The alkylation of nitrogen anions (nitranions) has played an important role in synthetic organic chemistry since Gabriel showed nearly a century ago that reactions of phthalimide ion with alkyl halides, followed by hydrolysis, could provide a preparative route. It is also noteworthy that eq 5 for $\rho^0$ is linear and exhibits the same slope as eq 6 for $\rho'$, although $\rho^0$ and not $\rho'$ depends on the charge-stable substituent distance (vide supra). The similarity in the behavior of these coefficients suggests that changes in charge distribution due to charge delocalization are similar in both reactions and proportional to the resonance effect on the thermodynamic contribution. This result is in agreement with recent findings of Jencks concerning the absence of a specific role of resonance delocalization on the transition-state position for proton-transfer reactions.

Concluding Remarks. Change in charge distribution due to delocalization in Y makes the rate–selectivity relationship curve for protonation and bromination of Y-substituted styrenes, when the selectivity coefficient is $\rho^0$. When $\rho'$, a coefficient insensitive to charge distribution, is chosen the same relationship is a straight line and the $\rho'$ variation is due only to thermodynamic and intrinsic dependence on Y is proportional to the effect of Y on bromination free energy. Whatever the restrictions imposed by eq 5 and 6

$$\alpha = \gamma \rho^0 + \Delta G^\circ / 8c \quad (10)$$

$$\frac{\Delta \alpha}{\Delta Y} = \frac{1}{8c} \frac{\Delta \Delta G^\circ}{\Delta Y} \quad (11)$$

on the relative variations of $\rho'$ and $\alpha$, our experimental results support a much higher intrinsic barrier for protonation than for bromination.

To go deeper in the meaning of the selectivity coefficients, it would be instructive to understand why such closely related electrophilic additions behave so differently as regards the dependence of the transition-state charge on the reactivity; further data on these reactions must be available before the various possible interpretations can be discussed.

Experimental Section

Synthesis of α-methoxystyrenes and the kinetic procedure have been published already.

Determination of k, the Rate Constant for the Free Bromine Addition. Experimental rate constants, $k_{exp}$, are measured at three bromide ion concentrations. As previously shown, the bromide ion effect follows eq 2 where K is the equilibrium constant of the Br$_2$/Br$^-$ equilibrium; $\beta$ is usually identified with $K_{Br^2-}$ whereas $K_{Br^-}$ is the rate constant for tri-bromide ion addition. Thus the plot of $k_{exp}(1 + K[Br^-])/[Br^-]$ gives K at [Br$^-$] = 0 and $K_{Br^-}$ from the slope (Table IV).

Registry No. 1a, 51440-56-3; 1b, 51440-57-4; 1c, 4747-13-1; 1d, 67471-38-9; 1e, 89726-07-8; 1f, 89726-05-6; 1g, 89726-06-1; 1h, 3440-23-1.

S$_2$O$_2$ Reactions of Nitrations with Benzyl Chlorides

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Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. Received August 29, 1983. Revised Manuscript Received January 10, 1984.

Abstract: The rates of S$_2$O$_2$ reactions of 19 nitrations with PhCH$_2$Cl and 9 nitrations with m-CF$_3$C$_6$H$_4$CH$_2$Cl were measured in Me$_2$SO at 25 °C. Bronsted plots of log k vs. pK$_{MA}$ for reactions of anion families derived from carbazoles, phenothiazines, and diphenylamines with PhCH$_2$Cl are linear with slopes of 0.32–0.33. Extension of the carbazole and phenothiazine family lines, which are collinear, provided a reference line by which nucleophilicities of other nitrations could be assessed at constant basicity. Nitrations of varied structural types were found to have remarkably similar nucleophilicities when compared at the same basicities. Steric effects caused rates of reactions of ArAr'N$^-$ ions and acetanilide ion to be retarded slightly and that of benzamidamide to be retarded appreciably. Evidence is presented to show that nitrations, like carbanions, utilize the electron pair in a p orbital for bonding to an electrophile whereas pyridines utilize a nonbonded electron pair. Comparisons with literature data on neutral nitrogen nucleophiles, such as $n$-BuNH$_2$ and PhNH$_2$, indicate that they are 10–100 times more reactive than nitranion nucleophiles of comparable basicity. The order of nucleophilicities toward PhCH$_2$Cl of anion families with different donor atoms when compared at the same basicity was found to be the following: 9-methylfluorene ion family (25) > 2-naphthoxide ion family (3) > carbazole ion family (1.0). The results show that basicity is the primary factor in controlling nucleophilicities of nitrations, carbanions, and oxanions of diverse structural types in S$_2$O$_2$ reactions. Donor atom, solvation, and steric effects generally play a secondary role.

