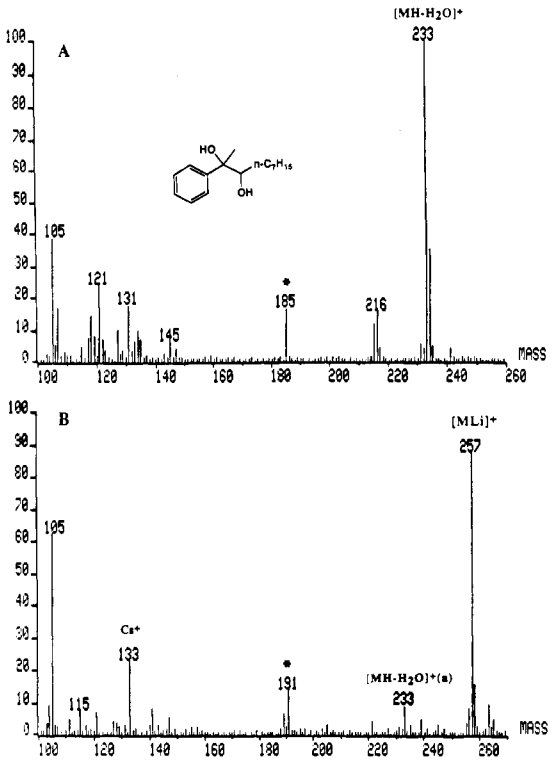


Figure 1. (A) Low-resolution FABMS of a 1:1 (threo:erythro) mixture of 2-phenyl-2,3-decanediol in a thioglycerol/glycerol matrix. (B) Low-resolution FABMS of 2-phenyl-2,3-decanediol in a thioglycerol/glycerol matrix after treatment with LiCl. The ion at m/z 133 comes from the cesium ion gun. (a) See reference 14 for an explanation of this ion. *Matrix and lithium-matrix ion in A and B, respectively.

additional proton with an alkali metal ion would result in the formation of a chelated complex[5,6] that should be more stable than an $[MH]^+$ ion.[7] Alkali metal impurities are often detected in the FABMS of polar molecules and show $[M + metal]^+$ ions.[8] More recently such metals have been purposely used in the detailed analysis of peptides.[9]

We chose to begin these studies with the lithium ion due to some previous work carried out by one of us.[10] A typical procedure involves dissolving or suspending either **1**, **2**, or **3** (less than 10 μg) in aqueous LiCl (0.07 M; 5 μL) and diluting with an equal volume of either 3-nitrobenzyl alcohol or a mixture of thioglycerol/glycerol (1:1) (5 μL).[11] The solution was agitated on a vortex mixer for several seconds, and then a portion (ca. 1 μL) was applied to a stainless steel probe tip. Analysis was carried out by bombarding the matrix mixture with either xenon atoms or cesium ions,[12] which led to the formation of abundant $[MLi]^+$ ions (Figure 1).[13] We have also used this procedure to analyze non-α-aryl 1,2-diols in cases where normal FABMS conditions gave little or no molecular ion information. Over 30 acyclic vicinal diols have been analyzed using this procedure. Stereochemical effects in the FABMS of metal–diol adducts as well as the use of metal ions in the mass spectrometric analysis of carbohydrates and related materials are in progress.

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735-02), the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735), Eli Lilly and Company, and Rohm and Haas Company for financial support. J.A.L. thanks Sherri Ogden for her assistance in running several FABMS on the diols discussed.

(5) For examples of alkali metal–diol complexes, see: (a) Kniep, R.; Welzel, W.; Weppner, W.; Rabenau, A. *Solid State Ionics*, **1988**, *28–30*, 1271. (b) Ballard, R. E.; Haines, A. H.; Norris, E. K.; Wells, A. G. *Angew. Chem.* **1974**, *86*, 555.

(6) Conformational properties will play an obvious role in the formation of such chelate structures.

(7) Loss of metal hydroxide seems unfavorable.

