# Participation of Heterocyclic Moieties in the Solvolytic Rearrangement of β-Arylethyl Tosylates[1]

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**Abstract:** The solvolytic rearrangement of seven β-heteroarylethyl tosylates has been studied kinetically in trifluoroethanol and acetic acid. For 2-(2-thienyl)ethyl tosylate (**3**) the rate is faster by a factor of 3 than that of 2-phenylethyl tosylate (**1**) in acetic acid, by a factor of 4 in formic acid, and by a factor of 6 in TFE. In acetic acid, **3** shows 80% scrambling as determined by isotope labeling, while scrambling is essentially complete in TFE. Scrambling for **1** in TFE is also almost complete. 2-(2-Furyl)ethyl tosylate shows 83 ± 3% scrambling in TFE. Rates of the participating pathway ($Fk_\Delta$) are deduced for all seven compounds studied. These rates do not correlate with either $\sigma$ or $\sigma^+$ values, but the Yukawa–Tsuno equation gives good results, which supports the concept that the transition state is an unsymmetrically bridged system leading to the arenonium ion intermediate.

The use of solvolytic reactivity has been shown to be a useful probe for the capabilities of electron-rich heterocyclic systems to promote reactions involving electron-deficient transition states. Hill, *et al.*,[3] have computed effective substituent constants for a wide variety of heterocyclic systems from such solvolytic reactivity. In parallel studies from these laboratories, we have investigated the transmission of substituent effects across furan,[4] thiophene,[5] and benzofuran[6] systems.

In the present study we extend these investigations to an examination of the effectiveness of such electron-rich aromatic moieties in the solvolytic rearrangement which accompanies the solvolysis of β-arylethyl systems. A very limited number of such systems have been previously studied. Julia, Sliwa, and Caubere[7] and Closson, *et al.*,[8] have examined the solvolysis of 2-(3-indolyl)ethyl tosylate; they observed complete scrambling of the carbons of the side chain during the solvolysis, which is very much more rapid than that of 2-phenylethyl tosylate (**1**). Participation by the ferrocenyl group accelerates the rate of solvolysis of 2-ferrocenylethyl tosylate, but, because of the unique geometry of the system, no scrambling ensues.[9] Azulene has recently been shown to be remarkably effective as a neighboring aromatic moiety.[10]

## Results

The solvolysis of 2-(2-furyl)ethyl tosylate (**2**) in acetic acid shows a very modest increase in rate over that obtained for the acetolysis of 2-phenylethyl tosylate; on the other hand, the solvolysis of 2-(2-thienyl)ethyl tosylate (**3**) shows a somewhat greater rate acceleration.

Table I gives additional results of rate measurements for the acetolysis of other heterocyclic systems.

**Table I.** Titrimetric Rate Constants for the Buffered Acetolysis of β-Arylethyl Tosylates[a]

| Compd solvolyzed Ar = | Temp, °C | $10^6k$, sec$^{-1}$ | Rel rates |
|---|---|---|---|
| Phenyl (**1**) | 75.1 | 0.644 ± 0.02 | (1.00) |
| | 90.0 | 2.23 ± 0.05 | |
| | 109.6 | 13.8 ± 0.2 | |
| 2-Thienyl (**3**) | (75.0)[b] | 1.86 | 2.9 |
| | 75.2 | 1.89 | |
| | 90.0 | 8.04 | |
| | 109.6 | 54.5 | |
| 5-Methyl-2-thienyl (**4**) | 75.0 | 13.7 | 21.3 |
| | 109.6 | 356 | |
| 2-Furyl[c] (**2**) | 75.0 | 0.939 ± 0.015 | 1.46 |
| Ferrocenyl[d] | 75.0 | 899 | 1,400 |
| 3-Indolyl[e] | 75.0 | 4630 | 7,200 |
| Azulyl | | | 68,000[f] |

[a] Tosylate, 0.025 *M*; sodium acetate, 0.035 *M*. [b] Extrapolated. [c] Experiment by D. A. Meyers. [d] Reference 9. [e] Reference 8. [f] Quoted ratio at 25°, ref 10.

In formic acid–sodium formate, the rate ratio between 2-(2-thienyl)ethyl tosylate and 2-phenylethyl tosylate is increased; the formolysis of 2-(2-furyl)-ethyl tosylate gives an approximate rate only, as appreciable decomposition occurs in this solvent for the acid-sensitive furan species (Table II).

The greater reactivity of the thiophene than of the furan derivative in acetolysis is surprising when con-

**Table II.** Rate Constants for the Buffered Formolysis of β-Arylethyl Tosylates[a]

| | Temp, °C | $10^5k$, sec$^{-1}$ | Rel rate |
|---|---|---|---|
| Phenyl | 75.2 | 4.38 | 1.0 |
| | 59.8 | 0.789 | |
| Thienyl | 44.8 | 0.615 | 3.9 |
| | 59.8 | 3.47 | |
| | 75.1 | 16.3 | |
| Furyl | 75 | 18.0[b] | 4 |

[a] Tosylate, 0.025 *M*; sodium formate, 0.035 *M*. [b] Approximate value only; decomposition occurs; see text.

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.
(2) National Science Foundation Trainee, 1969–1971.
(3) E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, 91, 7381 (1969).
(4) D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, 34, 1008 (1969); D. S. Noyce and H. J. Pavez, *ibid.*, 37, 2620, 2623 (1972).
(5) D. S. Noyce, G. M. Loudon, and C. A. Lipinski, *ibid.*, 35, 1718 (1970); D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *ibid.*, 37, 2615 (1972).
(6) D. S. Noyce and R. W. Nichols, *ibid.*, 37, 4306, 4311 (1972); D. A. Forsyth and D. S. Noyce, *Tetrahedron Lett.*, 3893 (1972).
(7) M. Julia, H. Sliwa, and P. Caubere, *Bull. Soc. Chim. Fr.*, 3359 (1966).
(8) W. D. Closson, S. A. Roman, G. T. Kwiatkowski, and D. A. Corwin, *Tetrahedron Lett.*, 2271 (1966).
(9) M. J. Nugent, R. E. Carter, and J. H. Richards, *J. Amer. Chem. Soc.*, 91, 6145 (1969).
(10) R. N. McDonald and J. R. Curtis, *ibid.*, 93, 2530 (1971).

sidered in the context of the relative susceptibilities to aromatic substitution observed for furan and thiophene. Marino[11] has carried out a number of studies of competitive substitution reactions; furan is almost invariably more reactive than thiophene. Application of the extended selectivity relationship for a wide variety of reactions to both furan[12] and thiophene[12] reinforces this generalization. From these relationships, "a substituent constant $\sigma_\alpha^+$ relative to the structural modification of a heteroatom for a CH=CH in the benzene ring may be calculated."[13] The value for the 2-furyl system, −0.93, is noticeably more negative than for the 2-thienyl system, −0.79.