The alkylation of nitrogen anions (nitranions) has played an important role in synthetic organic chemistry since Gabriel showed nearly a century ago that reactions of phthalimide ion with alkyl halides, followed by hydrolysis, could provide a preparative route to primary amines. Alkylation of these and other common nitrations, including those derived from sulfonamides, carboxamides, pyrroles, indoles, benzazines, and diphenylamines, have since been widely used in protons. In protonation there is no substantial dependence of the transition-state position on the reactivity so that the variation of the selectivity coefficient, $\rho^*$, for this reaction is mainly due to thermodynamic factors. Therefore, this addition is used as a reference for separating out the role of the change in transition-state position in bromination: the intervention of this latter term approximately doubles the sensitivity of bromination to the other selectivity-determining factors. It is noteworthy that the variation of the transition-state charge with the reactivity does not modify but only enhances the effect of the thermodynamic contribution. See References 5 and 6.


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The expected $S_2$ products were recovered in >85% yield from the reactions of Ph$_3$N$^+$, phenoxazine anion, phenothiazine anion, and benzanilide anion with PhCH$_2$Cl and carbazole anion with m-C$_6$H$_4$Cl$_2$CH$_2$Cl. Further details are presented in the Experimental Section.

**Discussion**

Do Nitrations Utilize Electrons in a Nonbonded Orbital or a $p$ Orbital for Bonding to Electrophiles? Carbazole ion, Cr$^+$ (1), and other nitrations used in this study, have two electron pairs on nitrogen, only one of which will be used for bonding to the substrate in an $S_2$ reaction. One pair is in a $p$ orbital, which allows maximum overlap with the rest of the aromatic $\pi$ system, while the other is in a nonbonded $sp^2$ orbital perpendicular to the $\pi$ system. By contrast, the carbon analogue of the carbazole ion, 1,9-$R$-fluorenone ion (2), has only a single electron pair in a $p$ orbital of an aromatic $\pi$ system that can be used for bonding to the substrate.

