pendence on Y is proportional to the effect of Y on bromination free energy. Whatever the restrictions imposed by eq 5 and 6

$$\alpha = \tfrac{1}{2} + \Delta G^\circ / 8c \quad (10)$$

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

on the relative variations of ρ^t and α, our experimental results support a much higher intrinsic barrier for protonation than for bromination.

It is also noteworthy that eq 5 for ρ^n is linear and exhibits the same slope as eq 6 for ρ^r, although ρ^n and not ρ^r depends on the charge-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[35] 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 curved for protonation and bromination of Y-substituted styrenes, when the selectivity coefficient is ρ^n. When ρ^r, a coefficient insensitive to charge distribution, is chosen the same relationship is a straight line and the ρ^r variation is due only to thermodynamic and intrinsic kinetic factors. In protonation there is no substantial dependence of the transition-state position on the reactivity so that the variation of the selectivity coefficient, ρ^r, 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.

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.

(35) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrick, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045-7051.

Experimental Section

Synthesis of α-methoxystyrenes and the kinetic procedure[11] have been published already.

Determination of k, the Rate Constant for the Free Bromine Addition. Experimental rate constants, k_{exptl}, 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_3^- equilibrium; β is usually identified with $Kk_{Br_3^-}$ where $k_{Br_3^-}$ is the rate constant for tribromide ion addition.[12] Thus the plot of $k_{exptl}(1 + K[Br^-])$ against $[Br^-]$ gives k at $[Br^-] = 0$ and $k_{Br_3^-}$ 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**, 89726-06-7; **1g**, 89726-05-6; **1h**, 3440-23-1.

S_N2 Reactions of Nitranions with Benzyl Chlorides

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Abstract: The rates of S_N2 reactions of 19 nitranions with $PhCH_2Cl$ and 9 nitranions with m-$CF_3C_6H_4CH_2Cl$ were measured in Me_2SO at 25 °C. Brønsted plots of log k vs. pK_{HA} for reactions of anion families derived from carbazoles, phenothiazines, and diphenylamines with $PhCH_2Cl$ 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 nitranions could be assessed at constant basicity. Nitranions 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 benzanilide ion to be retarded appreciably. Evidence is presented to show that nitranions, 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 for 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 $PhCH_2Cl$ of anion families with different donor atoms when compared at the same basicity was found to be the following: 9-methylfluorenide 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 nitranions, carbanions, and oxanions of diverse structural types in S_N2 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.[1] Alkylations of these and other common nitranions, including those derived from sulfonamides,[2,3] cyanamides,[4] carboxamides,[5] pyrroles,[6] indoles,[7] carbazoles,[8] phenothiazines,[9] and diphenylamines,[10] have since been widely used in

(1) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224; **1917**, *50*, 819. For a review, see: Gibson M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919-930.
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Table I. Rates of Reaction of Nitranions with $PhCH_2Cl$ and m-$CF_3C_6H_4CH_2Cl$ in Me_2SO Solution at 25 °C

nitranion	pK_{HA}[a]	$k(PhCH_2Cl)$[b]	$k(m\text{-}CF_3C_6H_4CH_2Cl)$[b]
carbazole ion (1)	19.9[c]	0.337	0.841
3-chlorocarbazole ion	18.50	0.111	0.286
3,6-dibromocarbazole ion	17.16	4.44×10^{-2}	9.06×10^{-2}
13*H*-dibenzo[*a,i*]carbazole ion (3)	17.69	3.15×10^{-3}	
Ph_2N^- (8)	24.95[d]	3.85	16.9
3-$ClC_6H_4NPh^-$	23.00	0.820	3.31
$(4\text{-}BrC_6H_4)_2N^-$	22.2[e]	0.490	
3,5-$Br_2C_6H_4NEt^-$	26.3[e]	10.1	
phenothiazine ion (7)	22.72	2.56	22.45
2-chlorophenothiazine ion	20.79	0.603	3.42
3,7-dibromophenothiazine ion	20.13	0.378	
3-*p*-tosylphenothiazine ion (13)	18.46	2.83×10^{-2}	0.114
phenothiazine 5,5-dioxide ion (14)	15.75	6.20×10^{-4}	9.39×10^{-4}
phenoxazine ion (11)	21.66	16.9	
iminostilbene ion (9)	26.10	12.1	
iminodibenzyl ion (10)	25.56	5.2	
acetanilide ion (16)	21.45[f]	0.101	
benzanilide ion (17)	18.8[f]	3.19×10^{-3}	
1,2,3,4-tetrahydroquinolin-2-one ion (15)	20.74[g]	0.907	

