tablish the applicability of calculations on H_2SO_4 to sulfate diesters (Table IV). Steric interactions involving the methyl groups are expected to be dominant in determining conformational energy. Nevertheless, the global minimum energy conformation is again +sc,+sc (72°,72°). Molecular models and minimal basis set ab initio calculations[21] predict that the +sc,-sc (90°,-90°) local minimum will be sterically destabilized. No minimum was located in this region. The relative energies and electron distribution of the other partially optimized conformers of dimethyl sulfate are consistent with the presence of similar stereoelectronic effects as postulated for H_2SO_4.

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Registry No. 2, 1073-05-8; **3**, 62822-77-9; **4**, 4988-33-4; H_2SO_4, 7664-93-9; 2-oxo-1,3,2-dioxathiane, 4176-55-0; 2-oxo-5-phenyl-1,3,2-dioxathiane, 62738-17-4; 1-oxothiane, 4988-34-5; pentamethylene sulfide, 1613-51-0; dimethyl sulfate, 77-78-1.

Supplementary Material Available: Tables of full geometrical parameters (bond lengths and angles), fractional atomic coordinates, and anisotropic temperature factors for compounds **2**, **3**, and **4** and full Mulliken population analysis for torsional conformation scan on H_2SO_4 (9 pages). Ordering information is given on any current masthead page.

Acidities of Glycine Schiff Bases and Alkylation of Their Conjugate Bases

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Abstract: Equilibrium acidities in Me_2SO are reported for six ketimines of the type $Ph_2C{=}NCH(R)CO_2Et$ and five aldimines, $ArCH{=}NCH(R)CO_2Et$. Changing R in the ketimine from H to Ph increased the pK_a by 2.2 units. This surprising acidity *decrease* for Ph substitution points to a substantial increase in steric effect, as do the increases in pK_a of 3.8 and 4.2 units observed for the replacement of hydrogen by Me and $PhCH_2$, respectively. Phase-transfer alkylation of the $Ph_2C{=}NCH_2CO_2Et$ ketimine gave over 90% of monoalkylate whereas, under similar conditions, the aldimine $4\text{-}ClC_6H_4CH{=}NCH_2CO_2Et$ gave a mixture of mono- and dialkylate. The difference is that the pK_a of the monoalkylated aldimine is essentially the same as that of the parent, which leads to rapid equilibration with the parent anion and consequent dialkylation. The rates of alkylation in Me_2SO of these parent and monoalkylated anions did not differ greatly, showing that the relative pK_{HA}s of the parent acid and its monoalkyl derivative, rather than the relative rates of the mono- and dialkylation reactions, is the principal factor that determines the extent of the competition between monoalkylation and dialkylation.

Introduction

Alkylation of derivatives of the simplest amino acid, glycine, has received considerable recent attention as a preparative route to higher amino acids. The overall strategy involves removal of an α-proton from a protected glycine derivative to give an α-anion of glycine, equivalent to **1**, which is then reacted with an electrophile such as an alkyl halide to form a new carbon–carbon bond. The final step in the sequence involves removal of the protecting groups to yield the desired amino acid. Protection of a primary amino group by reaction to form a Schiff base has the added bonus of acidifying the proton alpha to the nitrogen, thereby allowing for the use of milder basic conditions to effect deprotonation. The resulting carbon–nitrogen double bond stabilized carbanion (**2**) has been used in several routes to α-substituted primary amines.[1] In conjunction with the carboxyl or equivalent protecting group it has been used extensively in the synthesis of α-amino acids.[2-10]

1 **2**

One of us has reported the phase-transfer alkylation of benzophenone Schiff base derivatives of glycine ethyl ester (**3**) and aminoacetonitrile (**4**) as a particularly attractive route to higher amino acids.[11,12] Phase-transfer alkylations are often carried out in mixtures of aqueous sodium hydroxide and a nonpolar solvent, such as PhMe or CH_2Cl_2, in the presence of a tetraalkylammonium salt. The simple reaction procedure, mild conditions,