Examination of the extent to which rearrangement occurs during the solvolysis of these systems shows that extensive scrambling occurs. In acetic acid, there is 86% scrambling in the products of solvolysis of **2**; from **3**, the products show 80% scrambling. Herein lies an additional complexity. Though **2** shows a smaller rate of reaction in acetic acid, it nevertheless shows as much scrambling as does **3**. This point will be considered further below.

Because of the difficulties encountered with **2** in formic acid, we sought to find an additional solvent for the study of the solvolytic rearrangement which would be more suitable than formic acid but, at the same time, maintain many of the desirable characteristics of formic acid. 2,2,2-Trifluoroethanol (TFE) appears to be such a solvent.[14,15]

Most β-arylethyl tosylates solvolyze at a convenient rate in TFE without significant decomposition over at least 90% reaction. However, the 2-furyl derivative **2** showed extensive decomposition caused by the liberated *p*-toluenesulfonic acid in the solution, prompting the addition of sodium acetate (1.5 equiv) as a buffer. A few additional systems were also studied with buffering sodium acetate for comparison.

In TFE there is a very propitious increase in the spread of relative rates; moreover, the rate of 2-phenylethyl tosylate is substantially more rapid than that of a simple alkyl tosylate.[15] Results of the measurement of the rates of solvolysis of a number of heterocyclic systems in TFE are given in Table III. Again, two or three striking comparisons emerge. Compound **6**, 2-(3-thienyl)ethyl tosylate, is as reactive as **3**, though 3-thienylmethanol derivatives are generally much less reactive than their 2-thienyl counterparts.[3,5,11] A similar unexpected reactivity ratio shows up in considering the two benzothiophene derivatives, **7** and **8**. The reactivity order, phenyl < 2-furyl < 2-thienyl, is the same as in acetolysis. The large rate increases for the β-substituted tosylates over ethyl tosylate are a distinct advantage. The very low nucleophilicity of TFE suppresses the SN2 pathway, while its ionizing ability ($Y$ = 1.04[14]) allows the intramolecularly assisted reaction to proceed at a convenient rate.

Product studies with **1** and **3** show that the primary product in TFE is the β-aryl-β′,β′,β′-trifluorodiethyl ether. In the presence of sodium acetate large proportions of the acetate are formed as well.

**Table III.** Trifluoroethanolysis Rate Constants for β-Substituted Ethyl Tosylates at 75°

| Substituent | Buffer[a] | $10^6 k_t$, sec$^{-1}$ | Rel rate |
|---|---|---|---|
| Hydrogen | | 0.385[b] | 1.00 |
| Phenyl (**1**) | | 4.82 | 12.5 |
| Phenyl | NaOAc | 5.37 | 13.9 |
| 2-Furyl[c] (**2**) | NaOAc | 13.1 | 34.0 |
| 2-Thienyl (**3**) | | 26.3 | 68.3 |
| 2-Thienyl | NaOAc | 32.0 | 83.1 |
| 5-Methyl-2-thienyl (**4**) | | 297 | 771 |
| 5-Bromo-2-thienyl (**5**) | | 3.72 | 9.66 |
| 2-Benzothienyl (**7**) | | 2.21 | 5.74 |
| 3-Thienyl (**6**) | | 29.6 | 76.9 |
| 3-Benzothienyl (**8**) | | 39.2 | 102 |
| *p*-Methylphenyl (**9**) | | 53.1 | 138 |
| *p*-Methoxyphenyl (**10**) | | 339 | 880 |
| *p*-Nitrophenyl (**11**) | | 0.0168[b] | 0.044 |

[a] 0.03 *M*, where present; sulfonate, 0.02 *M*. [b] Calculated from data at other temperatures. [c] Data from ref 15.

Participating rearrangement during the trifluoroethanolysis was further verified by isotope position rearrangement. Specifically labeled tosylates were prepared by deuterium introduction. The results of six such experiments are recorded in Table IV. The large fraction of scrambling, nearly complete randomization, is consistent with the rearrangement pathway, $k_\Delta$, predominating over the unassisted pathway, $k_s$. To be noted, also, is the fact that there is relatively little ion pair return under the conditions which we have used.

Finally, the secondary isotope effects observed are large for α-substitution[15] and apparently near maximum. They compare very favorably with isotope effects which have been reported for formolysis.[16–18]

## Discussion

Attempted correlation of the observed rates of solvolysis of the various heteroarylethyl tosylates which we have studied presents some interesting facets. As these reactions are dominated by the participating pathway, the susceptibility to aromatic substitution might be a good model for such a correlation basis. Recently, a substantive body of information has accumulated with respect to the susceptibility of these heterocyclic systems to electrophilic reactions, both in terms of aromatic substitution and in terms of the solvolysis rates of heteroarylmethylcarbinol derivatives.[3,4,5,11,19] The attempted correlation of the latter with our measured rates from Table III is very poor (Figure 1) (correlation coefficient 0.59). Little improvement results by using the dissociation constants of the corresponding arene carboxylic acids as the abscissa.

Separation of rates for the participating, $k_\Delta$, and direct substitution, $k_s$, pathways for β-arylethyl systems was first treated by Jenny and Winstein,[20] using isotopically labeled substrates. Related studies by

(11) G. Marino, *Advan. Heterocycl. Chem.*, **13**, 235 (1971).
(12) S. Clementi, P. Linda, and G. Marino, *Tetrahedron Lett.*, 1389 (1970).
(13) Reference 11, p 276.
(14) V. J. Shiner, W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, **91**, 4838 (1969).
(15) D. S. Noyce, R. L. Castenson, and D. A. Meyers, *J. Org. Chem.*, **37**, 4222 (1972).
(16) W. H. Saunders, Jr., S. Asperber, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).
(17) W. H. Saunders, Jr., and R. Glaser, *ibid.*, **82**, 3585 (1960).
(18) C. C. Lee and L. Noszko, *Can. J. Chem.*, **44**, 2491 (1966).
(19) D. S. Noyce, C. A. Lipinski, and D. A. Forsyth, unpublished observations.
(20) W. H. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958).