[a] pK_a of the conjugate acid in Me_2SO at 25 °C; reproducible to ±0.05 pK_a unit. [b] Units for rate constants are M^{-1} s^{-1}; reproducible to ±3%. [c] Fried, H. E.; Drucker, G. E.; Bordwell, F. G. *J. Org. Chem.* **1981**, *46*, 632–635. [d] Algrim, D. Ph.D. Dissertation, Northwestern University, 1981. [e] Synthesized and the pK_a measured by S. Park, unpublished results. [f] Bordwell, F. G.; Algrim, D. *J. Org. Chem.* **1976**, *41*, 2507–2508. [g] Fried, H. E. Ph.D. Dissertation, Northwestern University, 1978.

organic synthesis. Despite the obvious importance of these reactions, quantitative measurements of the relative nucleophilicities of nitranions appear to be limited to a study of the reactions of the conjugate bases of succinimide, phthalimide, benzenesulfonamide, and *N*-methyl- and *N*-phenylbenzenesulfonamides toward methyl iodide in methanol.[11] The paucity of quantitative data is due primarily to the low acidity of most N–H bonds, which precludes the generation of sufficient concentrations of nitranions in the aqueous or alcoholic solvents originally favored by chemists for such studies. Also, the nitranions generated in the weakly polar solvents favored by synthetic chemists are strongly paired to counterions making quantitative comparisons of relative nitranion reactivities difficult or impossible. Use of the dipolar nonhydroxylic solvent dimethyl sulfoxide solves both of these problems. Furthermore, the observation that the rates of alkylation of families of nitranions, as well as carbanions, can be correlated with anion basicities through the Brønsted relationship[12,13] has provided a means of comparing nitranion nucleophilicities at constant nitranion basicities. In this paper we compare the reactivities of nitranions derived from carbazoles, phenothiazines, diphenylamines, and carboxamides with one another and with carbanions, oxanions, and neutral amines of similar structures.

Results

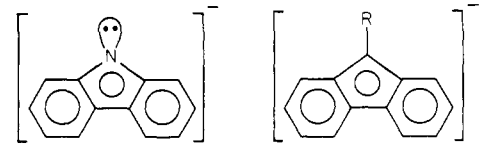
Rate constants for reactions of nitranions with $PhCH_2Cl$ and m-$CF_3C_6H_4CH_2Cl$ in Me_2SO solution at 25 °C are listed in Table I along with pK_a values of their conjugate acids in Me_2SO solution.

The rates were measured by following the decay of the colored nitranion by UV–vis spectroscopy as described earlier.[12] All reactions followed good second order kinetics for >3 half-lives; rate constants were generally reproducible to ±3%.

The expected S_N2 products were recovered in >85% yield from the reactions of Ph_2N^-, phenoxazine anion, phenothiazine anion, and benzanilide anion with $PhCH_2Cl$ and carbazole anion with m-$CF_3C_6H_4CH_2Cl$. Further details are presented in the Experimental Section.

Discussion

Do Nitranions Utilize Electrons in a Nonbonded Orbital or a p Orbital for Bonding to Electrophiles? Carbazole ion, Cb^- (**1**), and other nitranions 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_N2 reaction. One pair is in a p orbital, which allows maximum overlap with the rest of the aromatic π system, while the other is in a nonbonded sp^2 orbital perpendicular to the π system. By contrast, the carbon analogue of the carbazole ion, a 9-R-fluorenide ion (**2**), has only a single electron pair in a p orbital of an aromatic π system that can be used for bonding to the substrate.



1 2

There is evidence that (neutral) pyridine nucleophiles use the nonbonded electron pair on nitrogen in S_N2 reactions rather than the electrons in the p orbital that is part of the aromatic π system, since introduction of 2-alkyl substituents in the pyridine ring causes marked rate retardations.[14–16] A recent comparison of the effects on reactivities in S_N2 reactions of 2-R substituents in pyridines ($S°$ values) with those of 9-R substituents in 9-R-fluorenide ions, 9-R-Fl^- (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.[17] In contrast, nitranions 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 nitranions 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 $PhCH_2Cl$ 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 MeI in Me_2SO.[16] 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 electrons. Comparison of the effect of the fused benzene rings in **3C** with that of a single benzene ring in the fluorene 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-Benzofluorene 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 nitranion, **3C**, than of the rings in the carbanion **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 $PhCH_2Cl$, relative to the carbazole family Brønsted line, whereas the rate for **3F** reacting with *i*-PrBr fits nicely on the 9-hydrofluorene family Brønsted line.[17a] In **4** the presence of the peri methyl group should have little or no effect on the accessibility of the p-electron