(8) Martin, S. A.; Costello, C. E.; Biemann, K. *Anal. Chem.* **1982**, *54*, 2362.

(9) Leary, J. A.; Williams, T. D.; Bott, G. *Rap. Commun. Mass Spec.* **1989**, *3*, 192 and references therein.

(10) Leary, J. A.; Tolun, E. *Proceed. 36th Annual Conf. on Mass Spectrom. Allied Topics* **1988**, 779.

(11) Both matrices worked equally well in assisting production of the $[MLi]^+$ ions; the only difference being the background matrix ions observed at different masses.

(12) The experiments were performed using either a xenon atom gun (7 kV with 1.0 μA emission current) or a cesium ion gun (20 kV with 1.5 μA emission current).

(13) All FABMS data were obtained using either a Kratos MS-50 (Kratos, Greater Manchester, U.K.) or a VG ZAB2-EQ mass spectrometer (VG Analytical Ltd, Greater Manchester, U.K.). Single-scan data were collected and processed on either a DS-55 (Kratos) or an 11-250J (VG) data system. Resolution was measured at 1:1000 with 8 kV accelerating voltage.

(14) Tandem mass spectrometry (MS/MS) experiments on $[MLi]^+$ have demonstrated that this ion is not arising from loss of LiOH from $[MLi]^+$. Therefore, it must be derived from unlithiated diol as in Figure 1A. Incomplete adduct formation may be due to insufficient solubility of the diol and/or conformational differences associated with the two possible diastereomeric lithium–diol adducts (we began with a 1:1 mixture of diastereomeric diols).

Generation of Synthetic Equivalents of $RCH(Li)NH_2$ for the Synthesis of Primary Amines. Tin–Lithium Exchange on Carbamate-Protected (α-Aminoalkyl)stannanes

William H. Pearson* and Aline C. Lindbeck

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

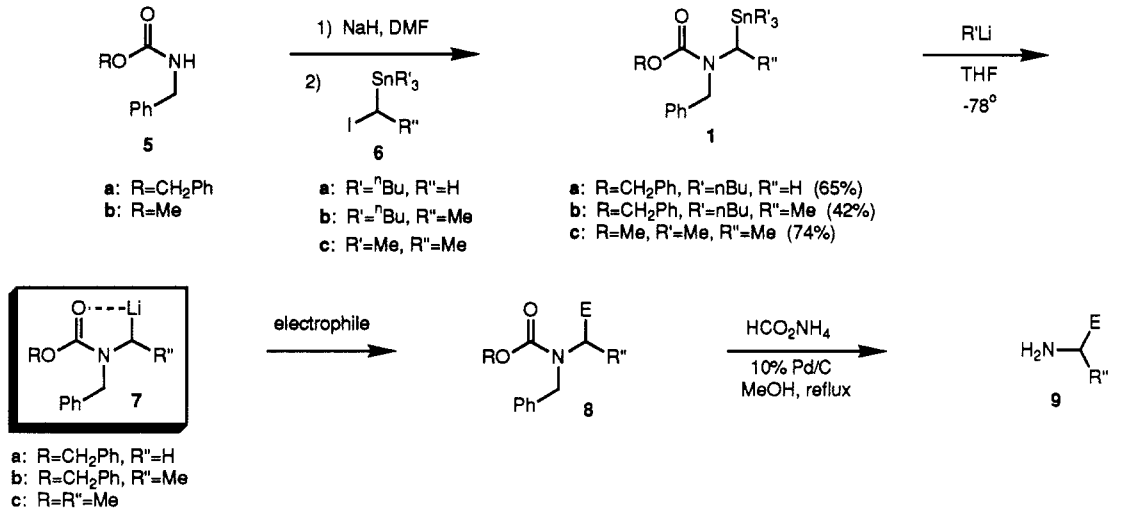
Received August 17, 1989

Summary: N-Alkylation of *N*-benzylcarbamates with (α-iodoalkyl)stannanes provided carbamate-protected (α-aminoalkyl)stannanes **1** and **11**. Tin–lithium exchange with an alkyllithium reagent produced nitrogen-substituted carbanions **7**, which reacted with electrophiles to provide adducts **8** and **12**. Deprotection by transfer hydrogenolysis then produced primary amines **9**.

