tween structures with different number of "long" pairings. Namely, the positive nonadjacent $p_{ik}$ contributions of a more excited structure may more than compensate for a decrease in $K$ index of a particular structure with fewer nonadjacent pairings but in which negative nonadjacent contributions are present.

The application of the outlined procedure to other molecules and their valence structures, including also excited valence formulas, may reveal additional interesting features, despite the admittedly somewhat arbitrary definition of the Kekulé index. An important result of the present work is that the proposed index makes it possible to investigate intimate relations between MO wave functions and VB valence structures. The suitability of this or another index for classification of VB structures should be tested systematically on extensive material. Tables I–IV contain information on some 20 molecules, which are selected for illustrative purposes. However, the conclusions are drawn and tested on altogether some 100 molecules and supplementary tables will be documented elsewhere.[16] The molecules represent a structurally diverse class of compounds: condensed benzene rings, nonbenzenoid alternant, and nonalternate hydrocarbons. Other definitions of an index to relate MO wave functions and VB structures, in fact MO wave functions associated with the latter, are possible.[22] Also "Kekulé solutions" consisting of ethylene-like molecular orbitals which are associated with each double bond of the given Kekulé structure are not the only, and even perhaps not the most opportune form for localized orbitals.[6] Some refinements and modifications can therefore be expected to be stimulated by the present work, and it remains to be seen to what extent they can introduce some novel features and enrich the present analysis.

**Acknowledgment.** We express our thanks to Professor C. A. Coulson and Professor J. Koutecký for their interest in this work, examination of the manuscript, and useful comments which have led to improved presentation of the material. Also we thank Drs. W. J. Campion and J. W. Sutherland who discussed the material and gave valuable advice on preparation of the manuscript. One of the authors (M. R.) is grateful to Professor E. Bright Wilson, Jr., for his support while part of the work was completed at Harvard University.

---

(22) Professor J. Koutecký (Freie Universitat Berlin, Germany) [private communication, 1973] considers a mean of bond orders associated with the pairs of carbon atoms connected with double bonds in the Kekulé structures as an alternative index. So modified index is simply related to Kelulé index $K$, in particular for alternate systems. We average $(1 + p_{ik})^{1/2}$ while modified index is the simple average of $p_{ik}$, both taken over the same set of paired atoms characterizing the particular valence structure. For neighboring atoms $p_{ik}$ are less than one; therefore the Kekulé index $K$ will always be larger than the simple average value of $p_{ik}$. For individual $p_{ik}$ contributions the increment is decreasing as $p_{ik}$ increases in the interval of interest. From the monotonic relationship of individual terms which contribute to the sum representing $K$ values or the modification of $K$, one may expect that essentially the same conclusions would be drawn. The situation may be somewhat different for nonalternate systems and excited valence structures when the simple monotonic behavior between the two schemes may break down.

---

# Acidity of Hydrocarbons. L. Equilibrium Ion Pair Acidities of Thiophene, Benzothiophene, Thiazole, Benzothiazole, and Benzofuran toward Cesium Cyclohexylamide in Cyclohexylamine[1]

**A. Streitwieser, Jr.,* and P. J. Scannon**

*Contribution from the Department of Chemistry, University of California,*
*Berkeley, California 94520.*
*Received April 2, 1973*

**Abstract:** Relative equilibrium ion pair acidities have been determined for several heterocyclic compounds by reference to hydrocarbon indicators having colored cesium salts in cyclohexylamine. p$K$ values for the 2 position (on a per-hydrogen basis) relative to 9-phenylfluorene = 18.49 are: thiophene, 38.42 ± 0.06; benzothiophene, 37.05 ± 0.23; benzothiazole, 28.08 ± 0.11; thiazole, 29.50 ± 0.11; benzofuran, 36.84 ± 0.18.

In recent years, there has been considerable interest in kinetic acidities of azolium salts,[2] azoles,[3] and five-membered monoheterocycles.[4] However, inconsistencies frequently exist in the relative rates observed. For example, in EtOH–EtOK, thiophene exchanges faster than furan,[4b] but benzoxazole exchanges faster than benzothiazole.[3a] Additional inconsistencies exist when comparisons are made of relative rates of compounds in different solvent systems. In $Me_2SO$–*t*-BuOK, 5-methoxythiophene-*2-d* exchanges slower than thiophene-*2-d*,[4a] whereas in MeOD–MeOK the order reverses.[5]

All previous available data relate to kinetic acidities, and because of the biological importance of these and related heterocycles,[2a] measures of equilibrium p$K_a$'s

---

(1) This research was supported in part by National Institutes of Health, U. S. P. H., Grant No. GM-12855.