There is evidence that (neutral) pyridine nucleophiles use the nonbonded electron pair on nitrogen in $S_2$ reactions rather than the electrons in the $p$ orbital that is part of the aromatic $\pi$ system, since introduction of 2-alkyl substituents in the pyridine ring causes marked rate retardations. A recent comparison of the effects on reactivities in $S_2$ reactions of 2-$R$ substituents in pyridines ($S^2$ values) with those of 9-$R$ substituents in 9-$R$-fluorenone ions, 9-$R$-$F^+$ ($r$ values), has revealed striking differences that are consistent with the view that pyridine nucleophiles use a nonbonded, rather than a $p$, electron pair in bonding to the substrate. In contrast, nitrations use an electron pair in a $p$ orbital, rather than a nonbonded pair. This conclusion is based in part on marked differences in the response of pyridines and carbazole nucleitans to the introduction of sterically blocking groups into the nucleophile. For example, the rate of reaction of 13-$H$-dibenzo[a,i]-carbazole ion (3C) with PhCH$_2$Cl is retarded by 20-fold, relative to the carbazole ion family, when compared at the same basicity, whereas 8-methylquinoline (4) reacts 1000-fold slower than quinoline with Me$_2$SO. In 3C the two fused benzene rings greatly reduce the accessibility of the nonbonded electron pair for bonding, but have relatively little effect on the accessibility of the $p$ orbital electrophiles. Comparison of the effect of the fused benzene rings in 3C with that of a single benzene ring in the fluorenone analogue 3F does give evidence of differences in both the equilibrium acidities and rates, however, which may be attributed to a steric effect. 1,2-Benzofluorenone is 2.9 $pK_a$ units more acidic than fluorene, but 13-$H$-dibenzo[a,i]carbazole is only 2.2 units more acidic than carbazole despite the presence of an additional fused benzene ring. Evidently there is more puckering of the rings in the dibenzocarbazole nitratnion, 3C, than of the rings in the carbabion 3F resulting in lesser stabilization of 3C by charge delocalization. This puckering effect shows up in the rate as a 20-fold retardation for 3C reacting with PhCH$_2$Cl, relative to the carbazole family Bronsted line, whereas the rate for 3F reacting with i-PrBr fits nicely on the 9-hydrofluoren family Bronsted line. In the presence of the peri methyl group should have little or no effect on the accessibility of the $p$-electron...

**Table I. Rates of Reaction of Nitrations with PhCH$_2$Cl and m-C$_6$H$_4$Cl$_2$CH$_2$Cl in Me$_2$SO Solution at 25 °C**

<table>
<thead>
<tr>
<th>Nitrination</th>
<th>$pK_a$ of the conjugate acid in Me$_2$SO at 25 °C</th>
<th>$(k_{(PhCH_2Cl)})^a$</th>
<th>$(k_{(m-C_6H_4Cl_2CH_2Cl)})^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbazole (1)</td>
<td>19.6</td>
<td>0.337</td>
<td>0.841</td>
</tr>
<tr>
<td>3-Chloroacarbazine</td>
<td>15.0</td>
<td>0.111</td>
<td>0.286</td>
</tr>
<tr>
<td>3,6-Dibromocarbazine ion (3C)</td>
<td>17.16</td>
<td>4.44 x 10$^{-2}$</td>
<td>9.06 x 10$^{-2}$</td>
</tr>
<tr>
<td>13-$H$-dibenz[a,i]carbazole</td>
<td>17.69</td>
<td>3.15 x 10$^{-3}$</td>
<td></td>
</tr>
<tr>
<td>Ph$_3$N$^+$ (8)</td>
<td>24.95</td>
<td>3.85</td>
<td>16.9</td>
</tr>
<tr>
<td>3-$CHCl_2$H$_2$NPh$^+$</td>
<td>23.00</td>
<td>0.820</td>
<td>3.31</td>
</tr>
<tr>
<td>(4-B$_2$C$_6$H$_4$N$^+$)</td>
<td>22.2</td>
<td>0.490</td>
<td></td>
</tr>
<tr>
<td>3,5-$Br$-CH$_2$H$_2$NPh$^+$</td>
<td>26.3</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Phenolthiazine ion (7)</td>
<td>22.7</td>
<td>2.56</td>
<td>22.45</td>
</tr>
<tr>
<td>2-Chlorophenolthiazine ion</td>
<td>20.79</td>
<td>0.603</td>
<td>3.42</td>
</tr>
<tr>
<td>3,7-Dibromophenolthiazine ion</td>
<td>16.9</td>
<td>0.378</td>
<td></td>
</tr>
</tbody>
</table>
| 3-$p$-tosylphenolthiazine ion|(13)                                           | 18.46                | 2.83 x 10$^{-2}$                | 0.114

similar reactivity patterns for phenoxazine vs. carbazole nitranions vs. Cb" nitranions as for Ph
CCN" vs. 9-CN-F1" carbanions; (2)

There is also evidence for a much larger steric hindering effect for the tert-butyl groups in 2,6-di-tert-butylpyridine (5) than for those in 1,3,6,8-tetra-tert-butylcarbazole ion (6), which suggests that the reacting electron pair in the pyridine is screened more effectively than that in the carbazole. Brown reported that 5 underwent no measurable reaction with Mel in CH2CN after 30 days at room temperature,14b while Neugebauer found that 6 reacted completely with Mel in DMF after 15 h at room temperature.18 Thus 5 was found to react several orders of magnitude slower than pyridine, whereas 6 reacts at roughly the same rate as does the carbazole anion.

