

## Communications to the Editor

### Halophilic Reactions: Anomalies in Bromine Transfer Reactions

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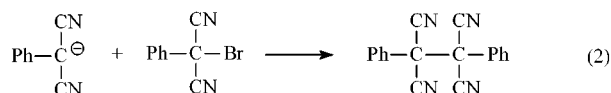
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While synthetic applications of halophilic reactions (nucleophilic attacks on halogens) are sporadically documented in the literature,<sup>1</sup> to the best of our knowledge, comprehensive mechanistic studies are nearly nonexistent.<sup>2</sup> This paucity of mechanistic studies is glaring in light of the fact that nucleophilic displacements are among the most thoroughly studied reactions in physical organic chemistry. Herein we report a quantitative study of nucleophilic attack on bromine, namely, its transfer between carbanions (eq 1). The rate constants found, summarized in Table



1, were determined spectroscopically by following, in most cases, the decrease in the absorption of the nucleophile. In the reactions of  $HC(CN)_2^-$  with  $BrPhC(CN)_2$  we monitored the increase in the absorption of the ionic product.

The progress of the reactions studied resulted in the simultaneous presence of  $PhC(CN)_2^-$  and  $BrPhC(CN)_2$ , one as a reactant and the other as a product. This led to a reaction between them resulting in a dimer formation (eq 2).<sup>3</sup> However, since the



dimerization is much faster than the other reactions ( $k = (3 \pm 0.1) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ , independently determined) it did not interfere with the kinetic studies.

The reactions were conducted in buffered aqueous solutions (sodium acetate, phosphate, and carbonate according to the required pH values) under pseudo-first-order conditions with a stopped flow spectrophotometer for the fast reactions.

Clearly, the reaction between  $PhC(CN)_2^-$  and  $BrPhC(CN)_2$ , leading to dimer formation, involves electron transfer. It is not clear, however, whether the reactions in Table 1 proceed by the direct  $SN_2$  mechanism or also involve an electron-transfer step. The fact that in these cases no dimerization was observed suggests that free radicals are not involved. Yet, we were unable to rule out the possibility of a cage process of an electron transfer yielding the radical anion of the substrate ( $R-Br$ ) that undergoes a mesolytic cleavage<sup>4</sup> to  $R^-$  and  $Br^\bullet$ . Combination of the latter with the radical derived from the nucleophile would provide the product.

(1) Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615 and references cited under "Synthetic applications of X-philic reactions".

(2) Following are some mechanistic studies of halophilic reactions: Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420. Differding, E.; Ruegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815. DesMarteau, D. D.; Xu, Z.-Q.; Witz, M. J. *Org. Chem.* **1992**, *57*, 629. Li, X. Y.; Tu, M. H.; Jiang, X. K. *Chin. Chem. Lett.* **1993**, *4*, 411. Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.

(3) Hartzler, H. D. *J. Org. Chem.* **1966**, *31*, 2654.

(4) Maslak, P.; Narvaez, J. N. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 283.

Figure 1 shows the Bronsted plot for the bromine transfer reactions with  $\log k$  plotted against the  $\Delta pK_a$  of the acids derived from the nucleophile and the substrate (when H substitutes for Br). The figure, surprisingly, reveals two unique features which are typical of proton-transfer reactions: the Pearson<sup>5</sup> and Kresge<sup>6</sup> nitro anomalies.

In 1953 Pearson and Dillon reported<sup>5</sup> a linear correlation between the kinetics and the thermodynamics of deprotonation reactions of carbon compounds. The reactivity of nitroethane and nitromethane deviated negatively from this linear correlation by ca. 5 orders of magnitude. It is important to point out that this behavior is unique to the case of a single nitro activating group. The presence of another activating group largely attenuates this anomaly. Thus, dinitromethane, for example, fits the linear correlation well. Anomalous behavior similar to the above is found in the bromine transfer reactions studied here. The largest rate constants are associated with bromine transfer between cyano-activated carbanions. The smallest relate to the removal of bromine from the nitromethane and nitroethane moieties. Intermediate within the same  $\Delta pK_a$  range is the bromine transfer reaction involving phenylnitromethane in which the phenyl group slightly attenuates the nitro anomaly effect.

The second anomaly, reported by Kresge,<sup>6</sup> relates to the series nitromethane, ethane, and isopropane. Contrary to expectations, in this series compounds with higher acidity undergo slower deprotonation. Namely, the Bronsted plot displays a negative slope.

The Bronsted plot in Figure 1 clearly shows that unlike any normal Bronsted plot which by definition displays a positive slope, that for  $MeNO_2$  and  $EtNO_2$  is negative. Thus, the resemblance between proton and bromine transfer reactions is again borne out.