Table IV. Deuterium Scrambling in the Products and Recovered Starting Materials from the Solvolysis of β-Arylethyl Tosylates

| Compd solvolyzed | Compd analyzed | % reaction | Solvent system | % scrambling |
|---|---|---|---|---|
| 2-(2-Thienyl)-*2,2*-$d_2$-ethyl tosylate (**12**) | ROAc | 100 | HOAc–NaOAc | 82 ± 2 |
| 2-(2-Thienyl)-*1,1*-$d_2$-ethyl tosylate (**13**) | ROTs | 31 | HOAc–NaOAc | 0 ± 2 |
| | ROTs | 67 | HOAc–NaOAc | 5.4 ± 2 |
| | ROAc | 31 | HOAc–NaOAc | 77 ± 1 |
| | ROAc | 67 | HOAc–NaOAc | 79 ± 1 |
| 2-(2-Furyl)-*1,1*-$d_2$-ethyl tosylate (**14**) | ROAc | 100 | TFE–NaOAc | 83 ± 1 |
| | $ROCH_2CF_3$ | 100 | TFE–NaOAc | 84 ± 4 |
| 2-Phenethyl-*1,1*-$d_2$-ethyl tosylate (**15**) | ROTs | 67 | TFE–NaOAc | 17 ± 2 |
| | ROAc | 67 | TFE–NaOAc | 77 ± 2 |
| | $ROCH_2CF_3$ | 67 | TFE–NaOAc | 102 ± 1 |
| 2-Phenethyl-*1,1*-$d_2$-ethyl tosylate | ROTs | 28 | TFE | 2.3 ± 2 |
| | ROTs | 61 | TFE | 8.3 ± 2 |
| | $ROCH_2CF_3$ | 28 | TFE | 97 ± 2 |
| | $ROCH_2CF_3$ | 61 | TFE | 104 ± 2 |
| 2-(2-Thienyl)-*1,1*-$d_2$-ethyl tosylate | ROTs | 65 | TFE | 9.2 ± 2 |
| | $ROCH_2CF_3$ | 65 | TFE | 101 ± 1 |

Clayton and Lee[21] and by Coke, *et al.*,[22] have extended this approach. In our studies, enough data were collected to allow reasonably good estimates for the constants: $k_\Delta$, $k_s$, $F$, and $k_{14}$. For 2-phenylethyl tosylate in TFE, $F$ is 0.94; *i.e.*, there is relatively little ion pair return leading to isotopically scrambled starting material. This is similar to the results obtained upon analysis of the formic acid data, where $F = 0.91$,[21] but in contrast to the situation in acetic acid where $F = 0.3$.[22]

Because $F$ is nearly unity in TFE, the simpler analysis of separation of the observed titrimetric rate ($k_t$) into assisted and nonassisted pathways as represented in eq 1 is preferred, and the term $Fk_\Delta$ is a close representation of $k_\Delta$, for the assisted pathway.

$$k_t = Fk_\Delta + k_s \qquad (1)$$

A very useful way of making this separation has been exploited by Schleyer, *et al.*[23] Schleyer separated the observed acetolysis rates for a series of meta- and para-substituted β-phenethyl tosylates into the assisted ($Fk_\Delta$) and unassisted ($k_s$) portion by plotting the titrimetric rate for each compound *vs.* $\sigma$. Using strongly electron withdrawing substituents as a base to define $k_s$, unassisted rates were calculated for all compounds. By difference, $Fk_\Delta$ is then determined for all the compounds.

We employed a slight modification of Schleyer's method to obtain both $Fk_\Delta$ and $k_s$ components of the observed trifluoroethanolysis rates. In our approach, instead of using $\sigma$ for the substituent on the ring, the $\sigma$ value is used to represent the entire aryl group.[24] The $k_s$ line will be defined by the titrimetric rate for a very deactivated aryl group, *i.e.*, 2-(*p*-nitrophenyl)-ethyl tosylate, and the titrimetric rate for ethyl tosylate. As a source for "replacement $\sigma$ values," $\sigma_{Ar}$, the dissociation constant of the appropriate arene carboxylic acid might be used. However, the literature data show that this is an unsatisfactory procedure.[25–28] We therefore chose to use as a basis for the definition of $\sigma_{Ar}$ the saponification rates for the appropriate esters. Data are available for the saponification rates for all of the heterocyclic systems which we have studied; for six compounds in 62% acetone,[29] for six compounds in 70% dioxane,[30] for two in 85% ethanol,[31] and two in 87.8% ethanol.[32] For ethyl 2-thienoate, concordant data are available from six independent sources; for ethyl 2-furoate, from four sources. There are scattered data for the other systems. Using phenyl as the basis for the "$\sigma$ replace-

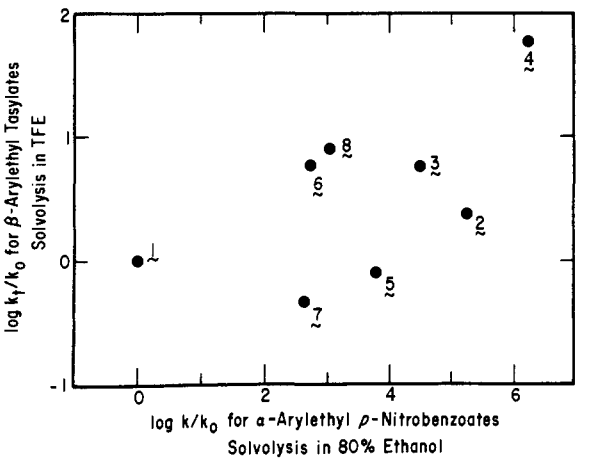



Figure 1. Reactivity of β-heteroarylethyl tosylates compared to reactivity of α-heteroarylethyl *p*-nitrobenzoates.

(21) J. W. Clayton and C. C. Lee, *Can. J. Chem.*, **39**, 1510 (1961).
(22) J. L. Coke, F. E. McFarlane, M. C. Mourning, and M. G. Jones, *J. Amer. Chem. Soc.*, **91**, 1154 (1969).
(23) J. M. Harris, F. L. Schadt, and P. v. R. Schleyer, *ibid.*, **91**, 7508 (1969), and references therein cited.
(24) The terminology of substituent constant in this context is somewhat troublesome. E. Fringuelli, G. Marino, and A. Taticchi, *J. Chem. Soc. B*, 1595 (1970); 2302, 2304 (1971), have cogently pointed out that the substituent constant for a heterocyclic moiety should be derived by substitution of the heterocyclic fragment for one of the ring hydrogens in a benzene derivative; *e.g.*, the dissociation constant of *m*-(2-thienyl)-benzoic acid defines $\sigma_m$ for the 2-thienyl group. We are interested here in the *replacement* of the entire phenyl moiety by the thienyl moiety. These replacement substituent constants should be designated in some different fashion. However, to call them "replacement $\sigma$ values," designated by $\sigma_{Ar}$, appears to avoid confusion in the present discussion.
(25) J. Nakaya, H. Kinoshita, and S. Ono, *Nippon Kagaku Zasshi*, **78**, 940 (1957).
(26) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).
(27) G. Kortum, W. Vogel, and K. Andrussow, *Pure Appl. Chem.*, **1**, 190 (1961).
(28) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(29) P. A. T. Thije and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **84**, 1169 (1965); we used the $\rho$ values reported in 60% acetone (ref 28).
(30) A. Feinstein, P. H. Gore, and G. L. Reed, *J. Chem. Soc. B*, 205 (1969); S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, **79**, 2547 (1957).
(31) Y. Otsuji, M. Kubo, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1300 (1959); *Chem. Abstr.*, **55**, 6467i (1961).
(32) K. Kindler, *Ber.*, **69**, 2792 (1936).