Supporting evidence for the utilization of p orbitals by nitranions in S_n,2 reactions is provided by the following comparisons with carbanion reactions of S_n,2. Examination of Figure 1 shows that the Cb" and Pz" ion families form a single line with a slope (Bronsted β) of 0.32. The extended Cb"/Pz" line can be used as a reference for comparison of the activities of other nitranions at the same basicity. The flat Cb" ion presents little steric hindrance to the approach of an electrophile to the electron pair in the p orbital. Since the Pz" ion family line is collinear with the Cb" ion family line, Pz" ions must also provide easy access to the p orbital of the nitranion. Examination of scalar molecular models shows, however, that the phenyl rings in the diphenylamide ion (8), like those in the diphenylmethide ion, are prevented from achieving coplanarity by interference of ortho hydrogen atoms. As a consequence, the ions in the ArAr'N" ion family suffer increased steric hindrance in the S_n,2 transition state, making them 4-fold slower to react with PhCH2Cl than expected from the Cb"/Pz" family line. The points for the ions derived from 5H-dibenzo[a,e]azepine (9, 11), iminodibenzyl nitranion, and its dihydro derivative, 10,11-dihydro-5H-dibenzo[a,e]azepine (10, 11), lay close to the Bronsted line for the ArAr'N" ion family, suggesting that these ions with flexible seven-membered rings also are subject to some crowding in the S_n,2 transition state.

Figure 1. Plot of log k vs. \( pK_{HA} \) for nitranions reacting with PhCH2Cl in Me2SO at 25 °C. Structures for points indicated by squares (3, 9, 10, 11, 13, 15, 16, and 17) are shown in the text; these points were not included in the correlation.

There are several noteworthy parallels between nitranion reactivities and those of their carbanion counterparts. For example, Bronsted plots for several 9-R-F1" carbanion families reacting with PhCH2Cl are parallel to those for carbazole, phenothiazine, and diphenylamine nitranion families.11 Secondly, the reactivity of the 9-CN-F1" ion (2, with R = CN) is 4-fold greater than that of its acyclic analogue, Ph2CCN"; when compared at the same basicity,17b due to increased steric hindrance in the latter. Likewise, the Cb" ion is 4-fold more reactive toward PhCH2Cl than its acyclic analogue, the Ph3N" ion. In another example, the 9-cyanoxanthenide ion (12) is 20-fold more reactive toward PhCH2Cl than the 9-CN-F1" ion (2, with R = CN),17b and insertion of oxygen has a similar effect in the nitranion analogues, i.e., phenoxazine (11) is 15-fold more reactive than carbanole (1). These similarities in structure-reactivity relationships for nitranions and carbanions further support the conclusion that nitranions utilize p-orbital electrons in reacting with alkyl halides, just as carbanions do. It is noteworthy that during S_n,2 reactions of


Table II. Relative Nucleophilicities of Nitranions of the Same Basicity toward PhCH$_2$Cl in Me$_2$SO at 25 °C