(11) Bunnett, J. F.; Beale, J. H. *J. Org. Chem.* **1971**, *36*, 1659–1661.
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(13) A preliminary account of this work has been reported: Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 169–170.
(14) (a) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1955**, *77*, 1715–1723. (b) Brown, H. C.; Kanner, B. *Ibid.* **1966**, *88*, 986–992.
(15) Berg, U.; Gallo, R.; Klatte, G.; Metzger, J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1350–1355.
(16) (a) Deady, L. W.; Finlayson, W. L; Korytsky, O. L. *Aust. J. Chem.* **1979**, *32*, 1735–1742. (b) Deady, L. W.; Zoltewicz, J. A. *J. Org. Chem.* **1972**, *37*, 603–607.
(17) (a) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1983**, *48*, 2207–2215. (b) *Ibid.* **1983**, *48*, 2216–2222.

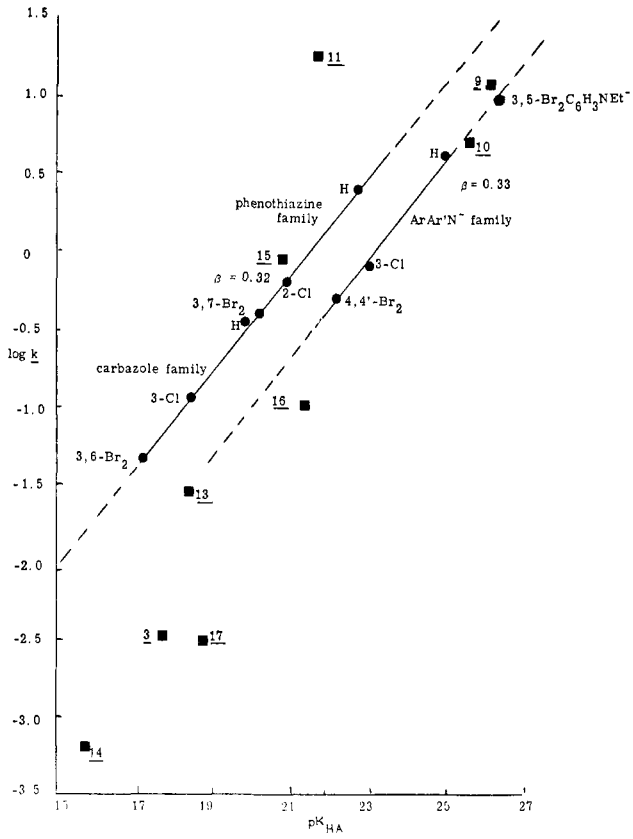
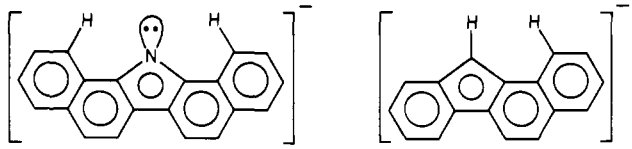


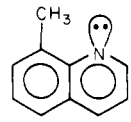
Figure 1. Plot of log k vs. pK_{HA} for nitranions reacting with $PhCH_2Cl$ in Me_2SO at 25 °C. Structures for points indicated by squares (**3**, **9**, **10**, **11**, **13**, **15**, **16**, and **17**) are shown in the text; these points were not included in the correlation.

pair to the electrophile, but evidently it screens the σ-electron pair effectively, causing the observed 1000-fold rate retardation.



3C

3F



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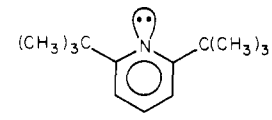
There is also evidence for a much larger steric hindering effect for the *tert*-butyl groups in 2,6-di-*tert*-butylpyridine (**5**) than for those in 1,3,6,8-tetra-*tert*-butylcarbazole ion (**6**), which suggests that the reacting electron pair in the pyridine is screened more effectively than that in the carbazole. Brown reported that **5** underwent no measurable reaction with MeI in CH_3CN after 30 days at room temperature,[14b] while Neugebauer found that **6** reacted completely with MeI 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_N2 reactions is provided by the following comparisons with structurally similar carbanions: (1) similar steric effects for Ph_2N^- vs. Cb^- nitranions as for Ph_2CCN^- vs. 9-CN-Fl^- carbanions; (2) similar β_{Nu} values for nitranion and carbanion families; and (3) similar reactivity patterns for phenoxazine vs. carbazole nitranions

(18) Neugebauer, F. A.; Fischer, H. *Chem. Ber.* **1972**, *105*, 2686–2693.