Table V. Rate Constants for Trifluoroethanolysis of β-Arylethyl Tosylates at 75°

| Compd | $\sigma^+$ a | $\sigma^+$ b | $\sigma^{c,d}$ | $10^6k_t$, sec$^{-1}$ | $10^6k_s$, sec$^{-1}$ | $Fk_\Delta \times 10^6$, sec$^{-1}$ | $Fk_\Delta/k_s$ |
|---|---|---|---|---|---|---|---|
| **10** | −0.778 | | −0.268 | 339 | 0.70 | 338 | 483 |
| **4** | −1.05 | −1.17 | −0.13 | 297 | 0.43 | 297 | 692 |
| **9** | −0.311 | | −0.170 | 53.1 | 0.50 | 52.6 | 106 |
| **8** | −0.57 | −0.52 | −0.08 | 39.2 | 0.36 | 38.8 | 108 |
| **6** | −0.49 | −0.47 | 0.00 | 29.6 | 0.27 | 29.3 | 109 |
| **3** | −0.79 | −0.84 | 0.00 | 26.3 | 0.27 | 26.0 | 96.6 |
| **2** | −0.90 | −0.94 | 0.33 | 13.1 | 0.083 | 13.0 | 157 |
| **1** | (0.00) | (0.00) | (0.00) | 4.82 | 0.27 | 4.55 | 16.9 |
| **5** | −0.67 | −0.70 | 0.36 | 3.72 | 0.074 | 3.65 | 49.3 |
| **7** | −0.51 | −0.43 | 0.30 | 2.21 | 0.092 | 2.12 | 23 |

[a] For hetero rings from ref 4, 5, and 19; for **9** and **10** from H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958). [b] From Hill, *et al.*, ref 3. [c] "Replacement σ values." [d] Data sources; see text and ref 29–32.

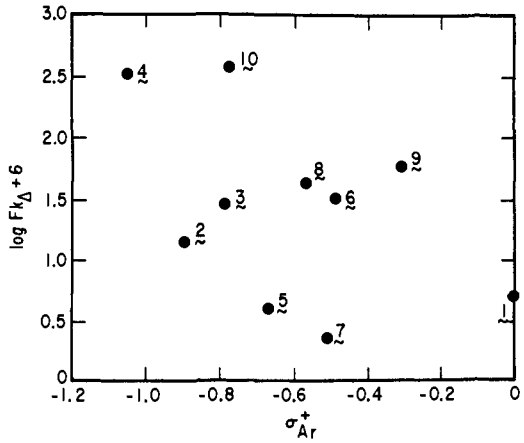



Figure 2. Attempted correlation of $Fk\Delta$ with solvolytic reactivity of α-heteroarylethyl systems ($\sigma_{Ar}^+$).

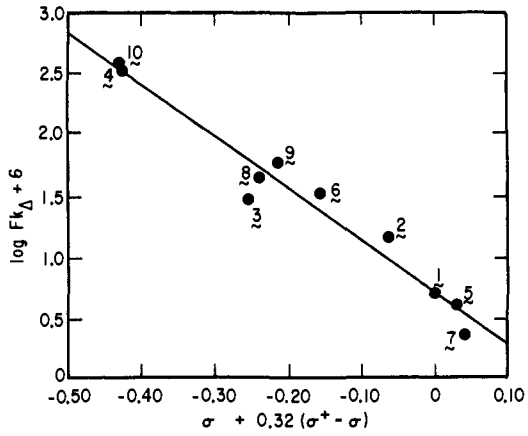
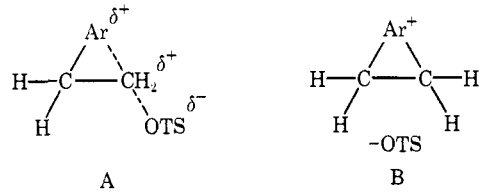



Figure 3. Correlation of $Fk\Delta$ for β-heteroarylethyl systems using the Yukawa–Tsuno equation.

ment values," $\sigma_{phenyl} = 0$, and the literature ρ values, the mean values for the heterocyclic systems in the present study were determined. "Replacement σ values" thus determined are recorded in Table V, column 4, and were used to obtain the $k_s$ and $Fk_\Delta$ values listed in columns 6 and 7, *via* Schleyer's method.

Separation of the $k_\Delta$ rates ($Fk_\Delta$, column 7, Table V) does not change the relative order of reactivity of compounds **1–10**. Consideration of the ratio ($Fk_\Delta/k_s$) does point to some differences. All compounds show a greater proportion of participating rearrangement than does **1**, a fact which could not be observed by examining the titrimetric rates alone for rate enhancement relative to the phenyl system. This type of treatment (use of $Fk_\Delta/k_s$) also explains why isotopic scrambling can be equally extensive in compounds with differing titrimetric rates. Further, the 2-furyl system **2** shows a higher ratio of participating rearrangement than does the 2-thienyl system **3**. This situation is more in accord with the generally greater susceptibility of furan to electrophilic attack. However, plotting $Fk_\Delta$ *vs.* $\sigma^+$ still gives an unsatisfactory correlation, Figure 2 (correlation coefficient 0.48).

Taking cognizance of the fact that the best current evidence suggests that the transition state for the participating rearrangement is an unsymmetrically bridged system (A) leading to the symmetrically bridged intermediate (B), we have explored the applicability of the Yukawa–Tsuno[33] relationship. Such an approach recog-




$$\log k/k_0 = [\sigma + r(\sigma^+ - \sigma)]\rho \qquad (2)$$

nizes that in A the stabilizing influences of the aromatic moiety (as reflected by electrophilic substituent constants, $\sigma^+$) are not yet fully developed. Such a transition state still maintains an appreciable proportion of the characteristics of a carbonium ion influenced by inductive factors (*e.g.*, σ). A similar treatment has previously been applied to the neophyl system with good success.[34]

Dramatic improvement in the quality of the correlation now emerges. Figure 3 shows the results visually; the correlation coefficient is now a satisfying 0.97, when $r = 0.32$.

An alternative procedure (which takes account of the very small fraction of participation suggested by this analysis for **11**) leads to minor changes in the numerical values recorded in Table V, columns 6, 7, and 8. There is no substantive change in the conclusions to be drawn from this information. Thus a blend of electrophilic substituent constants ($\sigma_{Ar}^+$) and inductive

(33) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 965 (1959).

(34) Y. Yukawa and Y. Tsuno, *ibid.*, **32**, 971 (1959).

substituent constants ($\sigma_{Ar}$) satisfactorily reproduces the observed behavior of a number of heterocyclic systems in facilitating the participating rearrangement of β-arylethyl tosylates.