<table>
<thead>
<tr>
<th>nitration conjugate acid</th>
<th>rel rate$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenoxazine (11)</td>
<td>15</td>
</tr>
<tr>
<td>1,2,3,4-tetrahydroquinolin-2-one (15)</td>
<td>1.6</td>
</tr>
<tr>
<td>carbazole (1) (family line)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>phenothiazine (7) (family line)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>ArArN$^+$ (8) (family line)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>3,5-Br$_2$C$_6$H$_4$NMe$^+$</td>
<td>0.28</td>
</tr>
<tr>
<td>iminobenzilene (9)</td>
<td>0.40</td>
</tr>
<tr>
<td>iminodibenzy (10)</td>
<td>0.26</td>
</tr>
<tr>
<td>3-p-tosylphenothiazine (13)</td>
<td>0.26</td>
</tr>
<tr>
<td>acetonilide (16)</td>
<td>0.11</td>
</tr>
<tr>
<td>benzanilide (17)</td>
<td>0.023</td>
</tr>
<tr>
<td>3,5-Dibenzo[a,i]carbazole (3)</td>
<td>0.053</td>
</tr>
<tr>
<td>phenothiazine 5,5-dioxide (14)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

$^a$ Rate constants are given in Table I.

carbazole nitranions the nonbonded pair on nitrogen must rehybridize into a p orbital so as to become part of the aromatic sextet, whereas this does not happen for fluorenide carbazones.

9-Substituted fluorenide ions (9-R-FI$^-$, Pz$^-$ ions, and Cb$^-$ ions might have been expected to show quite different behavior in $S_2$ reactions with PhCH$_2$Cl. Product formation requires a loss in aromaticity for 9-R-FI$^-$ ions and a presumed loss of antiaromaticity for Pz$^-$ ions, whereas for Cb$^-$ ions there is no change in aromaticity. These effects could result in rate retardation for 9-R-FI$^-$ ions and rate enhancement for Pz$^-$ ions, relative to Cb$^-$ ions. This is not observed. Instead, when comparisons are made at the same basicity, a rate enhancement of about 25-fold is observed for 9-MeFI$^-$ ions vs. Pz$^-$ and Cb$^-$ ions, which have about the same reactivity. The comparison at equal basicities takes into account the aromaticity effect for 9-MeFI$^-$ ions because their relatively low basicity (10 pK$_a$ units lower than Ph$_2$CH$^+$ ions) is caused primarily by the aromaticity of their anions. Acidity comparisons lend no support to the concept of antiaromaticity in phenothiazine nitranions, since PzH$_2$ is more acidic than the open chain analogue, Ph$_2$NH$_2$, by 2.2 pK$_a$ units (Table I). The nearly equal reactivities of Cb$^-$ and Pz$^-$ ions appear reasonable, therefore, but the enhanced reactivity of 9-MeFI$^-$ ions, relative to nitranions of similar structure, is surprising. It is possible that this may be caused by stronger solvation of the nitranions by Me$_2$SO.

The phenoxazine ion (11) reacts 15-fold faster with PhCH$_2$Cl than expected for a phenoxazine ion of the same basicity, resulting in a sizable positive deviation from the Cb$^-$/Pz$^-$ family line (Figure 1). This observation could be added to the list of enigmatic "a effects". Alternatively, one could visualize electron donation from oxygen that leads to a relative enhancement of electron density at the reactive site that affects the nucleophilicity more than the basicity. A similar effect is observed for the 9-cyanoxanthenide ion (12) when compared with a 9-CN-FI$^-$ ion of the same basicity.$^{170}$

Examination of Figure 1 shows that several other nitranions deviate from the Cb$^-$/Pz$^-$ ion family line. The 3-p-tosylphenothiazine ion (13) reacts 4-fold slower with PhCH$_2$Cl than predicted by the phenothiazine ion family line. A similar, but more pronounced, effect is observed for the ion of phenothiazine 5,5-dioxide (14), which reacts 23-fold slower with PhCH$_2$Cl. We have observed a similar effect of an electron-withdrawing group earlier, in which the rate for reaction of $p$-NO$_2$C$_6$H$_4$Cl$^-$ with $n$-BuCl was found to be 2-fold slower than predicted by the ArS$^-$ ion family line,$^{20}$ and similar deviations have also been observed for p-