(2) *Cf.* (a) R. Breslow, *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962); (b) P. Haake, L. Bauscher, and W. Miller, *J. Amer. Chem. Soc.*, **91**, 1113 (1969); (c) R. Coburn, J. Landesberg, D. Kemp, and R. Olofson, *Tetrahedron*, **26**, 685 (1970).

(3) (a) N. Zatzepina, Y. Kaminsky, and I. Tupitsyn, *Reakt. Sposobnost Org. Soedin.*, **4**, 433 (1967); (b) D. Brown and P. Ghosh, *J. Chem. Soc. B*, 270 (1969); (c) R. Olafson, J. Landesberg, K. Houk, and J. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966).

(4) (a) A. Shatenshtein, A. Kamrad, I. Shapiro, Yu. Ranneva, and E. Zvyaginseva, *Dokl. Akad. Nauk USSR*, **168**, 364 (1966); (b) N. Zatzepina, Y. Kaminsky, and I. Tupitsyn, *Reakt. Sposobnost Org. Soedin.*, **6**, 753 (1969).

(5) N. Zatzepina, Y. Kaminsky, and I. Tupitsyn, *Reakt. Sposobnost Org. Soedin.*, **6**, 448 (1969).

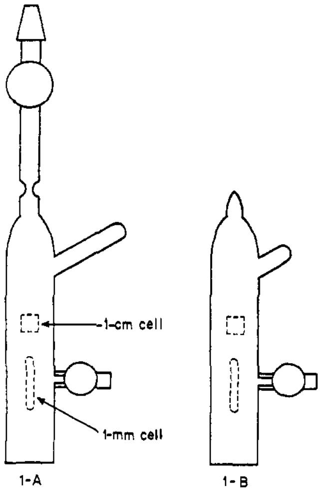


Figure 1. Apparatus for equilibrium acidity measurements.

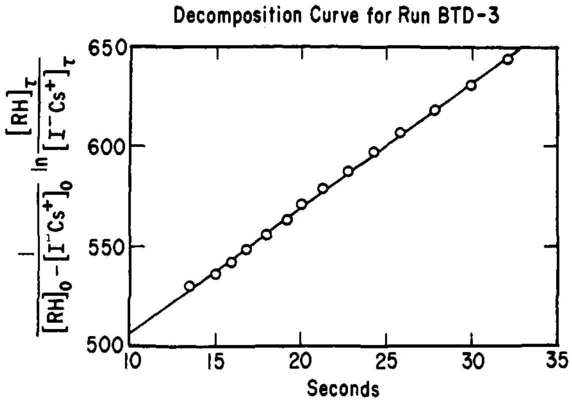


Figure 2. Typical decomposition kinetics for an assumed second-order reaction between the indicator anion, $I^-Cs^+$ (an experimental quantity), and the heterocyclic compound studied, RH. The concentration of RH, $[RH]_t = [RH]_0 - [I^-Cs^+]_0 + [I^-Cs^+]_t$. For this case, $k_2 = 6.3\ M^{-1}\ sec^{-1}$ and the intercept = 443 with $r = 0.999$.

of azoles and monoheterocycles are desirable. For several years we have measured equilibrium ion pair acidity differences using cesium salts of conjugated hydrocarbons in eq 1.[6,7] In the normal application of this method both carbanions are highly delocalized and colored and, by choosing systems with sufficiently different absorption spectra, the concentrations of both carbanions can be measured.

$$RH + I^-Cs^+ \overset{K_{rel}}{\rightleftharpoons} R^-Cs^+ + IH \qquad (1)$$

For those systems in which one hydrocarbon gives a localized and colorless anion this technique requires modification. In principle, one hydrocarbon in known concentration in the presence of its measurable carbanion serves as the indicator. Addition of a known amount of a second carbon acid, whose conjugate base is invisible, gives a measurable decrease in the indicator carbanion concentration from which the equilibrium constant is evaluated. In practice, this method is very sensitive to impurities, and great care must be taken to purify and dry all reagents and equipment used. The application of this method to phenylacetylene and *tert*-butylacetylene and to fluorinated benzenes has been communicated.[8] In this paper we apply the method to several heterocyclic aromatic compounds, and give full details of the general procedure.