## Experimental Section[35]

**2-(2-Thienyl)ethyl Tosylate (3).** From 4.2 g of thiophene in 20 ml of ether, the lithio derivative was prepared by reaction with *n*-butyllithium (in hexane, Foote Mineral Co.) at 0°. A solution of 2.7 g of ethylene oxide in ether was added slowly (20 min). To the thus formed 2-(2-thienyl)ethanol lithium salt was directly added a solution of 11.7 g of *p*-toluenesulfonyl chloride in 100 ml of ether. The reaction mixture was allowed to stand overnight at room temperature. Solvents were removed under reduced pressure and the resulting mixture was chromatographed on silica gel. Hexane eluted excess tosyl chloride while 3:1 hexane–ethyl acetate eluted 8.7 g (62% yield) of the tosylate. Recrystallization from hexane afforded pure 2-(2-thienyl)ethyl tosylate as white needles: mp 32.5–33.5°; nmr ($CCl_4$) δ 2.42 (s, 3, $CH_3$), 3.10 (t, 2, $J_{\alpha,\beta}$ = 6.5 Hz, $H_2C_\beta$), 4.12 (t, 2, $H_2C_\alpha$), 6.80–7.03 (m, 3, thienyl protons), 7.21 and 7.64 (dd, 4, $J$ = 8 Hz, $C_6H_4$).

*Anal.* Calcd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.00; S, 22.71. Found: C, 55.37; H, 5.18; S, 22.54.

**2-(2-Thienyl)-*1,1*-$d_2$-ethanol.** A mixture of 1 g (24 mmol) of lithium aluminum deuteride with 75 ml of ether was cooled to 0° and then 3.7 g (26 mmol) of 2-thienylacetic acid in 80 ml of ether was added over 50 min. The mixture was stirred for 11 hr at room temperature and then refluxed for 4 hr. After the reaction was quenched with an aqueous solution of sodium potassium tartrate, the ether layer was separated, and the solvent was removed under reduced pressure to give 2.74 g (81% yield) of the deuterated alcohol: nmr ($CCl_4$) δ 2.92 (s, 2, $H_2C_\beta$), 6.67–7.08 (m, 3, thienyl ring protons). The alcohol was not distilled but used directly in the next step.

**2-(2-Thienyl)-*1,1*-$d_2$-ethyl Tosylate (12).** To 2-(2-thienyl)-*1,1*-$d_2$-ethanol and triethylamine in 1,2-dichloroethane, *p*-toluenesulfonyl chloride in 1,2-dichloroethane was added rapidly. After stirring overnight, the mixture was worked up in the usual fashion. The resulting oil crystallized from a 1:2 v/v solution of low-boiling petroleum ether and benzene to yield **12**: mp 33.0–33.7°; nmr ($CCl_4$) δ 2.42 (s, 3, $CH_3$), 3.04 (s, 2, $H_2C_\beta$), 6.61–7.10 (m, 3, thienyl ring protons), and 7.21 and 7.64 (dd, 4, $J$ = 8 Hz, $C_6H_4$).

**2-Thienyl-α,α-$d_2$-acetic Acid.** A 0.1-g (4 mg-atoms) piece of sodium was added to 17 ml of deuterium oxide (98%) and after the sodium had completely reacted, 1.0 g (8 mmol) of 2-thienylacetonitrile was added. This mixture was then heated at 90° for 32 hr, cooled, and extracted with 10 ml of ether. The aqueous phase was acidified with dilute sulfuric acid and extracted with two 50-ml portions of ether. After drying over sodium sulfate, the solvent was removed under reduced pressure leaving 0.83 g (71% yield) of the 2-thienyl-α,α-$d_2$-acetic acid. The nmr spectrum showed no α protons, but a mass spectrum of the recrystallized product indicated that there was about 7% monodeuterio acid: nmr ($CCl_4$) δ 6.80–7.15 (m, thienyl protons).

When this procedure was repeated using more concentrated sodium deuteroxide, appreciable ring deuteration occurred.

**2-(2-Thienyl)-*2,2*-$d_2$-ethyl Tosylate (13).** 2-Thienyl-α,α-$d_2$-acetic acid was reduced with lithium aluminum hydride in ether, and the deuterated alcohol was converted directly to the tosylate in the usual fashion. After two recrystallizations from hexane–ethyl acetate, tosylate **13** was obtained: mp 32.1–32.8°; nmr ($CCl_4$) δ 2.42 (s, 3, $CH_3$), 4.06 (s, 2, $H_2C_\alpha$), 6.80–7.03 (m, 3, thienyl protons), 7.21 and 7.64 (dd, 4, $J$ = 8 Hz, $C_6H_4$).

**2-(5-Methyl-2-thienyl)ethyl Tosylate (4).** From 2-methylthiophene in ether and *n*-butyllithium in hexane followed by addition of ethylene oxide, 2-(5-methyl-2-thienyl)ethanol[36] was prepared following the procedure of Gol'dfarb and Konstantinov.[37] The alcohol was not isolated but was converted *in situ* directly to **4**: mp 35.5–36.5° (needles from hexane); nmr ($CCl_4$) δ 2.37 and 2.40 (two s, 6, $CH_3$ and $CH_3$), 2.99 (t, 2, $J_{\alpha\beta}$ = 6.5 Hz, $H_2C_\beta$), 4.04 (t, 2, $H_2C_\alpha$), 6.44 (s, 2, thienyl ring protons), and 7.21 and 7.64 (dd, 4, $J$ = 8 Hz, $C_6H_4$).

*Anal.* Calcd for $C_{14}H_{16}O_3S_2$: C, 56.75; H, 5.41; S, 21.62. Found: C, 56.64; H, 5.62; S, 21.60.

**2-(5-Bromo-2-thienyl)ethyl Tosylate (5).** A solution of 12.1 g (50 mmol) of 2,5-dibromothiophene in 200 ml of ether was cooled to −70° in a Dry Ice–2-propanol bath. Under positive nitrogen pressure, 32 ml (51 mmol) of *n*-butyllithium solution at −70° was added over 5 min. The mixture was stirred for 5 min, and then a solution of 4.40 g (100 mmol) of ethylene oxide in 40 ml of ether was added rapidly. The mixture was stirred at −70° for 2 hr and then the cooling bath was removed. When the mixture had warmed to room temperature, the suspension of the lithium salt of 2-(5-bromo-2-thienyl)ethanol was directly converted to **5** in the usual manner by treatment with *p*-toluenesulfonyl chloride. From hexane, **5** crystallized as fine white plates: mp 52.8–53.8°; nmr ($CCl_4$) δ 2.43 (s, 3, $CH_3$), 3.03 (t, 2, $H_2C_\beta$), 4.10 (t, 3, $J$ = 6 Hz, $H_2C_\alpha$), 6.75 and 6.53 (dd, 2, $J$ = 3 Hz, thienyl ring protons), and 7.65 and 7.23 (dd, 4, $J$ = 8 Hz, $C_6H_4$).