Anion 15, an analogue of 16 with the groups attached to the nitrogen and carbonyl carbon atoms tied back, presents little steric hindrance to the approach of PhCH$_2$Cl and reacts at a rate comparable to that of a Cb$^-$/Pz$^-$ ion of the same basicity. Although the negative charge is localized primarily on oxygen, this apparently does not affect the rate of alkylation on nitrogen. On the other hand, in 16 and 17 the phenyl rings are doubt twisted to relieve steric interactions across the short C=N bond. As a result approach of the electrophile is impeded and the points for these carboxamide ions fall well below the Cb$^-$/Pz$^-$ line, and somewhat below the ArArN$^+$ line in Figure 1.

A comparison of the nucleophilicities of nitranions relative to a Cb$^-$ or Pz$^-$ ion of the same basicity obtained by determining the vertical distance on the plot in Figure 1 between the subject nitranion and the Cb$^-$/Pz$^-$ ion family line at the pK$_{45}$ of the subject nitranion is given in Table II.
cleophilities extend over a 650-fold range, but this is not large considering the diversity of structural types represented. Also, it should be kept in mind that, if the $\beta$ values for the families to which compounds 11 and 13–17 belong differ appreciably from that of the Cb$^-$ family, their relative reactivities will change depending on the $pK_A$ values used for comparison.

It is significant that three cyclic nitranions of quite different structural types, Cb$^-$ (a heteroaromatic ion), Pz$^-$ (a hetero “antiaromatic” ion), and 1,2,3,4-tetrahydroquinolin-2-one-ion (15, an ambient carboxamide ion with the negative charge localized primarily on oxygen), all show closely similar nucleophilicities when compared at the same basicities (Figure 1). Also, the results indicate that even the open-chain ArAr$^N$ and ArNeEt$^-$ nitranions will have similar nucleophilicities when corrections are made for a small steric effect. Clearly, basicity is the primary factor determining the nucleophilicities of these nitranions. The same conclusion has been drawn for carbanion nucleophilicities, where $\alpha$-cyano carbanions differing markedly in shape, size, and charge distribution have all been found to have nearly the same nucleophilicity when compared at the same basicity.17b

A Brønsted plot is not shown for the reactions of m-CF$_2$C$_6$H$_4$CH$_2$Cl with Cb$^-$ and Pz$^-$ ions because of the limited data presently available. However, the Cb$^-$ and Pz$^-$ ion family lines are no longer collinear, the Pz$^-$ ion family being about 1.5-fold more reactive than the Cb$^-$ ion family. A $\beta_{Na}$ value of 0.35 was obtained for the Cb$^-$ family reacting with m-CF$_2$C$_6$H$_4$CH$_2$Cl, a value slightly higher than that for PhCH$_2$Cl (0.32). Enhanced $\beta_{Na}$ values for benzyl chlorides containing electron-withdrawing groups have been observed previously for 9-$\text{F}$-I$^-$ ions.12

Comparison of Nucleophilicities of Neutral and Anionic Nitrogen Nucleophiles. Use of literature data for reactions of neutral nitrogen nucleophiles with PhCH$_2$Cl and extrapolation of our Brønsted plots for nitranions reacting with PhCH$_2$Cl in Me$_2$SO allows a rough comparison of the reactivities of neutral and anionic nucleophiles at the same basicity (Figure 2).