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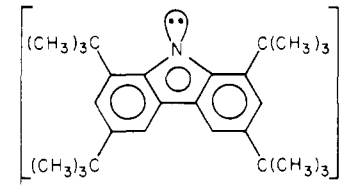

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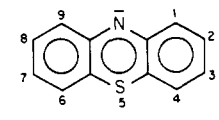
as for xanthene vs. fluorene carbanions. These comparisons are discussed in the next section.

Structure–Reactivity Relationships for S_N2 Reactions of Nitranions Brønsted plots for log k vs. pK_{HA} for nitranions reacting with $PhCH_2Cl$ are shown in Figure 1. For carbazole (Cb^-), phenothiazine (Pz^-), and diphenylamine ($ArAr'N^-$) ions (**1**, **7**, and **8**, respectively), remote substitution of halogen atoms into the benzene rings provides ion families wherein the basicity is changed without changing steric effects at the reaction site.



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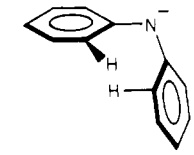

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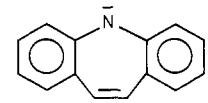
Examination of Figure 1 shows that the Cb^- and Pz^- ion families form a single line with a slope (Brønsted β) of 0.32. The extended Cb^-/Pz^- line can be used as a reference for comparison of the reactivities of other nitranions at the same basicity. The flat Cb^- ion presents little steric hindrance 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_N2 transition state, making them 4-fold slower to react with $PhCH_2Cl$ than expected from the Cb^-/Pz^- family line. The points for the ions derived from 5*H*-dibenz[*a*,*f*]azepine (**9**, iminostilbene nitranion) and its dihydro derivative, 10,11-dihydro-5*H*-bibenz-[*a*,*f*]azepine (**10**, iminodibenzyl nitranion), lie close to the Brønsted 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_N2 transition state.



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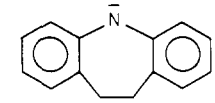

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There are several noteworthy parallels between nitranion reactivities and those of their carbanion counterparts. For example, Brønsted plots for several 9-R-Fl^- carbanion families reacting with $PhCH_2Cl$ are parallel to those for carbazole, phenothiazine, and diphenylamine nitranion families.[13] Secondly, the reactivity of the 9-CN-Fl^- ion (**2**, with R = CN) is 4-fold greater than that of its acyclic analogue, Ph_2CCN^-, when compared at the same basicity,[17a] due to increased steric hindrance in the latter. Likewise, the Cb^- ion is 4-fold more reactive toward $PhCH_2Cl$ than its acyclic analogue, the Ph_2N^- ion. In another example, the 9-cyanoxanthenide ion (**12**) is 20-fold more reactive toward $PhCH_2Cl$ than the 9-CN-Fl^- 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 carbazole (**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_N2 reactions of

Table II. Relative Nucleophilicities of Nitranions of the Same Basicity toward $PhCH_2Cl$ in Me_2SO at 25 °C

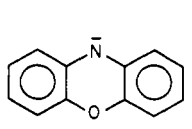
nitranion conjugate acid	rel rate[a]
phenoxazine (**11**)	15
1,2,3,4-tetrahydroquinolin-2-one (**15**)	1.6
carbazole (**1**) (family line)	(1.0)
phenothiazine (**7**) (family line)	(1.0)
$ArAr'N^-$ (**8**) (family line)	0.28
$3,5\text{-}Br_2C_6H_3NEt^-$	0.28
iminostilbene (**9**)	0.40
iminodibenzyl (**10**)	0.26
3-*p*-tosylphenothiazine (**13**)	0.26
acetanilide (**16**)	0.11
benzanilide (**17**)	0.023
13*H*-Dibenzo[*a*,*i*]carbazole (**3**)	0.053
phenothiazine 5,5-dioxide (**14**)	0.043

[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 carbanions.