## Experimental Section

Benzofuran, thiophene, and benzothiophene were purchased from Aldrich Chemical Co. Thiazole was purchased from Pfaltz and Bauer, Inc. Benzothiazole was the kind gift of Edward Gordon and Professor Donald Noyce of the University of California, Berkeley. Since all of these compounds are liquid at room temperature or are low melting, purification was easily accomplished by preparative gas chromatography. Thiophene and benzothiophene were purified on 20% Apiezon N on 60–80 mesh Chromasorb W. Benzothiazole was purified on 20% QF-1 on firebrick, and thiazole and benzofuran were purified on 20% SF-96 on 60–80 mesh Chromosorb W. All indicators were either gas chromatographed on the QF-1 column if liquid, or recrystallized and sublimed if solid. All liquids once purified were dried on molecular sieves and stored in tubes under positive argon pressure capped with heavy duty serum caps for removal of liquid by syringe as needed.

The basic procedure for an equilibrium run is summarized as follows. A known amount of indicator hydrocarbon was added through the side arm of the reactor 1-A in Figure 1. The side arm was sealed off and the reactor was weighed; the reactor was pumped out on a vacuum line, and dried cyclohexylamine was vacuum-transferred in. The reaction vessel was then pressured with argon, the top stopcock was sealed off at the constriction to yield reactor 1-B (Figure 1), and the two parts were weighed. The reactor 1-B was then taken to a glove box with a recirculating argon atmosphere (Vacuum Atmospheres Co.), and cesium cyclohexylamide was added until the absorbance from the indicator carbanion was approximately 1 absorbance unit in a 1-mm cell. Occasionally the 1-cm cell was used; for this reason the reactor contains cells of both sizes. The reactor was then taken from the glove box, and the spectrum was obtained on a Perkin-Elmer 202 uv-visible spectrophotometer after allowing the reactor to equilibrate to the spectrometer temperature of 34 ± 0.5°. The side stopcock of the reactor was then opened, a known amount of heterocycle was injected, and the spectrum was again taken. The observed general decrease in absorbance of the indicator carbanion results both from conversion of the heterocycle to its invisible anion and to reaction with adventitious moisture and other impurities admitted with the heterocycle. The contributions of impurities were minimized by extensive purification and drying of all reagents and equipment.

A complication to this procedure exists because most of these heterocycles decompose in the presence of indicator anion. Azoles have been shown to undergo addition at the 2 position followed by ring opening in the presence of either sodium hydroxide or *n*-butyllithium.[9] 3-Lithiothiophene,[10] 3-lithiobenzothiophene,[11] and 3-lithiobenzofuran[12] have been shown to undergo ring opening. Because of this decomposition, absorbance of the indicator anion was recorded as a function of time on an additional recorder held at the $\lambda_{max}$ of the indicator anion. The resultant plot was then extrapolated to zero time to yield the indicator anion concentration at equilibrium, $(I^-Cs^+)_e$. A typical second-order kinetic plot resulting from such a decomposition is shown in Figure 2. The difference between the concentrations of the indicator anion initially, $(I^-Cs^+)_0$, and at equilibrium, $(I^-Cs^+)_e$, yields the heterocycle anion concentration at equilibrium, $(R^-Cs^+)_e$. Because the initial weights of RH and IH are known, all quantities in eq 2 are established. The $pK_a$ of the heterocycle is calculated by eq 3.

---

(6) (a) A. Streitwieser, Jr., J. I. Brauman, and J. Hammons, *J. Amer. Chem. Soc.*, **87**, 384 (1965); (b) A. Streitwieser, Jr., E. Ciuffarin, and J. Hammons, *ibid.*, **89**, 63 (1967); (c) A. Streitwieser, Jr., C. J. Chang, and D. M. E. Reuben, *ibid.*, **94**, 5730 (1972).

(7) A. Streitwieser, Jr., J. R. Murdoch, G. Hafelinger, and C. J. Chang, *J. Amer. Chem. Soc.*, **95**, 4248 (1973).

(8) (a) A. Streitwieser, Jr., and D. M. E. Reuben, *J. Amer. Chem. Soc.*, **93**, 1794 (1971); (b) A. Streitwieser, Jr., P. J. Scannon, and H. M. Niemeyer, *ibid.*, **94**, 7936 (1972).