Kawabe measured a rate of $8 \times 10^{-5}$ M$^{-1}$ s$^{-1}$ for the reaction of Et$_3$N with PhCH$_2$Cl in Me$_2$SO at 25 °C.23 Extrapolation of the Cb$^-$/Pz$^-$ line [$\log k = 0.321 (pK_A - 6.88)$] to the $pK_A$ of Et$_3$N in Me$_2$SO (9.024) gives us an expected rate for a nitranion of $1 \times 10^{-4}$ M$^{-1}$ s$^{-1}$, a value only slightly greater than the rate constant observed for Et$_3$N. Since quinuclidine reacts 57–705-fold faster than Et$_3$N, depending on the alkyl halide,24,25 this comparison implies, however, that an unhindered neutral nucleophile would be $\sim 10^3$ more nucleophilic than a nitranion of equal basicity. When solvent effects for Menschutkin reactions reported in the literature are used, reasonable extrapolations to rates in Me$_2$SO can be made from rates for neutral nitrogen bases in other solvents. Kawabe has shown that rates in DMF are 4- to 5-fold slower than those in Me$_2$SO.23,24 Haberfield has shown that rates in MeOH and DMF are nearly equal,24 and Zoltewicz has found rates in Me$_2$SO to be 7-fold faster than those in PhNO$_2$.29 We have used these correction factors to estimate rate constants in Me$_2$SO at 25 °C for pyridine, n-BuNH$_2$, PhNMMe$_2$, and PhNH$_2$ reacting with PhCH$_2$Cl and have plotted the results in Figure 2. Inspection of Figure 2 shows that neutral nitrogen nucleophiles are up to 100-fold more reactive than a nitranion of comparable basicity.31 There are at least three factors that conceivably could contribute to the enhanced reactivity of neutral nitrogen bases vs. nitranions. (1) The neutral bases are using nonbonded electrons for bonding in the transition state whereas the nitranions are using electrons in more diffuse p orbitals. (2) The neutral bases give rise to a positively charged transition state, and Me$_2$SO solvent is known to solvate cations well. (3) Nitranions are more solvated than the neutral bases, which may lead to a relative lowering of nitranion reactivities.

Comparisons of Nucleophilicities of Carbanions, Nitranions, and Oxanions of the Same Basicity. A Brønsted plot including families of nitranions (Cb$^-$, Pr$^-$), carbanions (9-methylfluorenides),13 and oxanions (2-naphthoxides) reacting with PhCH$_2$Cl in Me$_2$SO solution at 25 °C is shown in Figure 3. The slopes of the lines

---

Figure 2. Plot of $\log k$ vs. $pK_A$ for neutral and anionic nitrogen nucleophiles reacting with PhCH$_2$Cl at 25 °C. The squares for neutral nitrogen nucleophiles represent estimated rates, usually in other solvents, taken from the literature. The $pK_A$ values for neutral nucleophiles are from ref 21 and 24.
are nearly the same ($\beta_{N^+} / N^+ \approx 0.32$), which allows comparisons of the relative nucleophilicities of the anion families to be made at the same basicities by relating the vertical distances between extended lines. The order of nucleophilicities toward PhCH$_2$Cl obtained in this way is the following: 9-MeFl$^+$ (25) > 2-NpO$^-$ (3) > Cb$^+$/Pz$^+$ (1.0). These ion families, wherein the donor atom is a first-row element, are $10^2$-$10^4$ less reactive than ions derived from second-row donor atoms, such as benzene dietholate ions. The order $O > N > C$ is unusual in that it follows neither the order of electronegativities ($O > N > C$) nor the order of polarizabilities of donor atoms ($C^+ > N^+ > O^+$). The differences in reactivities are not large, however, and are substrate dependent. For example, for $S_N$$_2$ reactions between $\alpha$-PR$_2$Os and these same anions the order changes to $O > N^+ > C^+$.$^{21}$

The constancy of $\beta_{N^+}$ for nitranions, as well as that for carbanions, over wide ranges of basicity is another significant point that emerges from this research. If $\beta_{N^+}$ represents the fraction of negative charge transferred from the anion to the electrophile in the transition state, this fraction evidently remains constant not only for structural changes in the carbon skeleton but also for changes in the nature of the donor atom from carbon to nitrogen to oxygen.$^{22}$

5. Neutral nitrogen nucleophiles are more reactive than nitranions of the same basicity by a factor of $10^2$-$10^3$.$^{23}$

Table III. Characterization of Products from Reactions of Nitranions with Benzyl Halides in Me$_2$SO Solution