9-Substituted fluorenide ions (9-R-Fl^-), Pz^- ions, and Cb^- ions might have been expected to show quite different behavior in S_N2 reactions with $PhCH_2Cl$. Product formation requires a loss in aromaticity for 9-R-Fl^- 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-Fl^- 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-MeFl^- 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-MeFl^- ions because their relatively low basicity (10 pK units lower than Ph_2CH^- 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 is more acidic than the open chain analogue, Ph_2NH, by 2.2 pK units (Table I). The nearly equal reactivities of Cb^- and Pz^- ions appear reasonable, therefore, but the enhanced reactivity of 9-MeFl^- 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_2SO.

The phenoxazine ion (**11**) reacts 15-fold faster with $PhCH_2Cl$ than expected for a phenothiazine 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 "α 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-Fl^- ion of the same basicity.[17b]



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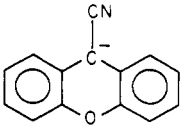
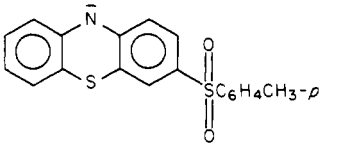


12

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 $PhCH_2Cl$ 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 $PhCH_2Cl$. We have observed a similar effect of an electron-withdrawing group earlier, in which the rate for reaction of $p\text{-}NO_2C_6H_4S^-$ 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 $p\text{-}MeSO_2C_6H_4O^-$ and $p\text{-}CO_2MeC_6H_4O^-$ ions relative to the ArO^- ion family line.[21] It seems likely that these deviations are caused by extensive delocalization of the negative charge into the electron-withdrawing group enhanced by a specific solvation effect in the anion. The existence of specific solvent-assisted resonance effects of this kind involving para electron-withdrawing groups, such as NO_2, has been postulated for phenoxide ions in water based on a correlation of acidities of phenols in water vs. the gas phase,[22a] and there is evidence that a similar effect is operative in Me_2SO solution.[22b] Evidently this delocalization of the charge from nitrogen in the nitranion, which is illustrated for **14** where the deviation is particularly large (Figure 1), causes a greater effect on the rate than for "normal" substituents.



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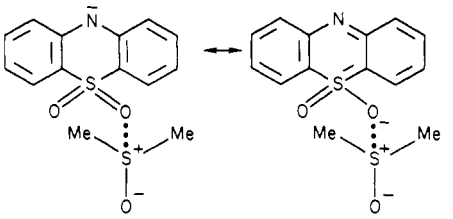
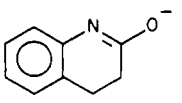


14

The relative reactivities of three carboxamide ions are also compared in Figure 1. The nitranion derived from 1,2,3,4-tetrahydroquinolin-2-one (**15**) reacts 1.6-fold faster than expected for a Cb^- or Pz^- ion of comparable basicity, whereas those derived from acetanilide (**16**) and benzanilide (**17**) reacted 9-fold and 44-fold slower, respectively. A product study with benzanilide showed that *N*-alkylation had occurred, with no evidence by NMR of the presence of an O-alkylated product.



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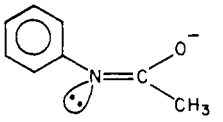

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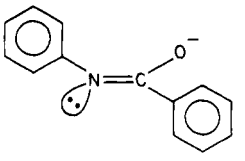

17

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 $PhCH_2Cl$ 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 no 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 $ArAr'N^-$ 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_{HA} of the subject nitranion is given in Table II. We note that the nu-

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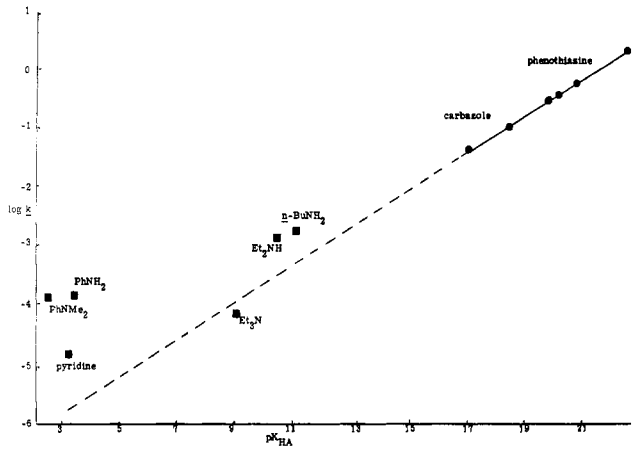