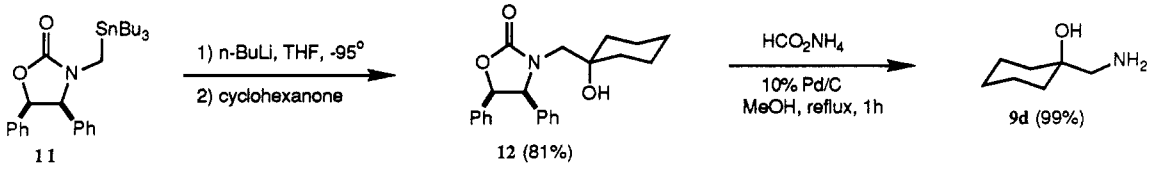
Sir: The generation and utilization of nitrogen-substituted carbanions continues to be an active area of research and has had a major impact on the synthesis of amines by carbon–carbon bond-forming reactions at nitrogen-bearing carbon. Synthetic equivalents of α-metalated primary, secondary, and tertiary amines have been reported, and are covered in excellent reviews by Beak.[1] We report that

0022-3263/89/1954-5651$01.50/0

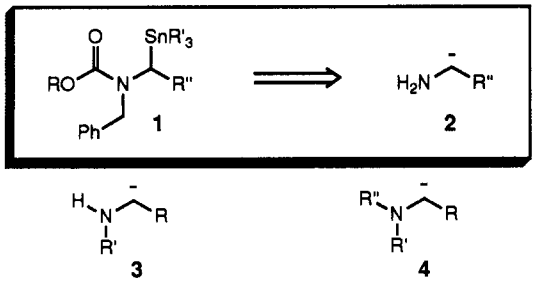
Scheme I



Scheme II



stannanes **1** are effective equivalents of α-metalated primary amines **2** and offer several advantages over existing methods.



Of the *nonconjugated* nitrogen-substituted carbanions, those that are synthetically equivalent to α-metalated secondary amines **3** are particularly well explored, where the nitrogen is derivatized by some removable group that serves both as a protecting group and as an activator for a prior deprotonation reaction. Protection of nitrogen as a formamidine (Meyers, Gawley),[1a,2] amide (Seebach, Beak),[1,3,4] or recently as a carbamate (Beak)[5] serves to illustrate this strategy. Of particular interest are activators that also serve as removable chiral auxiliaries.[2] Less well studied are synthons for tertiary amines **4**, which are generally obtained by tin–lithium exchange.[6-8] Synthetic equivalents of **2** where R = H are known, such as Kauffmann's $Ph_2C{=}NCH_2Li$, Hirao's $TMSCH_2NCS$, Schöllkopf's $LiCH_2NC$, Schell's $OSNCH_2Li$, and Tsuge's $PhthalNCH_2TMS$.[1a,9,10] Equivalents of **2** where R = alkyl are very rare, with Schell's RCH(Li)NSO being the only useful example.[9e,10] Furthermore, there are no examples of equivalents of **2** with a removable chiral auxiliary for the asymmetric synthesis of primary amines.[10] In order to generate equivalents of **2** where R is hydrogen or a nonconjugating alkyl group and where the incorporation of a removable chiral auxiliary is feasible, it seemed desirable to develop a route that did not rely on deprotonation reactions. Metalation of simple *N*-alkyl groups is possible but is limited by the types of primary amine protecting groups/chiral auxiliaries that are possible, since these are often sensitive to metalation as well. We have

(1) For reviews on nitrogen-substituted carbanions, see: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523. (b) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.

(2) (a) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. (b) Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 85. (c) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787, and earlier references therein. (d) Gonzalez, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1989**, *30*, 47–50. Related to amidines are the 2-aminooxazolines, which have recently been used in metalations by Gawley: (e) Rein, K. R.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211–2217, and earlier references therein.