<table>
<thead>
<tr>
<th>product</th>
<th>yield, $%$</th>
<th>reaction time $^b$</th>
<th>mp, $^\circ$C</th>
<th>$^1$H NMR, $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph$_3$NCH$_2$Ph</td>
<td>88</td>
<td>0.5 h</td>
<td>88-89 (EiOH),</td>
<td>4.9 (2 H, S, CH$_2$),</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>3 min</td>
<td>86-87 (EiOH)$^d$</td>
<td>6.8-7.3 (15 H, m)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>5 min</td>
<td>91-92 (EiOH),</td>
<td>4.9 (2 H, S, CH$_2$),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(lit.$^e$) 91-92</td>
<td>6.3-7.3 (13 H, m)</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>45 h</td>
<td>104.5-105 (hexane)</td>
<td>5.1 (2 H, S, CH$_2$),</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>0.5 h</td>
<td>90-92 (EiOH)$^d$</td>
<td>6.7-7.4 (15 H, m)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(lit.$^e$) 105</td>
<td>6.9-7.5 (12 H, m)</td>
</tr>
</tbody>
</table>

$^a$ Crude yield; product pure by TLC and NMR. $^b$ Reactant concentrations both ca. 0.1 M; room temperature. $^c$ Reference 44. $^d$ Mass spectrum: m/e 273 (M$^+$, 17%), 182 (phenoxyazinyl radical, 100%), 91 (benzyl radical, 16%). $^e$ Reference 45. $^f$ Reference 46. $^g$ Mass spectrum: m/e 325 (M$^+$, 100%), 166 (carbazole radical, 56%), 159 (m-CF$_3$C$_6$H$_2$CH$_2$+, 46%).

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References

(41) Prepared by Steve Park.
Total Synthesis of Anhydrocannabisativene

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Abstract: A stereoselective total synthesis of the macrocyclic spermidine alkaloid anhydrocannabisativene (2) has been executed in approximately 17 steps starting from pentadienylsilane 6. The pivotal step in construction of the tetrahydropyridine ring and for establishing the relative stereochemistry of the alkaloid involved an intramolecular imino Diels–Alder cycloaddition. An intramolecular sulfonamide alkylation was subsequently used to generate the 13-membered macrocyclic lactam ring of 2.

The common marijuana plant Cannabis sativa is the source of several non-cannabinoid nitrogenous compounds including the interesting spermidine alkaloids cannabi­cannabisativene (1) and anhydrocannabisativene (2).1,2 In recent years there has been considerable interest in developing synthetic routes to such macrocyclic spermine- and spermidine-derived alkaloids.3,4 We have previously described some model studies involving intramolecular Diels–Alder reactions of imino dienophiles which allow ready construction of trans-2,6-disubstituted tetrahydropyridines related to 1 and 2.5,6 We now describe the application of this methodology to an efficient stereospecific total synthesis of racemic anhydrocannabisativene.

The required starting material for our imino Diels–Alder approach to 2 was diene alcohol 4. Initially this compound was prepared by addition of pentadienyllithium (3)12 to n-hexanal, but this procedure was unattractive in that it afforded a 1:1 mixture of the desired diene alcohol 4 and the unwanted isomer 5 (Scheme I). Attempts to convert 5 to 4 via an anion-accelerated [1,3]-sigmatropic rearrangement using the conditions described by Wilson et al.9 were unsuccessful. A much better route to 4 was eventually developed using the pentadienylsilane 6 recently described by Seyferth10 and Sakurai.11 This compound, which is readily prepared from 3 by treatment with trimethylsilyl chloride, reacted with 1-hexanal in the presence of titanium tetrachloride to produce only the desired conjugated diene alcohol 4 (69%).

This alcohol was next transformed to the corresponding carboxamate 7 by using the cyanate procedure of Loev and Kornmendy12 (Scheme II) in 95% yield. The carboxamate reacted with anhydrous


