.
[b] H_2O is at 25 °C, 50% DMSO is 50% DMSO–50% water (v/v) at 20 °C, 50% MeCN is 50% MeCN–50% water (v/v) at 25 °C.
[c] $k_o = k$ when $\Delta G^o = 0$, in units of $l\,mol^{-1}\,s^{-1}$.
[d] 1,2,3,4-Tetrachloro-1,3-cyclopentadiene, Ref. 18.
[e] Ref. 26.

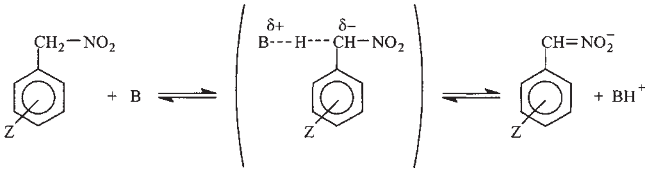
the barrier is high. The same barrier enhancement occurs in the reverse direction because most of the stabilization of the delocalized anion is lost at the transition state.

What is the evidence for transition state imbalance? The trend towards higher intrinsic barriers with increasing π-acceptor strength can itself be considered evidence. Additional, *independent*, evidence comes from the study of the effect of remote substituents. There are two relevant situations. In the first, the remote substitutent is closer to the site of charge development at the transition state than to the delocalized charge in the carbanion, as in the deprotonation of substituted phenylnitromethanes by amines, Eqn (3).[3] This leads to an exalted Brønsted α value, which exceeds the Brønsted β values obtained by varying the pK_a of the base B. Other examples with $\alpha > \beta$ are summarized in Table 2 (first three entries).

Table 2. Brønsted coefficients for the deprotonation of carbon acids by various bases[a]

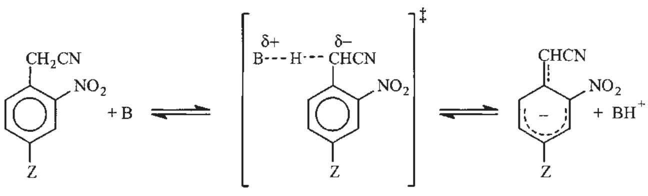
Carbon acid	Base	Solvent[b]	α	β
$ArCH_2NO_2$	R_2NH	H_2O	1.29	0.48
$ArCH_2CH(COMe)COOEt$	$RCOO^-$	H_2O	0.76	0.44
$ArCH_2CH(CN)_2$	$RCOO^-$	H_2O	0.98	0.83
2-NO_2-4-Z-$C_6H_3CH_2CN$[c]	R_2NH	90% DMSO	0.40	0.62
	RNH_2	H_2O	0.36	0.55
	R_2NH	50% DMSO	0.29	0.49

[a] Taken from Ref. 2.
[b] H_2O at 25 °C, 90% DMSO is 90% DMSO–10% water (v/v) at 20 °C, 50% DMSO is 50% DMSO–50% water (v/v) at 20 °C.
[c] Ref. 4.



(3)

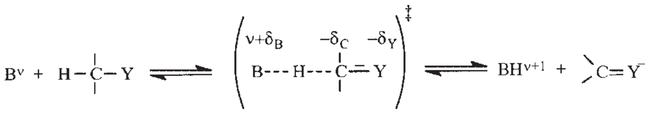
In the second situation, the remote substituent is closer to the delocalized charge in the anion than to the charge at the transition state. A case in point is Eqn (4). Here the substituent effect on the rate constant is disproportionately weak because, at the transition state, the negative charge is farther away from Z than in the anion and hence $\alpha < \beta$.[4] Other examples where $\alpha < \beta$ are given in Table 2 (last three entries).