(3) (a) For good coverage of Seebach's work, see ref 1a. (b) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1–13.

(4) (a) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145–8153. (b) Beak, P.; Lee, B. *J. Org. Chem.* **1989**, *54*, 458–464, and earlier references therein.

(5) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197–1200.

(6) (a) Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, 63. (b) Peterson, D. J. *Ibid.* **1974**, *66*, 209. (c) Peterson, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 159.

(7) (a) Pereyre, M.; Elissondo, B.; Quintard, J.-P. In *Selectivity-A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Weinheim, 1984; pp 191–212. (b) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. (c) Elissondo, B.; Verlhac, J.-B.; Quintard, J.-P.; Pereyre, M. *J. Organomet. Chem.* **1988**, *339*, 267–275, and earlier references cited therein.

(8) Recently, reduction of sulfides has been introduced to generate α-lithio tertiary amines: Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981–2984.

(9) (a) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627–639. (b) Kauffmann, T.; Koppelmann, E.; Berg, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 163. (c) Hirao, T.; Yamada, A.; Ohshiro, Y.; Agawa, T. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 126. (d) See ref 57–59 in Beak's review.[1a] (e) Schell, F. M.; Carter, J. P.; Wiaux-Zamar, C. *J. Am. Chem. Soc.* **1978**, *100*, 2894. (f) Tsuge, O. *Bull. Chem. Soc. Pn.* **1985**, *58*, 1991.

(10) Not included in this discussion are nitrogen-substituted carbanions that are stabilized by some conjugating substituent such as an alkene, arene, or carbonyl substituent. These anions have a rich chemistry of their own.[1a] See also ref 16 for a recent example of a $PhCH(Li)NH_2$ equivalent that uses a chiral oxazolidinone as a protecting/activating group.

Table I

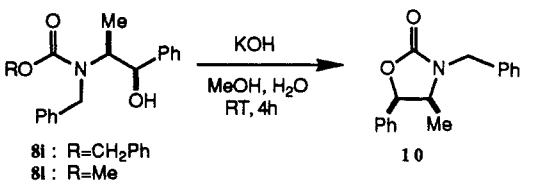
entry	substrate	electrophile	product (% yield)	yield of 9 (%)
1	1a	$PhCH_2CH_2CHO$	8a (72)	9a (99)
2	1a	iPrCHO	8b (78)	9b (97)
3	1a	$CH_3CH_2COCH_3$	8c (73)	9c (96)
4	1a	cyclohexanone	8d (82)	9d (98)
5	1a	cyclohex-2-en-1-one	8e (77)[a]	9d[b]
6	1a	$PhCH_2Br$	8f (71)	9f (98)
7	1a	CH_3CH_2I	8g (42)	c
8	1a	CH_2=$CHCH_2Br$	8h (40)	c
9	1b	PhCHO	8i (90)[d]	c
10	1b	cyclohexanone	8j (75)	c
11	1b	$PhCH_2Br$	8k (61)	c
12	1c	PhCHO	8l (82)[e]	c

[a] 1,2-Carbonyl addition only. [b] Produced by competing reduction of the double bond during deprotection. The yield was not determined. [c] Deprotection not attempted. [d] 3.0:1 mixture of erythro and threo diastereomers. [e] Erythro diastereomer only.

recently reported tin–lithium exchange as an effective method for the generation of 2-azaallyl anions, which have potential as α-amino anion equivalents.[11] Although these delocalized anions have not yet proven generally useful as equivalents of **2**, we were led to consider the generation of localized carbanions for this purpose. We now report that tin-substituted carbamates **1** are effective equivalents of anions **2**.