These surprising results are intelligible if one views bromine transfer and deprotonation reactions as simple  $SN_2$  reactions on Br and H, respectively. The anomalous behavior should then be traced to the leaving group effect. Clearly, since deprotonation reactions are not considered to involve an electron transfer component, the observed similarity argues against the possibility of the involvement of an electron transfer step in these bromine transfer reactions. Alternatively, it will be very surprising to learn that the nitro anomaly is manifested also under radical/radical-anionic conditions.

It is interesting to further compare the reactivities of the same carbanions in bromine-transfer and proton-transfer reactions. Using the reversible reactions in Table 1 in combination with the Marcus equation and assuming that the intrinsic barrier for bromine transfer reaction between  $PhC(CN)_2^-$  and  $BrPhC(CN)_2$  is nearly identical to the intrinsic barrier for the bromine transfer reaction between  $HC(CN)_2^-$  and  $BrCH(CN)_2$  ( $\Delta G_0$  for the first entry reaction in Table 1 is only  $\approx 3$  kcal/mol), we calculated the intrinsic barrier for the identity bromine transfer reactions between substituted bromomalononitriles ( $RCBr(CN)_2$ ) and their corresponding anions  $RC(CN)_2^-$  (Table 2). Since the intrinsic barrier for a non-identity reaction (second row in Table 1) is the average of the intrinsic barriers of the two relevant reactions, and since one of the two (that for the malononitrile derivatives) is already known (10.9 kcal/mol, Table 2), we can calculate the intrinsic barrier for the Br exchange between  $PhCHBrNO_2$  and the anion  $PhCHNO_2^-$  (Table 2). The intrinsic barrier for proton-transfer

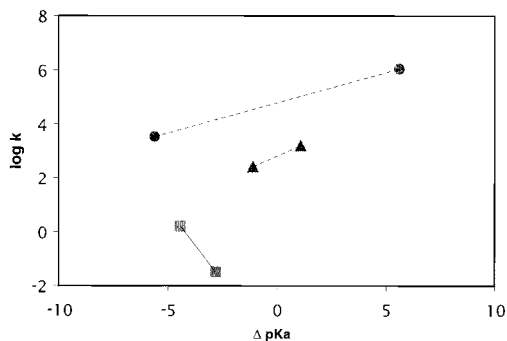
(5) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.

(6) Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897. For the latest work on this issue see: Yamataka, H.; Mustanir; Mishima, M. *J. Am. Chem. Soc.* **1999**, *121*, 10223.

**Table 1.** Rate Constants (at 25 °C) for Bromine Transfer Reactions<sup>a</sup>

reaction	$k, \text{M}^{-1} \text{s}^{-1}$	reaction	$k, \text{M}^{-1} \text{s}^{-1}$
$\text{PhC}(\text{CN})_2^- + \text{BrCH}(\text{CN})_2$	$(3.4 \pm 0.3) \times 10^3$	$\text{HC}(\text{CN})_2^- + \text{BrPhC}(\text{CN})_2$	$(1.1 \pm 0.3) \times 10^6$
$\text{PhC}(\text{CN})_2^- + \text{BrCHPhNO}_2$	$(2.7 \pm 0.4) \times 10^2$	$\text{PhCHNO}_2^- + \text{BrCPh}(\text{CN})_2$	$(1.6 \pm 0.1) \times 10^3$
$\text{PhC}(\text{CN})_2^- + \text{BrCH}_2\text{NO}_2$	$1.64 \pm 0.06$		
$\text{PhC}(\text{CN})_2^- + \text{BrCHMeNO}_2$	$(3.3 \pm 0.3) \times 10^{-2}$		

<sup>a</sup> The following  $\text{p}K_a$  values were used:  $\text{PhC}(\text{CN})_2\text{H}$ , 5.8;  $\text{CH}_2(\text{CN})_2$ , 11.4;  $\text{PhCH}_2\text{NO}_2$ , 6.87;  $\text{MeNO}_2$ , 10.22; and  $\text{EtNO}_2$ , 8.6.



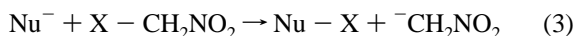
**Figure 1.** A plot of  $\log k$  for bromine transfer reaction vs  $\Delta \text{p}K_a$  ( $\text{p}K_a$  difference between the conjugated acids of the corresponding nucleophiles and leaving groups): (●) reactions of the first row in Table 1; (▲) reactions of the second row in Table 1; and (■) reactions of the third and fourth rows in Table 1.

**Table 2.** Intrinsic Barriers for Br and H Exchange Reactions

reaction	intrinsic barrier (kcal/mol)	
	X = Br	X = H
$\text{RC}(\text{CN})_2^- + \text{RCX}(\text{CN})_2$	10.9	14.8
$\text{PhCHNO}_2^- + \text{PhCHXNO}_2$	16.3	37.8

reactions between the same carbanions was computed using the same procedure<sup>7</sup> and literature data.<sup>8</sup> The results given in Table 2 clearly show that the bromine transfer reaction between the stated carbanions is faster by far than the proton-transfer reaction.