Figure 2. Plot of log k vs. pK_{HA} for neutral and anionic nitrogen nucleophiles reacting with $PhCH_2Cl$ at 25 °C. The squares for neutral nitrogen nucleophiles represent estimates made from rates, usually in other solvents, taken from the literature. The pK_{HA} values for neutral nucleophiles are from ref 21 and 24.

cleophilicities 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 β values for the families to which compounds **11** and **13–17** belong differ appreciably from that of the Cb^-/Pz^- ion family, their relative reactivities will change depending on the pK_{HA} 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 ambident 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 $ArNEt^-$ 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 α-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-$CF_3C_6H_4CH_2Cl$ 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 β_{Nu} value of 0.35 was obtained for the Cb^- family reacting with m-$CF_3C_6H_4CH_2Cl$, a value slightly higher than that for $PhCH_2Cl$ (0.32). Enhanced β_{Nu} values for benzyl chlorides containing electron-withdrawing groups have been observed previously for 9-R-Fl^- ions.[12]

Comparison of Nucleophilicities of Neutral and Anionic Nitrogen Nucleophiles. Use of literature data for reactions of neutral nitrogen nucleophiles with $PhCH_2Cl$ and extrapolation of our Brønsted plots for nitranions reacting with $PhCH_2Cl$ in Me_2SO allows a rough comparison of the reactivities of neutral and anionic nucleophiles at the same basicity (Figure 2).

Kawabe measured a rate of 8×10^{-5} M^{-1} s^{-1} for the reaction of Et_3N with $PhCH_2Cl$ in Me_2SO at 25 °C.[23] Extrapolation of the Cb^-/Pz^- line [$\log k = 0.321(pK_a) - 6.88$] to the pK_a of Et_3N^+H in Me_2SO (9.0[24]) gives us an expected rate for a nitranion of 1×10^{-4} M^{-1} s^{-1}, a value only slightly greater than the rate constant observed for Et_3N. Since quinuclidine reacts 57–705-fold faster than Et_3N, depending on the alkyl halide,[25,26] this comparison

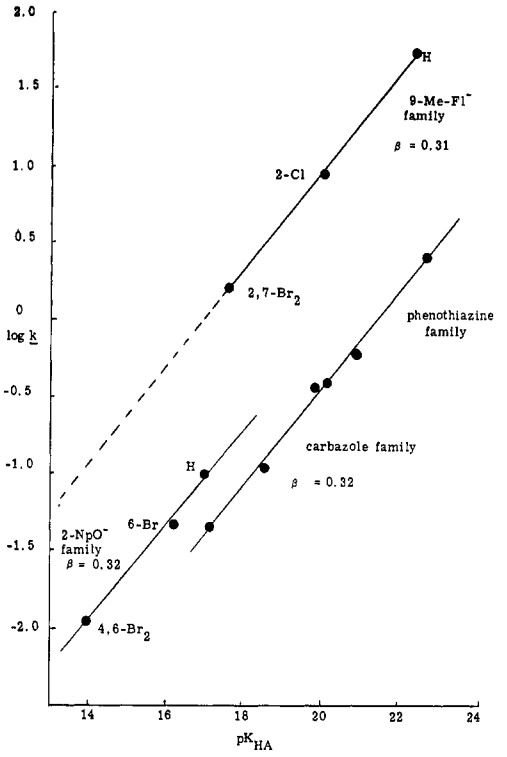

Figure 3. Plot of log k vs. pK_{HA} for nitranion, oxanion, and carbanion nucleophiles reacting with $PhCH_2Cl$ in Me_2SO at 25 °C.

implies, however, that an unhindered neutral nucleophile would be $\sim 10^2$ 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_2SO 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_2SO,[23,27] Haberfield has shown that rates in MeOH and DMF are nearly equal,[28] and Zoltewicz has found rates in Me_2SO to be 7-fold faster than those in $PhNO_2$.[29] We have used these correction factors to estimate rate constants in Me_2SO at 25 °C for pyridine,[28,30] n-$BuNH_2$,[27a] $PhNMe_2$,[30a] and $PhNH_2$[30b] reacting with $PhCH_2Cl$ 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_2SO 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^-, Pz^-), carbanions (9-methylfluorenides),[12] and oxanions (2-naphthoxides)[13] reacting with $PhCH_2Cl$ in Me_2SO solution at 25 °C is shown in Figure 3. The slopes of the lines

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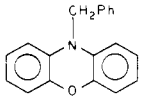
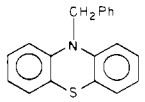
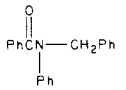
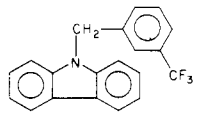
(31) Comparisons of our β_{Nu} values for nitranions with those obtained previously for alkylations of arylamines or pyridines would not be meaningful because the rate data in the solvent of choice have always been compared with pK_a data in water.