Peterson[6] and Quintard and Pereyre[7] have studied tin–lithium exchange as a method for tertiary amine synthesis. For example, treatment of [(*N*,*N*-dimethylamino)-methyl]tri-*n*-butylstannane with *n*-butyllithium affords [(*N*,*N*-dimethylamino)methyl]lithium. This method has not been extended to primary amine synthesis, presumably due to the difficulties encountered in the synthesis of the requisite protected stannanes.[7] We chose to examine the carbamate as a protecting group, since amides[1,3,4] and carbamates[5] are known to stabilize nitrogen-substituted organolithium compounds by dipole stabilization as well as internal lithium chelation.[1-4,12] Moreover, since our eventual aim is to develop chiral anions, we felt that the relatively defined cyclic structure of these chelated anions would be advantageous.

The preparation of stannanes **1a–c** was accomplished by alkylation of carbamates **5** with (α-iodoalkyl)stannanes **6**[13] as shown in Scheme I. Transmetalation of stannanes **1** with *n*-butyllithium or methyllithium proceeded smoothly at low temperature to generate the nitrogen-substituted carbanions **7**, which were quenched with various electrophiles as reported in Table I. Additions to carbonyl compounds were efficient, providing protected β-amino alcohols. Alkylations were less general, with reactive alkylating agents producing the best results. A particularly interesting observation was the diastereoselectivity of the addition of carbanions **7b** and **7c** to benzaldehyde (entries 9 and 12). The benzylcarbamate **7b** produced a 3:1 mixture of diastereomers, with the erythro isomer **8i** being favored, while the methyl carbamate **7c** gave the erythro diastereomer **8l** as the only detectable isomer. Structure assignment was made by base-promoted cyclization of **8i** and **8l** to the *cis*-oxazolidinone **10**, which was correlated with an authentic sample.[14]



8i: R=CH_2Ph
8l: R=Me

10

Deprotection of adducts **8** was best accomplished by transfer hydrogenolysis,[15] which proceeded faster and with less catalyst than other catalytic hydrogenolysis methods that were tested. If purified adducts **8** were used, the deprotections produced analytically pure amines **9** in near quantitative yields, with no aqueous workup or chromatography required (Table I). Deprotection of adduct **8e** resulted in reduction of the double bond, providing **9d**. We hope to overcome this limitation with other reduction conditions, or by selecting other nitrogen protecting groups.

To set the stage for work on chiral, nonracemic nitrogen-substituted organolithium reagents, we have found that oxazolidinones are also easily alkylated by iodo stannanes **6** and participate efficiently in tin–lithium exchange and reactions with electrophiles. For example, racemic oxazolidinone **11** gives the adduct **12** from cyclohexanone in good yield, and the auxiliary may be removed easily by transfer hydrogenolysis (Scheme II).[16] Our results using optically active **11** and related chiral auxiliaries for asymmetric synthesis will be reported separately. In particular, oxazolidinones derived from iodo stannane **6c** may provide interesting information regarding the configurational stability of α-amino anions in which the carbanionic center is stereogenic.

In summary, carbamates **1** are useful synthetic equivalents of unstabilized primary α-amino anions **2**. Advantages of the method include the ease of preparation of the anions and their precursors and the tolerance for easily removable nitrogen protecting groups. The generation of a variety of α-amino anions with other nitrogen protecting groups should now be possible. Efforts along these lines are underway.

General Procedure for Generation and Use of Carbanions (7) and for the Deprotection of Adducts 8. A solution of carbamate **1** in THF (0.1 M) was cooled to −78 °C and *n*-butyllithium or methyllithium (1.0 equiv of a solution in hexane or ether, respectively; ca. 2–3 M) was added in a dropwise fashion. After 10 min, 1.5 equiv of an electrophile was added, and the mixture was allowed to stir at −78 °C for 15 min. The reaction was quenched with acetic acid (20% in THF), and the resultant solution was diluted with water and extracted with ethyl acetate (3×). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (ethyl acetate/hexane) gave the pure adduct **8**.