(9) R. Elderfield, Ed., "Heterocyclic Compounds," Vol. 5, Wiley, New York, N. Y., 1957.

(10) P. Moses and S. Gronowitz, *Ark. Kemi*, **18**, 119 (1962).

(11) R. Dickinson and B. Iddon, *J. Chem. Soc. C*, 3447 (1971).

(12) H. Gilman and S. Melstrom, *J. Amer. Chem. Soc.*, **70**, 1655 (1948).

**Table I.** Experimental Equilibrium Data for the 2 Position of Some Heterocyclic Compounds in Cyclohexylamine at 34°

| Run[a] | Indicator[b] | $[IH]_0 \times 10^3$, $M$ | $[I^-Cs^+]_e \times 10^4$, $M$ | $[RH]_0 \times 10^3$, $M$ | $[R^-Cs^+]_e \times 10^4$, $M$ | $K_{rel}$ | $pK_a^{RH}$[c] |
|---|---|---|---|---|---|---|---|
| T-25 | PPT | 6.842 | 1.771 | 3.700 | 1.322 | 2.092 | 38.41 |
| T-26 | PPT | 8.742 | 2.663 | 8.539 | 2.648 | 1.528 | 38.55 |
| T-27 | PPT | 11.283 | 3.221 | 8.424 | 3.666 | 2.322 | 38.36 |
| T-28 | PPT | 9.205 | 2.190 | 11.328 | 4.232 | 2.388 | 38.35 |
| BT-5 | BDMPM | 4.229 | 1.698 | 5.015 | 0.150 | 0.143 | 37.14 |
| BT-7 | BDMPM | 0.181 | 0.178 | 2.091 | 0.083 | 0.074 | 34.43 |
| BT-8 | BDMPM[d] | 0.249 | 0.275 | 1.573 | 0.112 | 0.116 | 37.43 |
| BTD-2 | BDMPM | 4.382 | 2.092 | 4.535 | 0.467 | 0.415 | 36.68 |
| BTD-3 | BDMPM | 9.986 | 2.079 | 7.964 | 0.241 | 0.286 | 36.84 |
| BTD-5 | BDMPM | 0.283 | 0.086 | 1.850 | 0.076 | 0.263 | 36.88 |
| BTD-6 | BDMPM | 1.465 | 1.815 | 2.293 | 0.189 | 0.118 | 37.23 |
| BTD-9 | BDMPM | 3.331 | 1.601 | 4.973 | 0.419 | 0.327 | 36.77 |
| BTD-12 | BDMPM | 5.097 | 2.329 | 9.340 | 0.271 | 0.121 | 37.22 |
| BTAZ-5 | PX | 2.933 | 0.818 | 3.324 | 1.553 | 1.724 | 28.25 |
| BTAZ-9 | DMPDA | 3.955 | 2.809 | 0.737 | 0.417 | 0.784 | 28.12 |
| BTAZ-12 | DMPDA | 3.483 | 0.891 | 5.652 | 1.486 | 1.029 | 28.00 |
| TAZ-1[e] | DMPDA | 5.313 | 4.092 | 17.018 | 0.521 | 0.037 | 29.44 |
| TAZ-2[e] | BDPM | 3.626 | 0.148 | 10.018 | 1.271 | 3.082 | 29.68 |
| TAZ-3[e] | BBPM | 2.889 | 0.015 | 7.808 | 0.538 | 27.307 | 29.39 |
| BF-3 | BDMPM | 4.072 | 1.629 | 8.427 | 0.356 | 0.204 | 36.99 |
| BF-5 | BDMPM[d] | 3.095 | 3.444 | 3.636 | 1.228 | 0.554 | 36.55 |
| BF-6 | BDMPM[d] | 4.721 | 2.189 | 4.842 | 0.505 | 0.434 | 36.66 |
| BF-7 | BDMPM | 5.135 | 2.138 | 3.470 | 0.166 | 0.221 | 36.95 |
| BF-8 | BDMPM | 5.495 | 2.427 | 12.672 | 0.530 | 0.181 | 37.04 |