Table III. Characterization of Products from Reactions of Nitranions with Benzyl Halides in Me_2SO Solution

product	yield,[a] %	reaction time[b]	mp, °C	^1H NMR, δ
Ph_2NCH_2Ph	88	0.5 h	88–89 (EtOH) (lit.[c] 86.5–87)	4.9 (2 H, S, CH_2), 6.8–7.3 (15 H, m)
	86	3 min	126–127 °C (EtOH)[d]	4.7 (2 H, s, CH_2), 6.1–6.8 (8 H, m, phenoxazine H), 7.2 (5 H, s, phenyl H)
	96	5 min	91–92 (EtOH) (lit.[e] 91–92)	4.9 (2 H, s, CH_2), 6.3–7.3 (13 H, m)
	97	45 h	104.5–105 (hexane) (lit.[f] 105)	5.1 (2 H, s, CH_2), 6.7–7.4 (15 H, m)
	90	0.5 h	90–92 (EtOH)[g]	5.4 (2 H, s, CH_2), 6.9–7.5 (12 H, m)

[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 (phenoxazinyl 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-$CF_3C_6H_4CH_2\cdot$, 46%).

are nearly the same ($\beta_{Nu} \simeq 0.32$), 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 $PhCH_2Cl$ 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 10^3–10^5 less reactive than ions derived from second-row donor atoms, such as benzenethiolate ions.[20] The order C$^-$ > O$^-$ > N$^-$ is unusual in that it follows neither the order of electronegativities (O > N > C) nor the order of polarizability of donor atoms (C$^-$ > N$^-$ > O$^-$). The differences in reactivities are not large, however, and are substrate dependent. For example, for S_N2 reactions between *n*-PrOTs and these same anions the order changes to O$^-$ > N$^-$ > C$^-$.[21]

The constancy of β_{Nu} for nitranions, as well as that for carbanions, over wide ranges of basicity is another significant point that emerges from this research. If β_{Nu} 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.[32]

Conclusions

1. The nucleophilicities of nitranions derived from carbazole (**1**), phenothiazine (**7**), and diphenylamine (**8**) are remarkably similar in reactions with benzyl chloride to those of 9-R-fluorenyl (**2**) and α-cyanoaryl carbanions, suggesting that nitranions use p-orbital electrons, as do carbanions, for bonding in S_N2 reactions, instead of the lone-pair electrons in the sp^2 orbital.

2. Differences in size, shape, charge distribution, aromaticity, or "antiaromaticity" of the ions turn out to introduce little or no effect on nucleophilicity when comparisons are made at the same basicity by means of Brønsted plots (Figures 1–3).

3. Solvation effects apparently change monotonically with basicity, as measured by pK_a values in Me_2SO solution, and nucleophilicity in Me_2SO solution is directly related to basicity.

4. Enhanced solvation effects on certain para substituents have been observed to cause deviations in Brønsted plots. It appears likely that anions with different donor atoms, such as nitranions and carbanions, are solvated to different degrees which causes differences in their nucleophilicities when compared at the same basicities.

5. Neutral nitrogen nucleophiles are more reactive than nitranions of the same basicity by a factor of 10–100.

(32) It is possible that β may be determined by factors other than the fraction of charge transferred. For example, we have suggested that the height of the activation barrier may also be important.[33]

Experimental Section

Materials. Carbazole, 13*H*-dibenzo[*a,i*]carbazole, diphenylamine, 3-chlorodiphenylamine, phenothiazine, 2-chlorophenothiazine, phenoxazine, iminodibenzyl, and iminostilbene were commercially available and were recrystallized or distilled before use. Acetanilide,[34] benzanilide,[34] 3-chlorocarbazole,[35] 3,6-dibromocarbazole,[36] 3,7-dibromophenothiazine,[37] 3-*p*-tosylphenothiazine,[38] phenothiazine 5,5-dioxide,[39] and 4,4′-dibromodiphenylamine[40] were prepared as described in the literature. 3,5-$Br_2C_6H_3NHEt$ was prepared by $LiAlH_4$ reduction of 3,5-$Br_2C_6H_3NHCOCH_3$.[41] 1,2,3,4-Tetrahydroquinolin-2-one was prepared by H. Fried.[42]

Rates were measured by following the decay of the colored nitranion by UV–vis spectroscopy as described before.[12]

Acidity measurements were made by the overlapping indicator method described previously.[43]

Solvent. Anhydrous Me_2SO, purified as described earlier,[43] was used as solvent in all acidity and rate measurements.