A flask containing a mixture of **8** and 10% palladium on charcoal (75 mg/mmol of **8**) in methanol (0.05 M) was evacuated and purged with nitrogen. Ammonium formate (15 equiv) was added, and the mixture was refluxed for 1.5 h and monitored by TLC. After cooling, the reaction mixture was filtered through Celite using methanol washes, and the filtrate was concentrated. The residue was dissolved in chloroform, filtered through sodium sulfate, and

(11) Pearson, W. H.; Szura, D. P. *Tetrahedron Lett.* **1988**, *29*, 761–764.
(12) Bartolotti, L. J.; Gawley, R. E. *J. Org. Chem.* **1989**, *54*, 2980–2982, and references therein.
(13) (a) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151–166. (b) Seyferth, D.; Andrews, S. B.; Lambert, R. L. *Ibid.* **1972**, *37*, 69–76.
(14) Norephedrine was converted to its oxazolidinone, then alkylated with NaH/$PhCH_2Br$ to provide an authentic sample of **10**. See: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(15) Ram, S.; Spicer, L. D. *Synth. Commun.* **1987**, *17*, 415–418.
(16) Gawley has recently reported the deprotonation of *N*-benzyloxazolidinones to produce chiral N-substituted organolithium reagents. Our method is complementary, in that conjugating substituents such as aryl are not required for anion generation, and our auxiliaries may be removed by a simple one-step procedure that is compatible with β-amino alcohols. See: Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002–3004.

concentrated to produce the amine **9**, which required no further purification.

Acknowledgment. We thank the National Institutes of Health (GM-37100), Eli Lilly & Co., and The University of Michigan (Gomberg and Riggs fellowships to A.C.L.) for support of this work.

Supplementary Material Available: Experimental details for the preparation of **1**, **5**, and **8-12** and physical data for all compounds (8 pages). Ordering information is given on any current masthead page.

Variable Transition-State Structure in the Solvolyses of Substituted-Benzyl *p*-Toluenesulfonates†

Dennis N. Kevill* and Haobo Ren

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

Received September 25, 1989

Summary: Specific rates of solvolysis of seven benzyl *p*-toluenesulfonates (tosylates) in 11 solvents have been analyzed for each substrate in terms of the extended Grunwald-Winstein equation and for each solvent in terms of the Hammett equation; of especial interest is that the Hammett ρ values give a good correlation with a linear combination of solvent nucleophilicity and solvent ionizing power values.

Sir: The extent to which changes in reactant and substrate bring about changes in transition-state structure for bimolecular substitution reactions at carbon has been described as highly controversial.[3] In reactions of *p*-nitrobenzyl sulfonates, only small changes in selectivities were observed over large ranges of reactivities.[3] In contrast, in an approximate analysis[4,5] of the solvolyses of a series of substituted benzyl tosylates using the extended Grunwald-Winstein equation (1),[1,2]

$$\log (k/k_0) = lN + mY \qquad (1)$$

where k and k_0 are the specific solvolysis rates in a given solvent and in the standard solvent (80% ethanol), extremely large variations in the sensitivities (l) toward solvent nucleophilicity (N) were observed. The sensitivities (m) toward solvent ionizing power (Y) showed only modest variations (l = 0, m = 0.47 for the *p*-methyl derivative, varying to l = 1.5, m = 0.38 for the *p*-nitro derivative).

The estimated values[4] are unusual in that a large variation in l is accompanied by only a small variation in m, contrary to what one would expect from the concept of the variation being related to the "tightness" of the transition state. Further, the l value of zero for the *p*-methyl derivative is accompanied by a m value much lower than the value of close to unity that one would expect for a reaction without nucleophilic assistance.

Our detailed analysis avoids any approximations, other than those inherent in linear free energy relationships, and it has been carried out using Y_{OTs} values,[2,6] with either $N_{Et_3O^+}$ values[7-9] or N_{OTs} values.[2] The results (Table I) show the same general trends[4] but a much more reasonable variation pattern; using N_{OTs}, values range from 0.31 to 0.89 for l and from 0.91 to 0.33 for m.