*Anal.* Calcd for $C_{13}H_{13}BrO_3S_2$: C, 43.22; H, 3.63; Br, 22.12; S, 17.75. Found: C, 43.33; H, 3.69; Br, 21.96; S, 17.56.

**2-(3-Thienyl)ethanol.** In our hands the method of Gronowitz[38] was unsatisfactory, as the material of appropriate boiling range showed a plethora of additional nmr bands. The following indirect route was quite satisfactory. 1-(3-Thienyl)ethanol[5a] was dehydrated by the procedure of Troyanowski,[39] to give 3-vinylthiophene, mp 48–51° (19.5 mm) [lit.[39,40] 46–48° (15 mm), 50.5° (20 mm)].

3-Vinylthiophene, 3.85 g in 20 ml of tetrahydrofuran, was cooled to 0° under a nitrogen atmosphere. A solution of bis(3-methyl-2-butyl)borane (52 mmol) in THF was added dropwise over 10 min, and the solution was allowed to warm to room temperature. After the mixture was stirred for 2 additional hr, 18 ml of a 3 *N* sodium hydroxide solution was added slowly followed by 18 ml of a 30% solution of hydrogen peroxide. This mixture was poured into an equal volume of water and extracted with three 150-ml portions of ether. After the combined ether fractions were dried over sodium sulfate, the solvent was removed under reduced pressure. The resulting liquid was distilled to yield about 2.5 ml of 3-methyl-2-butanol, bp 31–35° (8 mm), followed by 2.9 g (62% yield) of 2-(3-thienyl)ethanol: bp 105–108° (9 mm) [lit.[41] bp 120° (16 mm)]; nmr ($CCl_4$) δ 2.72 (t, 2, $J_{\alpha\beta}$ = 6.5 Hz, $H_2C_\beta$), 3.63 (t, 2, $H_2C_\alpha$), and 6.67–7.20 (m, 3, thienyl ring protons).

**2-(3-Thienyl)ethyl Tosylate (6).** 2-(3-Thienyl)ethanol was converted to the tosylate in the usual fashion. Crystallization from hexane gave the pure tosylate **6**: mp 47.2–47.8°; nmr ($CCl_4$) δ 2.38 (s, 3, $CH_3$), 2.90 (t, 2, $H_2C_\beta$), 4.10 (t, 2, $J_{\alpha\beta}$ = 6.5 Hz, $H_2C_\alpha$), 7.20–6.70 (m, 3, thienyl ring protons), and 7.62 and 7.20 (dd, 4, $J$ = 8 Hz, $C_6H_4$). The mixture melting point with the 2-thienyl isomer was 28–42°.

*Anal.* Calcd for $C_{13}H_{14}O_3S_2$: C, 55.29; H, 5.00; S, 22.71 Found: C, 55.50; H, 5.12; S, 22.62.

**2-(2-Benzothienyl)ethyl Tosylate (7).** Metalation of benzothiophene with *n*-butyllithium and subsequent addition of ethylene oxide afforded 2-(2-benzothienyl)ethanol (58% yield): mp 74–77° (lit.[42] 76–79.5°); nmr ($CDCl_3$) δ 3.15 (t, 2, $J_{\alpha\beta}$ = 6 Hz, $H_2C_\beta$), 3.97 (t, 2, $H_2C_\alpha$), 7.07–7.98 (m, 5).

For preparation of the tosylate **7**, the alcohol was not isolated, but the lithium salt was directly treated with *p*-toluenesulfonyl chloride. Work-up in the usual fashion afforded **7**, crystallized from hexane–ethyl acetate: mp 78.0–78.8°; nmr ($CDCl_3$) δ 2.35 (s, 3, $CH_3$), 3.20 (t, 2, $J_{\alpha\beta}$ = 6.5 Hz, $H_2C_\beta$), 4.32 (t, 2, $H_2C_\alpha$), 6.95–7.82 (m, 9).

*Anal.* Calcd for $C_{17}H_{16}O_3S_2$: C, 61.42; H, 4.85; S, 19.29. Found: C, 61.19; H, 4.80; S, 19.48.

**2-(3-Benzothienyl)ethanol.** 3-Bromobenzothiophene (14.9 g, 70 mmol) in 150 ml of ether was cooled to 0° in a flame-dried flask. Under positive nitrogen pressure and with vigorous stirring, 48 ml (77 mmol) of *n*-butyllithium solution was added over 10 min. The solution was stirred for 30 min at 0° and then 5 ml (100 mmol) of ethylene oxide in 30 ml of ether was added over 5 min. After an

(35) Melting points and boiling points are uncorrected. Analyses are by the Chemical Analytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif. 94720.

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additional 30 min of stirring, the mixture was poured into 250 ml of water. The organic phase was separated and the aqueous phase was extracted with two 150-ml portions of ether. After the combined ether fractions were dried over sodium sulfate, the solvent was removed under reduced pressure. The resulting oil failed to crystallize from *m*-hexanes, chloroform, or benzene. A nmr spectrum of the crude product indicated that the oil was a mixture of the **2** and **3** isomers in a ratio of about 3:1, respectively. Elution of the oil through a silica gel column with hexane did not significantly alter the isomer ratio. No further attempts were made to separate the isomers. The crude product was used directly in the next step.

**2-(3-Benzothienyl)ethyl Tosylate (8).** A solution of 2.3 g (12 mmol) of *p*-toluenesulfonyl chloride in 20 ml of methylene chloride was added to a solution of 1.3 g (13 mmol) of triethylamine and 2.0 g (11 mmol) of an isomeric mixture of 2-(2- and 3-benzothienyl)-ethanols in 25 ml of methylene chloride. The resulting solution was stored in a refrigerator overnight and was then poured into 100 ml of water. The organic phase was separated and the aqueous phase was extracted with 100 ml of methylene chloride. After the combined organic layers were dried over sodium sulfate, the solvent was removed under reduced pressure. The resulting oil did not crystallize from *m*-hexanes. A nmr spectrum of the crude product indicated that it was a mixture of the 2 and 3 isomers. Elution of the crude product through a silica gel column with hexane slightly enriched the mixture in the desired 3 isomer, but complete separation was not accomplished. The first fractions from the column solidified to a white, waxy solid. This solid was shown by nmr analysis to contain only the two isomeric tosylates. This solid was solvolyzed directly. Since the rate of the 2 isomer was known and the ratio of the rates for the two isomers was about 20, the rate of the 3 isomer was easily obtained. The kinetic study showed that the solvolyzed mixture contained 62% of the 2 isomer and 38% of the 3 isomer: nmr ($CCl_4$) $\delta$ 2.40 (s, 3, $CH_3$), 3.00–3.27 (m, 2, $H_2C_\beta$), 4.20 (t, 2, $J$ = 7 Hz, $H_2C_\alpha$), and 6.86–7.75 (m, 9, aromatic).