[a] T = thiophene, BT = benzothiophene, BTD = benzothiophene-*3-d*,[14] BTAZ = benzothiazole, TAZ = thiazole, BF = benzofuran. [b] PPT = *p*-phenyltoluene, $pK_a$ = 38.73; BDMPM = bis(2,4-dimethylphenyl)methane, $pK_a$ = 36.30; PX = 9-phenylxanthene, $pK_a$ = 28.49; DMPDA = 9,9-dimethyl-10-phenyl-9,10-dihydroanthracene, $pK_a$ = 28.01; BDPM = biphenylyldiphenylmethane, $pK_a$ = 30.17; BBPM = bis-*p*-biphenylylmethane, $pK_a$ = 30.83 (ref 7). [c] $pK_a$'s are listed per hydrogen. [d] All runs using BDMPM were accomplished at $\lambda_{max}$ 448 nm except for runs BT-8, BF-5, and BF-6 for which $\lambda_{max}$ 494 nm was used. [e] Thiazole did not appreciably decompose in strong base over a 20-min period. All other compounds decomposed and $(I^-Cs^+)_e$ is the value obtained by back extrapolation to $t = 0$.

$$\frac{[IH]_e[R^-Cs^+]_e}{[RH]_e[I^-Cs^+]_e} = \frac{([IH]_0 - [I^-Cs^+]_e)([I^-Cs^+]_0 - [I^-Cs^+]_e)}{([RH]_0 - [I^-Cs^+]_0 + [I^-Cs^+]_e)[I^-Cs^+]_e} = K_{rel} \quad (2)$$

$$pK_a^{RH} = pK_a^{IH} + pK_{rel} \quad (3)$$

The experimental data are listed in Table I. 4-Phenyloxazole, benzoxazole, and furan were also studied by this technique, but experimental difficulties were too great to obtain useful results. Benzothiophene-*3-d* was synthesized by refluxing 3-iodobenzothiophene in dioxane, $D_2O$, and zinc dust.[13,14] 3-Iodobenzothiophene was synthesized by refluxing benzothiophene in benzene in the presence of iodine and yellow mercuric oxide.[15]

## Discussion

Repeat runs by the general procedure gave results with excellent precision; the p*K* values have uncertainties of ±0.1–0.2 unit. That this uncertainty reflects accuracy as well as precision was established in two cases where it was feasible to use two different indicator anions. In these cases, both indicators gave concordant results. This agreement carries a further important implication. The experimental procedure measures an equilibrium in which an indicator carbanion is converted to an invisible product. The equilibrium involved is *assumed* to be that of proton transfer; the demonstrated dependence of the equilibrium constant on the p*K* of the indicator is important evidence that this assumption is valid.

The resultant average p*K* values are summarized in Table II and are assumed to pertain only to the 2 or α hydrogens in these heterocycles. This assumption is required because we have no direct way of establishing the hydrogens involved. Nevertheless, the assumption appears to be well founded on the basis of other results. For example, the kinetic acidities of the 2 hydrogens for all of these heterocycles are far greater than any of the other positions.[2–4] Metalation experiments give the same general result;[16] in particular, benzofuran[16] and benzothiophene[17] are metalated by *n*-butyllithium in the 2 position rather than in the benzene ring.

**Table II.** Ion Pair $pK_a$'s for the 2 Position in Cyclohexylamine at 34°

| Compd | $pK_a$[a,b] |
|---|---|
| Thiophene | 38.42 ± 0.06 |
| Benzothiophene | 37.05 ± 0.23 |
| Benzothiazole | 28.08 ± 0.11 |
| Thiazole | 29.50 ± 0.11 |
| Benzofuran | 36.84 ± 0.18 |

[a] Error limits calculated from experimental averages. [b] $pK_a$'s are per hydrogen.

The p*K*'s listed in Table II refer to eq 1 in which the standard, 9-phenylfluorenes, is assigned a p*K* = 18.49. Although this value for 9-phenylfluorene corresponds approximately to the dilute aqueous solution standard state, the aqueous solution p*K*'s for the heterocycles no longer necessarily correspond to the

---

(13) National Research Council, Canada British Patent 822,617 (1959); *Chem. Abstr.*, 54, 10857g (1960).

(14) Benzothiophene decomposed very rapidly in the presence of the indicator anion and thus was difficult to study. Benzothiophene-*3-d* was synthesized with the hope that the deuterium isotope effect might slow down the decomposition. However, proton abstraction apparently is not rate determining because benzothiophene-*3-d* decomposed at essentially the same rate as benzothiophene.