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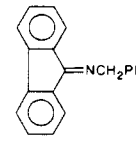
inexpensive and safe reagents and solvents as well as the ready availability of starting substrates and the ability to scale-up the reaction all combine to widen the scope and applicability of the phase-transfer technique.[13] The method has been extended to the alkylation of aldimine derivatives **5**, as well as phase-transfer alkylations under a variety of mild, basic conditions.[14] Several

$Ph_2C{=}NCH_2CO_2Et$ (**3**) $Ph_2C{=}NCH_2CN$ (**4**) $ArCH{=}NCH_2CO_2Et$ (**5**)

interesting amino acids, such as α-methyl amino acids,[14b] 1-aminocyclopropane-1-carboxylic acid,[15] and 3-fluorophenylalanine,[16] have also been prepared by using this procedure. A general observation in these reactions is that, whereas the aldimine esters **5** can be readily djalkylated at the α-carbon, the corresponding benzophenone Schiff base esters are readily monoalkylated but do not generally undergo dialkylation at the α-carbon. Since monoalkylation of active methylene compounds is a long-standing synthetic problem,[17] the possibility of selectively introducing a single alkyl group on the α-carbon of a protected glycine derivative (**3** or **4**) is of considerable synthetic potential.[18,19]

Table I. Equilibrium Acidities in Dimethyl Sulfoxide Solution at 25 °C

compd	structure	pK_a[a]
3	$Ph_2C{=}NCH_2CO_2Et$	18.7
4	$Ph_2C{=}NCH_2CN$	17.8
6	$Ph_2C{=}NCH_2Ph$	24.3 (24.1[b])
7		14.5
8	$Ph(EtO)C{=}NCH_2CO_2Et$	22.1
9	$PhCH{=}NCH_2CO_2Et$	19.5
10	$4\text{-}ClC_6H_4CH{=}NCH_2CO_2Et$	18.8
11	$Ph_2C{=}NCH(CH_3)CO_2Et$	22.8
12	$4\text{-}ClC_6H_4CH{=}NCH(CH_3)CO_2Et$	19.2[c]
13	$Ph_2C{=}NCH(CH_2Ph)CO_2Et$	23.2[c]
14	$4\text{-}ClC_6H_4CH{=}NCH(CH_2Ph)CO_2Et$	19.0
15	$Ph_2C{=}NCH(Ph)CO_2Et$	21.2[c]
16	$4\text{-}ClC_6H_4CH{=}NCH(Ph)CO_2Et$	17.2

[a] Determined by the method described in ref 21. The anions derived from the Schiff bases are colored and pK_a measurements were generally made against two (colorless) standard acids with the Schiff bases as indicators. The values are reproducible to ±0.05 pK_a unit. [b] Corrected for tautomerism; see ref 39. [c] Equilibrations in these titrations were slow (due to steric hindrance in these systems), but the values are reproducible.

The success of these phase-transfer alkylations depends on the protected amino compound being acidic enough so that sufficient proton removal can be brought about by the base to allow the reaction to proceed at a practical rate. Most substrates for phase-transfer alkylations have acidities in the range of pK_a = 16–23: e.g., dimethyl malonate and fluorene have pK_a values in Me_2SO of 15.7[20] and 22.6,[21] respectively. Fluorene has historically been cited as the weakest carbon acid that can be deprotonated and alkylated under phase-transfer conditions involving an interfacial mechanism.[22,23]

To better understand the processes involved in the alkylation of protected amino acid derivatives, the pK_a values of **3**–**5** and related compounds have been measured in dimethyl sulfoxide.[24,25] Since the acidity of the product plays a key role in determining whether or not dialkylation will compete with monoalkylation, acidities of several alkylation products have also been measured for selected examples. Relative steric effects in two substrates and their monoalkyl derivatives have been compared by measuring rate constants of their alkylation in Me_2SO.