**2-(2-Furyl)ethyl Tosylate (2).** Furfuryl chloride was converted to 2-furylacetonitrile by the procedure of Novitskii, *et al.*,[43] which was hydrolyzed to 2-furylacetic acid, and the acid was reduced with lithium aluminum hydride in ether to 2-(2-furyl)ethanol.[44] The alcohol in pyridine was treated with *p*-toluenesulfonyl chloride; after standing overnight the reaction mixture was poured into *cold*, dilute hydrochloric acid. Extraction with ether, drying, and removal of the solvent under reduced pressure afforded an oil which crystallized on cooling. Careful recrystallization from hexane afforded the very unstable tosylate **9**, as colorless crystals, mp 29–30°, which suffered visible decomposition within 1 hr at room temperature. The nmr was entirely consistent with the assigned structure: nmr ($CCl_4$) $\delta$ 2.39 (s, 3, $CH_3$), 2.91 (t, 2, $J_{\alpha\beta}$ = 7 Hz, $H_2C_\beta$), 4.07 (t, 2, $H_2C_\alpha$), 5.98 (m, 1, $HC_3$), 6.16 (m, 1, $HC_4$), 7.17 (m, 1, $HC_5$), and 7.21 and 7.67 (dd, 4, $J$ = 8 Hz, $-C_6H_4-$).

**2-(2-Furyl)-*1,1*-$d_2$-ethyl tosylate (14)** was prepared in a similar fashion, substituting lithium aluminum deuteride in the reduction step.

**2-Phenylethyl tosylate (1),[45] 2-(*p*-methoxyphenyl)ethyl tosylate (10),[46] 2-(*p*-methylphenyl)ethyl tosylate (9),[47] and 2-(*p*-nitrophenyl)-ethyl tosylate (11)[48]** were prepared by literature procedures.

**Kinetic procedures** have been described previously.[15]

**Product Studies. A. 2-(2-Thienyl)ethyl Tosylate (3) in Buffered Acetic Acid.** A solution (100 ml) of 2-(2-thienyl)ethyl tosylate (0.025 *M*) and sodium acetate (0.035 *M*) in acetic acid was sealed in a Kjeldahl flask and heated at 110° for several half-lives. After work-up in the usual fashion, there was obtained 0.334 g (92% of theory) of crude 2-(2-thienyl)ethyl acetate. Upon gas chromatography, only one peak representing more than 99% of the material was obtained at several column temperatures. It was identified as 2-(2-thienyl)ethyl acetate: nmr ($CCl_4$) $\delta$ 6.70–7.08 (m, 3, thienyl ring protons), 4.16 (t, $J$ = 7 Hz, 2, $H_2C_\alpha$), 3.03 (t, 2, $H_2C_\beta$), and 1.93 (s, 3, $O_2CCH_3$); ir ($CCl_4$) 1749 $cm^{-1}$ (C=O); mass spectrum (70 eV) *m/e* (rel intensity, ion) 110 (100, $ArCHCH_2^+$), 97 (43, $ArCH_2^+$), and 43 (43, $CH_3CO^+$).

*Anal.* Calcd for $C_8H_{10}O_2S$: C, 56.44; H, 5.93; S, 18.83. Found: C, 56.53; H, 6.14; S, 18.75.

**B. 2-(2-Thienyl)ethyl Tosylate (3) in Buffered Trifluoroethanol.** A solution (100 ml) of 2-(2-thienyl)ethyl tosylate (0.02 *M*) and sodium acetate (0.03 *M*) in trifluoroethanol was heated at 75° for 109 hr (about 17 half-lives). The solution was then poured into 400 ml of water and extracted with five 100-ml portions of ether. The ether had extracted large amounts of TFE along with the solvolysis products. After the combined ether layers were dried over sodium sulfate, the solution was concentrated under reduced pressure. The crude product gave rise to two peaks on gc and these had an area ratio of 27:73; 0.073 g (21% of theory) of the compound with the shorter retention time and 0.146 g (53% of theory) of the other compound were collected. The first compound was identified as $\beta$-(2-thienyl)-$\beta'$,$\beta'$,$\beta'$-trifluorodiethyl ether: nmr ($CCl_4$) $\delta$ 6.70–7.08 (m, 3, thienyl ring protons), 3.82 (t, $J$ = 6 Hz, 2, $H_2C_\alpha$), 3.79 (q, $J_{HF}$ = 8 Hz, 2, $OCH_2CF_3$), and 3.12 ppm (t, 2, $H_2C_\beta$); mass spectrum (70 eV) *m/e* (rel intensity, ion) 210 (100, $P^+$), 111 (7.3, $ArCH_2$-$CH_2^+$), and 97 (91, $ArCH_2^+$).

The second product was identified as 2-(2-thienyl)ethyl acetate.

**C. 2-(2-Furyl)-*1,1*-$d_2$-ethyl Tosylate (14) in Buffered Trifluoroethanol.** 2-(2-Furyl)-*1,1*-$d_2$-ethyl tosylate (0.02 *M*) was solvolyzed in TFE buffered with sodium acetate (0.03 *M*) at 75° for 94 hr (about 6.5 half-lives). The work-up was the same as that described for the previous product study. The vapor phase chromatogram of the crude product showed two components in a ratio of 28:72. These were collected and the minor component (73 mg, 23% of theory) of the crude product mixture was shown to be the trifluoro ether: nmr ($CCl_4$) $\delta$ 7.23 (broad s, 1, 5-H), 6.20 (dd, $J_{4,5}$ = 1 Hz, $J_{3,4}$ = 3.5 Hz, 1, 4-H), 6.00 (d, 1, 3-H), 3.80 (s, $H_2C_\alpha$), 3.70 (q, $J_{HF}$ = 8 Hz, 2, $OCH_2CF_3$), and 2.90 (s, $H_2C_\beta$). The methylene proton section of the spectrum was expanded and a series of integrals was obtained. The very similar chemical shifts of the methylene protons $\alpha$ to the oxygen in the trifluoro ether complicate the scrambling analysis. Changing solvents accomplished no substantive improvement of the chemical shifts.

Deuterium analysis by the falling drop method of 2-(2-furyl)-*1,1*-$d_2$-ethanol, used to prepare the tosylate, showed it to be 98.6% $^2H$ and 1.4% $^1H$ initially at the $\alpha$ carbon. The nmr integrals for $H_2C_\alpha$ plus $H_2C_{\alpha'}$ and $H_2C_\beta$ were obtained and averaged. Since $H_2C_{\alpha'}$ ($(CF_3CH_2)O$) is always two protons, $H_2C_\alpha + H_2C_\beta = H_2C_{\alpha'}$. Using this equation and correcting for the initial isotopic impurity, the scrambling at 100% reaction was calculated to be 84 ± 4%.