(4)

The connection between charge delocalization/resonance and the effect of transition state imbalance on the intrinsic barriers is a manifestation of the Principle of Nonperfect Synchronization;[2,5] it not only applies to resonance effects but to any product stabilizing factor (e.g. solvation, electrostatic effects, steric effects) in any chemical reaction. The PNS states that a product stabilizing factor that lags behind bond changes at the transition state increases the intrinsic barrier, while a product stabilizing factor that develops ahead of bond changes lowers the intrinsic barrier. *This principle is mathematically provable and hence there can be no exception.*[2]

The observed lag in the delocalization of the anionic charge is also a general phenomenon that not only applies to proton transfers and to negative charge but to any reaction which involves resonance effects, e.g. carbocation reactions.[6,7] In other words, charge delocalization/resonance always lags behind bond changes at the transition state and hence, due to the PNS, always increases the intrinsic barrier. The reason for this is that there are constraints which prevent extensive delocalization at the transition state. This was first pointed out by Kresge[8] in the context of the deprotonation of nitroalkanes but can be generalized to Eqn (5): the charge on Y (δ_Y) at the transition state is essentially proportional to the C—Y π-bond order and to the charge



(5)

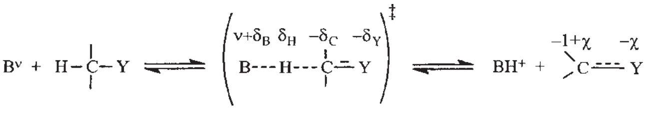
transferred from B (δ_B) [Eqn (6)] while the π-bond order is essentially proportional to δ_B [Eqn (7)]. Hence δ_Y is given by Eqn (8) and is small since it represents only a fraction of a

$$\delta_Y \approx \pi_{\text{b.o.}} \cdot \delta_B \tag{6}$$

$$\pi_{\text{b.o.}} \approx \delta_B \tag{7}$$

$$\delta_Y \approx (\delta_B)^2 \tag{8}$$

fraction. Further generalization and refinement is shown in Eqn (9) which allows for *in*complete



(9)

charge delocalization in the anion with weaker π-acceptors, and for accumulation of positive charge on the proton in flight (δ_H), as indicated by *ab initio* calculations.[9–12] Equations (6), (7) and (8) then become Eqns (10), (11) and (12)[11] with $n = 2$. If there is less than perfect proportionality

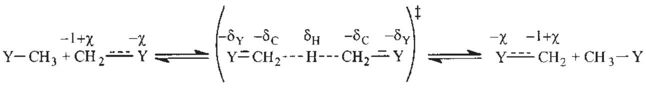
$$\delta_Y = \pi_{\text{b.o}}(\delta_C + \delta_Y)^x \tag{10}$$

$$\pi_{\text{b.o}} = \chi(\delta_C + \delta_B)^y \tag{11}$$

$$\delta_Y = \chi(\delta_C + \delta_Y)^n \tag{12}$$

between delocalization and π-bond order and/or between π-bond order and $\delta_C + \delta_Y, n = x + y$ may be >2 or <2; as long as $n > 1$ there is imbalance in the sense that charge delocalization lags behind proton transfer.

For gas phase identity proton transfers of the type shown in Eqn (13),[11,12] the group



(13)

charges computed by *ab initio* methods allowed a determination of the imbalance parameter n via Eqn (14), which is the logarithmic form of Eqn (12). These parameters are reported in Table 3 for a representative series of the Y group; n is seen to be >1 in all cases.

$$n = \frac{\log(\delta_Y/\chi)}{\log(\delta_C + \delta_Y)} \tag{14}$$

Table 3. Imbalance parameters for gas phase identity proton transfers $CH_3Y + CH_2{=}Y^- \rightleftarrows CH_2 = Y^- + CH_3Y$[a]

CH_3Y	n	CH_3Y	n
$CH_3CH{=}CH_2$	1.61	$CH_3CH{=}S$	1.42
CH_3CN	1.51	$CH_3CH{=}NH$	1.58
$CH_3CH{=}O$	1.52	$CH_3C{\equiv}CH$	2.26
CH_3NO_2	1.59	$CH_3CH{=}OH^{+b}$	1.69
CH_3NO	1.28	$CH_3NO_2H^{+c}$	1.42

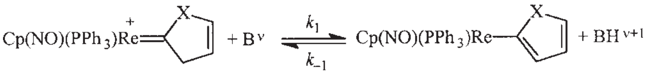
[a] From Ref. 12.
[b] From Ref. 13.
[c] From Ref. 14.