Results and Discussion

Acidities in Dimethyl Sulfoxide Solution. Most substrates alkylated under phase-transfer conditions are too weakly acidic for

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pK_a values to be determined in water, but their acidities can be measured in the dipolar nonhydroxylic solvent dimethyl sulfoxide.[21,26] Table I presents pK_a values for the benzophenone imine of ethyl glycinate (**3**) and related compounds that are of interest for the preparation of amino acid derivatives by phase-transfer alkylations.

Examination of Table I shows that most of the imines have pK_a values in the range 14–23, where phase-transfer alkylation should be successful. The acidities of **3** and **4** are 3.2 and 4.1 pK_a units greater, respectively, than that of $PhCH_2CN$ (pK_a = 21.9[27]). (The larger acidifying effect of CN than CO_2Et has been observed previously, e.g., $PhCH_2CN$ is 0.8 pK_a unit more acidic than $PhCH_2CO_2Et$.[28]) The larger acidifying effect of the $Ph_2C{=}N$ function, relative to Ph, is due primarily to its superior ability to delocalize the negative charge in the anion. The electronegativity of nitrogen also plays a role as shown by the fact that $Ph_2C{=}NCH_2Ph$ (**6**)[29] is 1.3 pK_a units more acidic than its carbon analogue, $Ph_2C{=}CHCH_2Ph$ (pK_a = 25.6).[21] The relative acidities are reversed, however, in more crowded systems such as $Ph_2C{=}NCHPh_2$ (pK_a = 26.5)[29] and its carbon analogue, $Ph_2C{=}CHCHPh_2$ (pK_a = 25.8).[29] Here the greater stabilizing effect of the sp^2 nitrogen atom in the anion of 1,1,3,3-tetraphenyl-2-azapropene than the sp^2 carbon atom in the anion of 1,1,3,3-tetraphenylpropene is offset by the greater crowding of the phenyl rings in the 1,1,3,3-tetraphenyl-2-azapropenide ion. This more severe crowding (a consequence of the shorter C=N bond) causes the phenyl rings to twist farther out of planarity and results in inhibition of both resonance and solvation. The increased twisting also manifests itself in a slower rate of S_N2 reaction for the 1,1,3,3-tetraphenyl-2-azapropenide ion than for the 1,1,3,3-tetraphenylpropenide ion,[29] despite the higher basicity of the former.

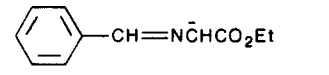
Attempts were made to measure the acidities of the aldimines derived from benzylamine and either benzaldehyde ($PhCH{=}NCH_2Ph$) or 4-pyridinecarboxaldehyde ($4\text{-}C_5H_4NCH{=}NCH_2Ph$), but the absorbances attributed to these anions were not stable, thereby making acidity measurements unreliable.

The difference in acidity (9.8 pK_a units) between the structurally similar benzylamine ketimines derived from fluorenone (**7**) and benzophenone (**6**) is large. This is not unexpected since fluorene itself is 9.6 units more acidic than Ph_2CH_2[30] due to the enforced coplanarity of its benzene rings and the aromatic character of the 14-π-electron system present in its anion.[32]

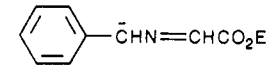
Replacement of a Ph group in **3** by OEt to give the imidate ester **8** causes a 3.4 pK_a unit decrease in acidity. This is likely to be associated with the stabilizing effect of OEt on the undissociated acid, since the inductive effect on the anion would be expected to be acid strengthening. The cyclic analogue of **8**, 2-phenyl-2-oxazolin-5-one, gave an unstable anion on attempted pK_a measurement. Similarly, anions of both amidine esters $Ph(Me_2N)C{=}NCH_2CO_2Et$ and $Me_2NCH{=}NCH_2CO_2Et$ were unstable in Me_2SO, so that accurate measurements of their acidities were not possible. With the latter compound it was necessary to use the conjugate base of a standard acid with a pK_a in the range of 26–27 for any color change to occur, which implies that this derivative is the least acidic of the compounds being studied. This result is reasonable since the possibility of phenyl group resonance has been removed and, in addition, the Me_2N group is known to be one of the best electrically neutral species for resonance electron donation,[33] which would stabilize the undissociated acid as discussed above for ethoxy compound **8**.