The major product component (59% of theory) was shown to be the acetate. A series of integrals of the methylene region was obtained and averaged. After correcting for initial isotopic purity, the scrambling in the acetate at 100% reaction was 83 ± 1%.

**D. 2-(2-Thienyl)-*1,1*-$d_2$-ethyl Tosylate (13) in Buffered Acetic Acid.** A solution of 2-(2-thienyl)-*1,1*-$d_2$-ethyl tosylate (0.025 *M*) in acetic acid buffered with sodium acetate (0.035 *M*) was prepared and 48 ml of it was sealed in each of two Kjeldahl flasks. Both were heated at 75°. The first sample was quenched after 55 hr and the second after 165 hr. Neglecting any isotope effects, these times correspond to 31% reaction and 67.5% reaction, respectively. Each sample was diluted with 200 ml of water and extracted with three 100-ml portions of ether. The combined ether layers were thoroughly washed with 10% aqueous sodium carbonate solution and finally with 100 ml of water. After drying over sodium sulfate, the ether was removed under reduced pressure to yield a viscous yellow liquid. The crude product obtained after removal of the solvent was dissolved in low-boiling petroleum ether (30–60°) and stored in a freezer overnight. The tan solid which separated was collected by filtration and recrystallized from hexane to give 0.11 g of the tosylate (mp 33.9–34.2°) from the first sample and 0.09 g of the tosylate (mp 32.9–33.8°) from the second.

For each sample, the petroleum ether and hexane solutions were combined and the solvent was removed under reduced pressure. The resulting oil was purified by vpc and identified as the acetate by nmr and ir.

The initial isotopic purity of the starting tosylate was calculated from mass spectral data on 2-(2-thienyl)-*1,1*-$d_2$-ethyl chloride, made from the same batch of deuterated alcohol. The chloride gave strong parent peaks which were used to show that the starting tosylate was 96.1% $-C_\alpha D_2-$, 3.6% $-C_\alpha HD-$, and 0.3% $-C_\alpha H_2-$. In calculating the rearrangements, a 98% initial isotopic purity was used.

Scrambling analyses on the recovered tosylate and acetate product were carried out by nmr as the $ArCD_2^+$ region of the mass spectrum was complicated by other peaks.

A series of nmr integrals was obtained and averaged for all four

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compounds. After correcting for this initial 2% hydrogen at the $\alpha$ carbon, the scramblings were obtained and are given in Table IV.

**E. 2-Phenyl-1,1-$d_2$-ethyl Tosylate (15) in Buffered Trifluoroethanol.** 2-Phenyl-1,1-$d_2$-ethyl tosylate (0.02 *M*) was solvolyzed in TFE buffered with sodium acetate (0.03 *M*) at 75° for 67 hr (about 67% reaction assuming $k_H/k_D = 1.21$). Isolation was carried out as described above (**B**). The acetate and trifluoro ether products were separated by vpc and were in a ratio of 54:46, respectively. The nmr spectra of the recovered tosylate and the recovered ether were identical (except for the relative integrals of the $H_2C_\alpha$ and $H_2C_\beta$ peaks) with previously obtained spectra.

The scramblings in the recovered tosylate and acetate were obtained from integrations of multiple nmr scans and are 17.1 and 77.4%, respectively. The scrambling in the trifluoro ether was calculated from mass spectral data by two methods, 103 and 100%, respectively.

# Hydrolysis of Imidate Esters Derived from Weakly Basic Amines. Influences of Structure and pH on the Partitioning of Tetrahedral Intermediates[1a,b]

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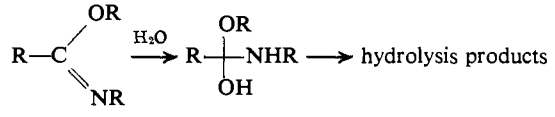
**Abstract:** A study has been made of the kinetics and products of the hydrolysis of ten imidate esters, derived from amines varying in basicity by more than 15 p$K$ units. The influence of pH on the nature of the hydrolysis products is strongly dependent on the structure of the imidate ester. Ethyl *N*-arylformimidates (I–V) derived from amines of $pK_a > 0$ produce *decreasing* yields of amine as pH is increased. Imidate esters (VIII, X) derived from very weakly basic amines ($pK_a < -6$) produce *increasing* yields of amine as pH is increased. The yield of 2,4-dinitroaniline formed on hydrolysis of VI varies with pH in a complex manner, with a *minimum* in the yield of amine at pH 4.5. The pH dependence of the rates and products of hydrolysis has been interpreted in terms of a mechanism involving cationic, neutral, and anionic tetrahedral intermediates.

The hydrolysis of imidate esters offers a convenient and useful approach to the study of the properties of the unstable tetrahedral addition intermediates




believed to participate in many acyl transfer reactions.[2,3] The important investigation by Martin, *et al.*,[4] of the hydrolysis of 2-methyl-$\Delta^2$-thiazoline was followed by studies of the aminolysis[5] and hydrolysis of imidate esters[6] which revealed that the products of nucleophilic attack at the imidate carbon atom were sensitive functions of pH and general acid–base catalysts. The present state of knowledge of the pathways of breakdown of the tetrahedral addition intermediates generated in the hydrolysis of imidate esters may be summarized as follows. Cyclic and acyclic imidate esters yield amines and esters in acidic solution, and amides (and alcohols) at higher pH.[6a,7–9] The transition in products occurs near neutral pH[6a,7,8] and follows accurately the sigmoid curve characteristic of the ionization of a monovalent acid.[6a,8] Cyclic[10] ($\Delta^2$-thiazolines) and acyclic[11] thioimidate esters, as well as an imidate ester derived from phenol,[9,12] yield decreasing amounts of amine as pH is increased, but the principal product transition takes place at pH 2–3; these compounds (with the exception of $\Delta^2$-thiazolines which could not be studied at sufficiently high pH) also show a second product transition at pH values near neutrality.[11b,12a] In general, the yield of amine formed on hydrolysis of imidates and thioimidates at constant pH increases with increasing buffer concentration, bifunctional buffers (phosphate, bicarbonate) being particularly effective in this regard.[6–8,11]

Little information is available concerning the effect of imidate structure on the behavior of the derived tetrahedral intermediates. Increasing the acidity of the alcohol portion of *N*-methylacetimidate esters resulted in a shift from pH 9.8 (for *O*-ethyl) to pH 6.5 (for *O*-trifluoroethyl) in the midpoint of the product transition.[9] That increasing basicity of the amine tends to facilitate amine expulsion from the tetrahedral intermediate was deduced from the kinetics of the

(1) (a) This work is taken in part from a dissertation presented by D. J. S. in partial fulfillment of the requirements for the M.D. degree, Yale University, 1969. (b) Financial support by the National Institutes of Health and the National Science Foundation is gratefully acknowledged. (c) On leave from the faculty of Engineering Science, Osaka University. (d) Postdoctoral Research Fellow of the National Institutes of Health, 1969–1970.

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