REACTIONS INVOLVING AROMATIC COMPOUNDS

Do the rules that govern resonance/delocalization effects on transition state imbalances and intrinsic barriers apply to aromaticity as well, i.e. does development of product aromaticity lag behind bond changes and increase intrinsic barriers? In view of the centrality of the concept of aromaticity it is surprising that this question has not been answered. Perhaps even more surprising is the fact that this question has not been asked. We have recently begun to approach this question both experimentally and computationally with surprising results.

Experimental Study

The conjugate bases of the rhenium carbene complexes **1H—X**$^+$ represent aromatic heterocycles, i.e. substituted furan (X = O), selenophene (X = Se) and thiophene derivatives (X = S) [Eqn (15)]. The aromatic stabilization of the 5-membered heterocycles is known to follow the order furan < selenophene < thiophene.[15] As one would expect, the acidities of **1H—X**$^+$ in 50% MeCN–50% H_2O reflect this order, i.e. pK_a(**1H—O**$^+$) = 5.78, pK_a(**1H—Se**$^+$) = 4.18, pK_a (**1H—S**$^+$) = 2.50.[16]



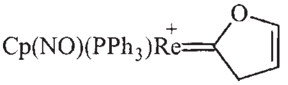
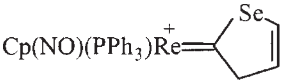
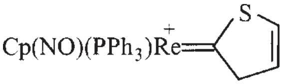
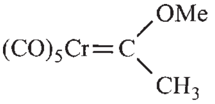
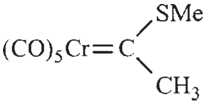
1H-O$^+$ (X = O)
1H-Se$^+$ (X = Se)
1H-S$^+$ (X = S)

1-O (X = O)
1-Se (X = Sc)
1-S (X = S)

(15)

A study of the reversible proton transfer involving **1H**—X$^+$ with a series of carboxylate ions, primary aliphatic and secondary alicyclic amine buffers allowed the determination of the statistically corrected intrinsic rate constant, $k_o[k_o = k_1/q = k_{-1}/p$ where$(\log K_1 + \log p/q) = 0]$ by suitable interpolation or extrapolation of Brønsted plots.[16] These k_o values are reported in Table 4. For all three buffer families they follow the trend k_o(**1H—O**$^+$) < k_o(**1H—Se**$^+$) < k_o(**1H—S**$^+$), i.e. k_o increases with increasing aromaticity of the conjugate base. Surprisingly, this trend is opposite to what one would expect if aromaticity behaved in the same manner as common resonance effects. This raises the question whether aromaticity may only play a minor role in affecting the intrinsic rate constants, and that the

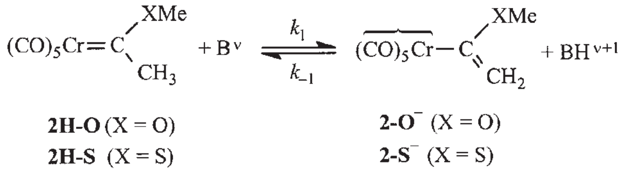
Table 4. Intrinsic rate constants for the deprotonation of carbene complexes by carboxylate ions and primary aliphatic and secondary alicyclic amines in 50% MeCN–50% water (v/v) at 25 °C

Carbene complex		$\log k_o(RCOO^-)$	$\log k_o(RNH_2)$	$\log k_o(R_2NH)$
	**1H—O**$^{+a}$	−0.01	−0.83	−0.46
	**1H—Se**$^{+a}$	0.72	0.14	0.92
	**1H—S**$^{+a}$	1.21	0.27	1.05
	**2H—O**^{b}		3.04	3.70
	**2H—S**^{b}		2.09	2.61

[a] Ref. 16.
[b] Ref. 17.

observed trend is the result of other factors associated with the nature of the heteroatom X (π-donor, inductive and steric effects),[17] which mask the true dependence of k_o on aromaticity.