There is only a small acidifying effect (0.8 pK_a unit) associated with the second phenyl ring[34] in the benzophenone-derived Schiff base of glycine ethyl ester (**3**), as revealed by comparing the acidity of **3** with that of compound **9** (the Schiff base derived from benzaldehyde). Presumably steric interactions require the second phenyl group in the conjugate base of **3** to lie almost orthogonal to the plane of the C=N=C$^-$ anion system, or more likely, require both rings to be twisted out of this plane. The situation is similar to that for Ph_2CH_2 and Ph_3CH in which the additional phenyl ring in the triphenylmethane increases its acidity by only 1.9 pK_a units.[36]

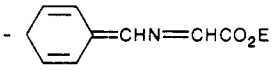
Resonance delocalization into the benzene ring, as shown in contributor **9c**, for the anion derived from **9** and similar delocalization for its *p*-Cl derivative (**10**) must be substantial, judging by the 0.7 pK_a unit greater acidity of the latter (this corresponds to a Hammett ρ of about 3) (the *p*-NO_2 derivative, $4\text{-}NO_2C_6H_4CH{=}NCH_2CO_2Et$, gave an unstable anion on attempted pK_a measurement). Similar charge delocalization must also be important in the conjugate base of **7** and no doubt occurs to some extent in all of the anions derived from the compounds in Table I.



9a

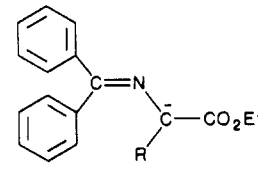


9b

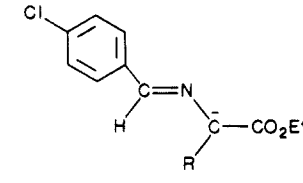


9c

Alkylation of **3** and **10**, which have essentially the same acidity, gives rise to α-alkyl derivatives (**11**, **13** and **12**, **14**) that have quite different acidities.[37] The lower acidities of **11** and **13** ($Ph_2C{=}NCH(R)CO_2Et$) than **12** and **14** ($4\text{-}ClC_6H_4CH{=}NCH(R)\text{-}CO_2Et$) by about 4 pK_a units must be caused by steric crowding between Ph and R in the conjugate bases of the α-alkyl substituted ketimines (**11a** and **13a**) that inhibits both solvation and resonance into the ester and π imine systems.[37a] These 1,3-steric interactions can be classified as $A^{1,3}$ strains.[38] Steric crowding is evidently less severe in the conjugate bases of the α-alkylaldimines (**12a** and **14a**) since the acidities of **12** and **14** differ but little from that of their parent (**10**) when statistical corrections for the number of acidic hydrogens are taken into account.[35]



11a: R = CH_3
13a: R = CH_2Ph
15a: R = Ph



12a: R = CH_3
14a: R = CH_2Ph
16a: R = Ph

Large acidifying effects as a result of an α-phenyl substitution are expected in the absence of steric crowding.[31] When R = Ph,

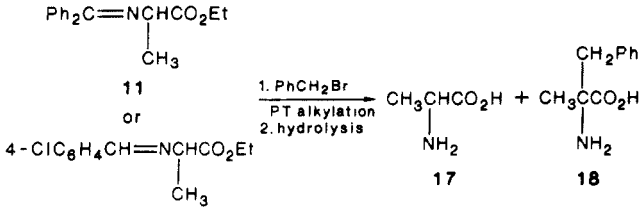
(26) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305–3313 and references cited therein.
(27) Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391–2395.
(28) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.
(29) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1983**, *48*, 2216–2222.
(30) The pK_a values of fluorene and diphenylmethane, in Me_2SO, are 22.6[27] and 32.2,[31] respectively.
(31) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325.
(32) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632–635.
(33) Hine, J.; Linden, S.-M.; Wang, A.; Thiagarajan, V. *J. Org. Chem.* **1980**, *45*, 2821–2825.