These results raise a fundamental quandary regarding nucleophilicity. Let us use the nitromethide residue as the carrier of X in reactions with a nucleophile (Nu; eq 3) to demonstrate this point.



The classical substrate for  $\text{S}_{\text{N}}2$  reactions is no doubt the “Me-leaving group”. Yet, to the best of our knowledge, reaction 3 does not exist for  $\text{X} = \text{Me}$ .<sup>9</sup> Namely, nitroethane has never been known to be a methylating agent.<sup>10</sup> Thus, the established order of reactivity for X is  $\text{Br} > \text{H} \gg \text{Me}$ .

(7) Bernasconi, C. F.; Ni, J. X. *J. Am. Chem. Soc.* **1993**, *115*, 5060.

(8) The intrinsic barrier is known for the deprotonation of malonitrile derivatives and phenylnitromethane by amines (7.9 and 19.4 kcal/mol respectively; Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335). The intrinsic barrier for proton transfer between amines is 1 kcal/mol. From these we calculate the intrinsic barrier for proton transfer between  $\text{PhCH}_2\text{NO}_2$  and its anion.

This reactivity order hardly fits any of the existing models for nucleophilic activity. The LUMO energies follow the order  $\text{C}-\text{H} > \text{C}-\text{Me} > \text{C}-\text{Br}$ ;<sup>11</sup> the softness varies in the order  $\text{Br} > \text{Me} > \text{H}$ <sup>12</sup> and the bond strength varies in the order  $\text{C}-\text{H} > \text{C}-\text{Me} > \text{C}-\text{Br}$ .<sup>13</sup> Thus, according to these models, Me, contrary to our observations, should have exhibited an intermediate reactivity between that of Br and H.<sup>14</sup> Moreover, the sheer use of the term nucleophilicity, which implies “going for the nucleus”, becomes unjustified. The high reactivity in proton-transfer reactions may be expected considering the fact the H is close to a bare proton. Since the bromine nucleus is deeply buried in a cloud of electrons, it should have exhibited reactivity that is much lower than that of H, and Me should have displayed an intermediate reactivity. Yet, Br transfer reactions are faster than proton transfer reactions, whereas methyl transfer reactions do not exist at all. These observations strengthen the notion that the more data are gathered the less we understand nucleophilicity. The frustration in the attempts to “really” understand nucleophilicity was nicely phrased by a referee who was quoted by Ritchie<sup>15</sup> as saying that “...the search for an understanding [of] nucleophilic reactivity [is comparable] to the search for the Holy Grail”.

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(9) We have calculated at the B3LYP/6-31+G\* level using the Gaussian98 software the intrinsic barriers for H and Me transfer between two acetonitrile carbanions ( $\text{CH}_2\text{CN}^-$ ). The barrier for H transfer was found to be 5.00 kcal/mol whereas that for Me transfer was found to be 36.2 kcal/mol.

(10) It is clear that under severe basic conditions deprotonation of the  $\alpha$  carbon will take place. However, in most cases, only a small fraction of the nitroethane will be ionized and therefore this cannot be the reason for its lack of reactivity as a methylating agent.

(11) Pross, A. *Theoretical & Physical Principles of Organic Reactivity*; Wiley: New York, 1995; Chapter 2.

(12) Pearson, R. G. *Coord. Chem. Rev.* **1990**, *100*, 403. *Hard and Soft Acids and Bases*; Pearson, R. G., Ed.; Dowden, Hutchinson and Ross: Stroudsburg, PA, 1973. Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1.

(13) Isaacs, N. S. *Physical Organic Chemistry*; Longman: New York, 1987; Chapter 1.

(14) It should be pointed out that we were unable to find, within the framework of a single model, an explanation for these observations. However, if one wishes to make an individual case of each of three (Br, Me, and H) transfer reactions, it is possible to suggest an explanation for the above observations. The high-energy barrier for the Me transfer stems from the deformation energy needed to planarize the Me at the transition state. (This is a common explanation although the authors of the present paper always felt that this distortion lowers the transition state energy rather than raises it and that  $\text{sp}^2$  bonds at the transition state are stronger than the  $\text{sp}^3$  bonds in the ground state.) Br transfer is faster than H transfer because bromine can expand its shell better than hydrogen. However, making patches such as these signals, according to Kuhn, the end of a paradigm (Kuhn, T. S. *The Structure of Scientific Revolutions*, 2nd ed.; University of California Press: Chicago (enlarged), 1970).

(15) Ritchie, C. D. 2nd Conference on Physical Organic Chemistry, Brazil, 1983.