To answer this question we turn to a comparison of the k_o values for the deprotonation of the carbene complexes **2H—O** and **2H—S**.[17] In this case the conjugate base of the carbene



(16)

complex is not aromatic and hence any dependence of k_o on X should only reflect these other factors [Eqn (16)]. The $\log k_o$ values for the reactions of **2H—O** and **2H—S** with amines are included in Table 4. They show the thia derivative to have a *lower* intrinsic rate constant than the oxa derivative, which contrasts with the reactions of the rhenium carbene complexes where the thia derivative has a higher intrinsic rate constant than the oxa analogue. Hence the trend in the k_o values for the rhenium carbene complexes must reflect the trend in the aromaticity of the conjugate bases. This means, based on the rules of the PNS,[2] that one is forced to conclude that the development of aromatic stabilization at the transition state does not lag behind *but is ahead of proton transfer.*

Our findings shed new light on the previously reported deprotonation of 1,2,3,4-tetrachloro-1,3-cyclopentadiene[18] whose conjugate anion is aromatic. The $\log k_o$ value of 3.59 (Table 1) for this reaction is only slightly lower than that for the deprotonation of Meldrum's acid and higher than that for the deprotonation of 1,3-indandione. This high value is surprising because the stabilization of the 1,2,3,4-tetrachloro-1,3-cyclopentadienyl anion by delocalization/resonance is expected to be much greater than that for the anions of Meldrum's acid and 1,3-indandione, particularly because of the extra stabilization derived from the chlorine substitutents. This suggests that the high k_o value is the result of the k_o-enhancing aromaticity effect which (partially) offsets the k_o-lowering delocalization/resonance effect.

Computational Study

Two identical proton transfer reactions involving the prototypical aromatic compounds cyclopentadienyl anion [Eqn (17)] and benzene [Eqn (18)] as the base were subject to similar

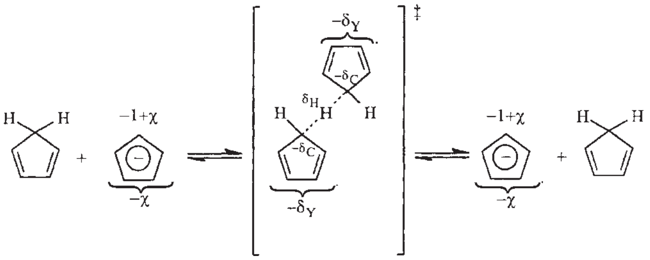
(17)

(18)

calculations as the $CH_3Y/CH_2{=}Y^-$[19] systems mentioned in the Introduction. We asked three questions.

(1) Does charge delocalization lag behind proton transfer, as is commonly observed in nonaromatic systems? (2) Is the development of product aromaticity probed by independent criteria ahead of proton transfer or does it lag behind proton transfer? (3) Are the intrinsic barriers enhanced or lowered relative to similar non-aromatic systems?

Regarding the first question, calculations of NPA group charges as defined in Eqns (19) and (20) allowed determination of the imbalance parameter according to Eqn (14). For both systems n was found to be 2.03, indicating that charge delocalization indeed lags behind proton transfer.



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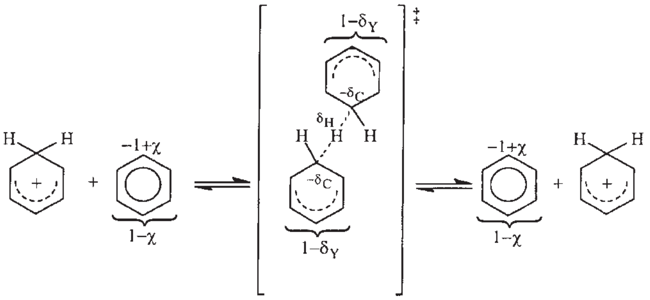


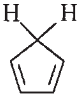
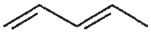
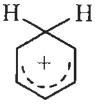
(20)

To answer the second question, commonly used aromaticity indices such as the Julg parameters,[20,21] the Bird Index,[22] the Harmonic Oscillator Model of Aromaticity (HOMA)[23,24] and the Nucleus-Independent Chemical Shifts (NICS)[25] were calculated for reactants, products and transition states. They are summarized in Table 5. All indices show more than 50% development of aromaticity at the transition state, implying that aromaticity develops ahead of proton transfer.