(34) This contrasts sharply with the 4.7 pK_a unit effect of an additional phenyl group on the acidity of phenylacetonitrile (the pK_a of diphenylacetonitrile in Me_2SO is 17.5[31,35]).
(35) When comparing the acidities of two compounds (A and B) that do not have the same number of potentially acidic hydrogens (such as $PhCH_2CN$ and Ph_2CHCN), it is appropriate to make a statistical correction to the difference between their acidities. This is done by using the following equation:

$$\text{difference in acidity} = \left|(pK_a \text{ of A}) - (pK_a \text{ of B}) + \log\left(\frac{\text{no. of acidic hydrogens in A}}{\text{no. of acidic hydrogens in B}}\right)\right|$$

(36) The pK_a values of triphenylmethane and diphenylmethane in Me_2SO, are 30.6 and 32.2, respectively.[31,35]
(37) (a) Bordwell, F. G.; Bartmess, J. E.; Hautala, J. A. *J. Org. Chem.* **1978**, *43*, 3095–3101. (b) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 6188–6189.
(38) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413 (see pp 397–8).

Table II. Product Studies in the Alkylation of Schiff Base Esters of Alanine by Different Phase-Transfer (PT) Methods



experiment	imine	PT alkylation method[a]	% **17**[b]	% **18**[b]
a	**11**	IPE	82 (98)	0 (2)
b	**12**	IPE	5 (6)	91 (94)
c	**11**	PTC	63 (91)	23 (9)
d	**12**	PTC	7 (8)	94 (92)

[a] IPE = ion-pair extraction; PTC = phase-transfer catalysis. See text for discussion. [b] Values from amino acid analyses of product mixtures. Values in parentheses calculated from elemental analyses of product mixtures based on % carbon and assuming % **17** + % **18** = 100%. See the Experimental Section.

the α-substituted ketimine **15** is 2.2 pK_a units *less* acidic than the parent **3** while aldimine **16** is 1.9 pK_a units more acidic than the parent **10**.[34]

Tautomerization of Schiff Bases during pK_a Measurements. The pK_a values reported in Table I assume that the structure shown is strongly favored at equilibrium. This is not always true. For example, when **6** is dissolved in Me_2SO in the presence of a catalytic amount of *t*-BuOK, equilibration to a mixture containing a predominant amount of tautomer **6′** (67% by NMR analysis) occurred rapidly (eq 1). This means that the true pK_a of **6** is

$$\underset{\mathbf{6}\ (33\%)}{Ph_2C{=}NCH_2Ph} \underset{DMSO}{\overset{KO^tBu\ (cat.)}{\rightleftharpoons}} \underset{\mathbf{6'}\ (67\%)}{Ph_2CHN{=}CHPh} \qquad (1)$$

24.1 rather than the value of 24.3 recorded in Table I, and that **6′** has a pK_a of 24.4.[39] A similar equilibration of the carbon analogue of **6′**, $Ph_2CHCH{=}CHPh$, revealed that the equilibrium position was in the reverse direction (eq 2). Therefore, the Schiff

$$\underset{85\%\ (pK_a = 25.7)}{Ph_2C{=}CHCH_2Ph} \underset{DMSO}{\overset{KO^tBu\ (cat.)}{\rightleftharpoons}} \underset{15\%\ (pK_a = 25.0)}{Ph_2CHCH{=}CHPh} \qquad (2)$$

bases **6** and **6′** are more acidic than their carbon analogues by 1.6 and 0.6 pK_a unit, respectively. Comparable equilibration studies with **3**, **4**, and **10** showed that only the tautomeric forms shown in Table I were present.