(15) R. Gaertner, *J. Amer. Chem. Soc.*, 74, 4950 (1952).

(16) H. Gilman and J. W. Morton, Jr., *Org. React.*, 8, 258 (1954).

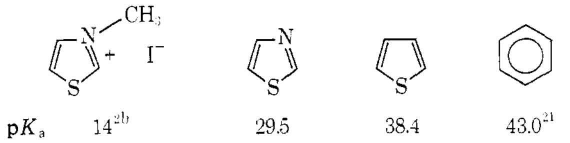
(17) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, 72, 2788 (1950); 74, 664 (1952).

values in Table II. Highly delocalized carbanions appear to involve little specific solvation and the corresponding hydrocarbons have acidities whose relative values are not seriously solvent dependent. For such hydrocarbons the ion-pair acidities given in the cesium cyclohexylamide system appear to reflect relative aqueous p$K$'s.[18] However, the anions from the heterocycles are localized and for such compounds ionic acidities are generally lower than ion-pair acidities relative to hydrocarbons with delocalized carbanions.[7,19] On the other hand, localized anions are expected to be more stabilized by hydrogen bonding than delocalized anions and this effect will at least partially compensate for lack of ion-pair stabilization in water. Thus, the relative ion-pair acidities as given in cyclohexylamine might not be too different from the aqueous ionic acidities involving localized carbanions stabilized by hydrogen bonding with water. In this regard, we note that the relative kinetic acidities of benzene and fluorinated benzenes are the same in methanol as in cyclohexylamine.[8b] On the other hand, we expect the free ion p$K$'s to be relatively higher in polar aprotic solvents such as $Me_2SO$.

The ion pairs in the cyclohexylamine system involve $Cs^+$ as cation and should be well described as contact ion pairs with relatively large anion–cation distances. Accordingly, the present equilibrium acidity results should serve adequately for discussion of structural effects on heterocycle acidity.

Comparing benzothiophene to thiophene and benzothiazole to thiazole, the benzo group enhances acidity by 1.4 p$K$ units. This result agrees well with the p$K$ data of Corey, Konig, and Lowry[20] on cyclic disulfones for which the benzo group was found to enhance acidity by 1.3 p$K$ units in $H_2O$ at 25°. Comparing thiophene to thiazole and benzothiophene to benzothiazole, the aza effect (*i.e.*, N *vs.* CH) is found to enhance acidity by 9.0 p$K$ units. Comparison of benzothiophene to benzofuran indicates that the oxygen enhances thermodynamical acidity more than sulfur by 0.2 p$K_a$ unit. Although the available kinetic data for thiophene and furan contradict this result,[4a,b] the present results indicate that the electronegativity effect of oxygen in stabilizing a carbanion is slightly more important than any stabilizing interaction of the carbanion with sulfur.

The ion-pair p$K_a$ of benzene has recently been determined as 43.0 ± 0.1 per hydrogen in cyclohexylamine at 34°;[8b] Haake has estimated the p$K_a$ of *N*-methylthiazolium iodide to be 14 in water.[2b] These p$K_a$'s in conjunction with the data in Table II allow a derivation of the various effects that enhance the acidity of the thiazolium salt over benzene. The following series indicates that the positive charge is the largest contributor (15.5 p$K_a$ units) in enhancing the acidity of the thiazolium salt. The aza effect ranks second in importance (9.0 p$K_a$ units), whereas the sulfur in thiophene has an enhancement effect of 4.6 p$K$ units relative to benzene. Although oxygen appears to enhance acidity slightly more than sulfur, thiazole in the presence of indicator anion did not appreciably decompose over a 20-min period whereas the oxazoles studied decomposed almost instantly. This result confirms Haake's suggestion[2b] that Nature uses a thiazolium salt as vitamin B-1 despite a lower acidity than the corresponding oxazolium salt because the conjugate base derived from the oxazolium salt is unstable.



---

[18] M. Szwarc, P. C. Mowery, and A. Streitwieser, Jr., in "Ions and Ion Pairs in Organic Reactions," Vol. 2, M. Szwarc, Ed., Wiley, New York, N. Y., in press.

[19] J. R. Murdoch and A. Streitwieser, Jr., *Intra-Sci. Chem. Rep.*, in press.

[20] E. Corey, H. Konig, and T. Lowry, *Tetrahedron Lett.*, 515 (1962).