Product studies for five nitranions reacting with $PhCH_2Cl$ or m-$CF_3C_6H_4CH_2Cl$ were carried out by using the method outlined in an earlier paper.[12] Characterization of these products is given in Table III.

Acknowledgment. This work was supported by grants from the National Science Foundation. A generous supply of Me_2SO was donated by the Chemical Products Division of Crown-Zellerbach, Vancouver (Orchards), Washington.

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Registry No. 1, 23560-25-0; **3**, 89486-33-9; **7**, 76069-04-0; **8**, 61057-05-4; **9**, 52890-26-3; **10**, 89486-34-0; **11**, 76069-03-9; **13**, 89486-35-1; **14**, 89486-36-2; **15**, 89486-37-3; **16**, 61057-08-7; **17**, 61057-09-8; 3-$ClC_6H_4NPh^-$, 78525-46-9; $(4\text{-}BrC_6H_4)_2N^-$, 79990-95-7; $PhCON(Ph)CH_2Ph$, 19672-91-4; $m\text{-}CF_3C_6H_4CH_2Cl$, 705-29-3; $PhCH_2Cl$, 100-44-7; Ph_2NCH_2Ph, 606-87-1; 3-chlorocarbazole anion, 80010-03-3; 3,6-dibromocarbazole anion, 79990-92-4; 2-chlorophenothiazine anion, 79990-93-5; 3,7-dibromophenothiazine anion, 79990-94-6; *N*-benzylphenoxazine, 89486-38-4; *N*-(*m*-(trifluoromethyl)benzyl)carbazole, 89486-39-5; *N*-benzylphenothiazine, 58478-75-4.

Total Synthesis of Anhydrocannabisativene

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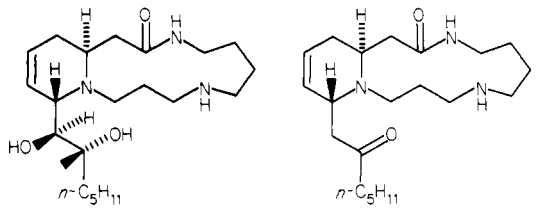
Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received November 25, 1983*

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**.

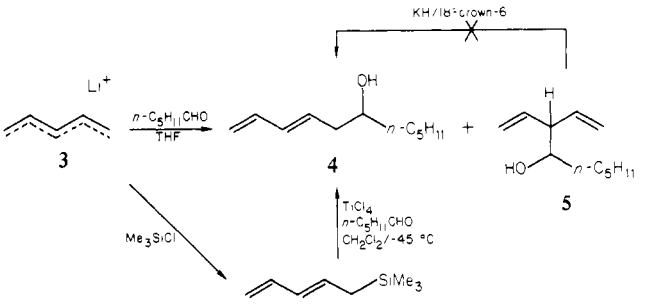
The common marijuana plant *Cannabis sativa* is the source of several non-cannabinoid nitrogeneous compounds including the interesting spermidine alkaloids cannabisativene (**1**) and anhydrocannabisativene (**2**).[1,2] In recent years there has been considerable interest in developing synthetic routes 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.



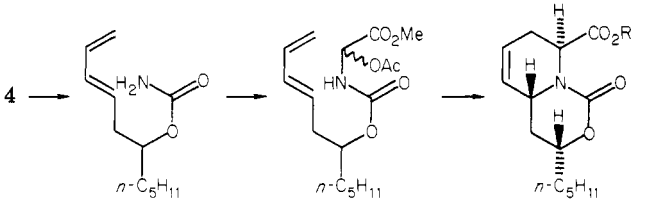
1 2

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**)[7,8] 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 Seyferth[10a] and Sakurai.[10b] 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%).[10]

Scheme I



Scheme II



7 8 9, R = Me; 10, R = H

This alcohol was next transformed to the corresponding carbamate **7** by using the cyanate procedure of Loev and Kormendy[11] (Scheme II) in 95% yield. The carbamate reacted with anhydrous

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