Linear Hammett plots are obtained for the parent together with derivatives having positive σ values.[10] The slopes (ρ values) range from -1.3 to -5.1. If the magnitude is considered to reflect charge developed on the α carbon, a trend of increased charge (looser transition state) with either an increase in Y or decrease in N can be seen. Indeed, a good correlation of ρ with N and Y (modified eq 1) is observed; with N_{OTs} and Y_{OTs}, l = 0.60, m = -0.44 (r = 0.971), and with $N_{Et_3O^+}$ and Y_{OTs}, l = 0.70, m = -0.36 (r = 0.954).[11] In acetic acid and 95% acetone specific rates were obtained at 50.0 °C for the *p*-methyl derivative. These points lie appreciably above the Hammett plots based on the other substituents,[12] by 1.26 and 0.87 log k units, respectively.

Table I. Correlation of the Specific Rate of Solvolysis of Substituted Benzyl *p*-Toluenesulfonates at 50.0 °C,[a] Using Y_{OTs} Values and either $N_{Et_3O^+}$ or N_{OTs} Values within the Extended Grunwald-Winstein Equation[b]

subst	l[c]	m[c]	r[d]
(a) Using $N_{Et_3O^+}$ Values[e]			
p-Me[f,g]	0.467 ± 0.165	1.027 ± 0.092	0.979
H	0.770 ± 0.094	0.827 ± 0.049	0.988
p-Cl	0.755 ± 0.105	0.785 ± 0.054	0.983
p-Br	0.820 ± 0.120	0.797 ± 0.062	0.978
m-F	1.003 ± 0.086	0.666 ± 0.044	0.983
p-CF_3	1.167 ± 0.094	0.654 ± 0.049	0.981
p-NO_2	1.229 ± 0.108	0.562 ± 0.056	0.972
(b) Using N_{OTs} Values[h]			
p-Me[f,g]	0.314 ± 0.150	0.908 ± 0.117	0.956
H	0.496 ± 0.104	0.646 ± 0.075	0.956
p-Cl	0.488 ± 0.110	0.609 ± 0.079	0.946
p-Br	0.571 ± 0.125	0.654 ± 0.090	0.940
m-F	0.702 ± 0.090	0.474 ± 0.065	0.955
p-CF_3	0.842 ± 0.072	0.443 ± 0.051	0.977
p-NO_2	0.893 ± 0.050	0.334 ± 0.036	0.989

[a] Using log k values from studies in the 11 solvents listed in Table II. [b] Log $(k/k_0) = lN + mY$ (see text for definitions). [c] With associated standard errors. [d] Correlation coefficient. [e] Using a Y_{OTs} value of -2.95 for 95% acetone. [f] At 0.0 °C. [g] Excluding HCOOH (specific rate not available). [h] Unless otherwise indicated, using data in ten solvents; the value for 95% acetone is excluded (N_{OTs} value not available).

† Dedicated to Professor Christoph Rüchardt on the occasion of his 60th birthday.

(1) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700.
(2) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem.Soc.* **1976**, *98*, 7667.
(3) Dietze, P.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 5880.
(4) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288.
(5) Using a technique developed by Kaspi, J.; Rappoport, Z. *Tetrahedron Lett.* **1977**, 2035.
(6) Kevill, D. N.; Hawkinson, D. C. *J. Org. Chem.* **1989**, *54*, 154.
(7) Kevill, D. N.; Lin, G. M. L. *J. Am. Chem. Soc.* **1979**, *101*, 3916.
(8) Kevill, D. N.; Kamil, W. A. *J. Org. Chem.* **1982**, *47*, 3785.
(9) Kevill, D. N.; Anderson, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 1579.
(10) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
(11) Although Wells (Wells, P. R. *Chem. Rev.* **1963**, *63*, 171) suggested that "a fruitful venture may be the analysis of the Hammett reaction parameters in terms of solvent and reagent variations", the authors are not aware of any previous analysis of this type.
(12) Kochi, J. K.; Hammond, G. S. *J. Am. Chem. Soc.* **1953**, *75*, 3445.

0022-3263/89/1954-5654$01.50/0