Table 5. Computed aromaticity indices at the MP2//6–31+G(d,p) level

System	Julg	Bird Index	HOMA	NICS
		Eq (17)		
Cyclopentadiene	0.49	39.3	−1.31	−3.2
TS	0.85	74.7	0.56	−10.9
Cp anion	1.00	95.1	0.78	−14.3
Progress at TS (%)	70.6	63.4	89.4	69.4
		Eq (18)		
Benzenium ion	0.32	70.7	0.34	−0.5
TS	0.78	92.2	0.90	−7.0
Benzene	1.00	100	0.97	−9.7
Progress at TS (%)	67.6	73.4	83.6	70.6

Table 6. Gas phase acidities (ΔH^{o}) and intrinsic barriers ($\Delta H^{\ddagger}$) for Eqns (17), (18), (21) and (22) (MP2/6–31G(d,p)[a]

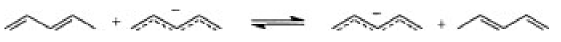
CH acid	Eqn	ΔH^{o}	$\Delta\Delta H^{ob}$	$\Delta H^{\ddagger}$	$\Delta\Delta H^{\ddagger c}$
	17	350.9		0.1	
	21	376.1	−25.2	8.9	−8.8
	18	174.8		−9.2	
	22	204.5	−29.7	1.0	−10.2

[a] In kcal mol^{-1} (1 kcal = 4.184 kJ).

[b] $\Delta\Delta H^{o} = \Delta H^{o}$ (aromatic system) − ΔH^{o} (non-aromatic system), measures the acidity enhancement owing to aromaticity.

[c] $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}$ (aromatic system) − $\Delta H^{\ddagger}$ (non-aromatic system), measures the barrier reduction owing to aromaticity.

To answer the third question, gas phase acidities (ΔH^{o}) and intrinsic barriers ($\Delta H^{\ddagger}$) for Eqns (17) and (18) are reported in Table 6, along with ΔH^{o} and $\Delta H^{\ddagger}$ values for Eqns (21) and (22)



(21)

(22)

which can be regarded as non-aromatic models for Eqns (17) and (18), respectively. The higher acidities of cyclopentadiene relative to 1,3-pentadiene and of the benzenium ion relative to the hexatrienyl cation reflect the aromaticities of $C_5H_5^-$ and benzene, respectively. As to the intrinsic barriers, the $\Delta H^{\ddagger}$ values for the aromatic systems are significantly lower than for the respective non-aromatic models, consistent with the aromaticity indices that suggest more than 50% development of aromaticity at the transition state. The numbers in Table 6 actually underestimate the barrier lowering effect of early aromaticity development because the transition states for Eqns (17) and (18) are more crowded than the respective transition states for Eqns (21) and (22), which should enhance the barriers for Eqns (17) and (18). This enhancement is estimated to be ≈0.7 kcal mol^{-1}.[17]

CONCLUSIONS

Kinetic data on the solution proton transfer reactions of Eqn (5) as well as computational results on the gas phase proton transfers of Eqns (17) and (18) suggest that development of product aromaticity is ahead of proton transfer at the transition state. This contrasts with proton transfer reactions that lead to charge delocalized/resonance stabilized non-aromatic products where resonance development invariably lags behind proton transfer. It appears that the constraints that prevent resonance/delocalization effects from developing in proportion to proton transfer do not apply to the development of aromaticity. Future work in my laboratory is aimed at testing the generality of these conclusions.

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