Schiff Base Alkylation Studies. Alkylation of $Ph_2C{=}NCH_2CO_2Et$ (**3**) with alkyl halides using LDA in THF/HMPA at −78 °C,[11a] phase-transfer conditions with n-$Bu_4N^+HSO_4^-$/NaOH/CH_2Cl_2,[11a] or *t*-BuOK/Me_2SO[40] gave good yields of monoalkylation products in which the alkyl group is α to the ester function.[41] Similarly, only monoalkylation was observed for the phase-transfer alkylation of $Ph_2C{=}NCH_2CN$ (**4**).[11b] However, treatment of 4-$ClC_6H_4CH{=}NCHCO_2Et^-$, the conjugate base of **10**, with 1 equiv of $PhCH_2Cl$ in Me_2SO gave roughly equal amounts of mono- and dialkylation.[14a]

(39) The value of the pK_a of a tautomer A can be calculated by using the following equation:

$$pK_a \text{ of tautomer A} = pK_a \text{ of mixture} + \left[(X \text{ of tautomer B}) \log\left(\frac{\text{tautomer A}}{\text{tautomer B}}\right)\right]$$

in which pK_a of mixture is the equilibrium acidity of the tautomer mixture, X of tautomer B is the mole fraction of tautomer B at equilibrium with tautomer A and log (tautomer A/tautomer B) is the log of the ratio of the two tautomeric forms at equilibrium. The acidity of tautomer B can be calculated by an analogous equation.

(40) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314–3320.

(41) We have not observed γ alkylation in the reaction of alkyl halides with Schiff base esters. For an example of γ alkylation, see: Harris, C. J. *Tetrahedron Lett.* **1981**, *22*, 4863–4866.

Table III. Rate Constants for the Alkylation Reaction of the Conjugate Bases of Imines with Benzyl Chloride in Me_2SO at 25 °C

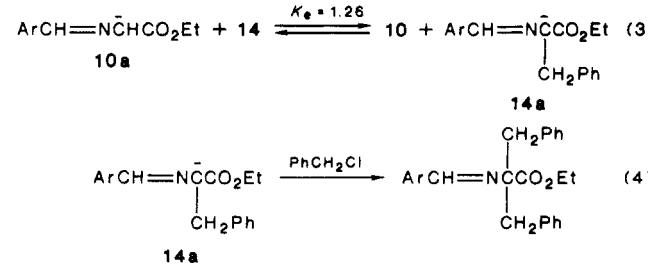
imine	pK_a[a]	k, M^{-1} s^{-1} [b]
$Ph_2C{=}NCH_2CO_2Et$ (**3**)	18.7	2.11 ± 0.02
$Ph_2C{=}NCH(CH_3)CO_2Et$ (**11**)	22.8	7.13 ± 0.03
4-$ClC_6H_4CH{=}NCH_2CO_2Et$ (**10**)	18.8	7.6 ± 0.2[c]
4-$ClC_6H_4CH{=}NCH(CH_3)CO_2Et$ (**12**)	19.2	8.5 ± 0.2

[a] Values taken from Table I. [b] Average and standard deviation of three or more runs with varied pseudo-first-order excess concentrations of benzyl chloride. [c] Value taken from the first half-life of the alkylation reaction. The ratio of **10** to its conjugate base was roughly two while the benzyl chloride concentration was >10 times the concentration of the nucleophile.

These observations have been confirmed by additional product studies (see Table II) in which the benzophenone and 4-chlorobenzaldehyde Schiff base esters of alanine (**11** and **12**, respectively) were alkylated with benzyl bromide under ion-pair extraction (IPE) conditions[11a] and the phase-transfer catalysis method (PTC) with K_2CO_3 in refluxing CH_3CN.[14c] To facilitate product identification, the crude alkylation mixtures were hydrolyzed to the amino acids, which were then analyzed by amino acid as well as elemental analysis. These reaction conditions could represent the second alkylation step (resulting in "dialkylation") when the glycine derivatives **3** and **10** are used as the starting substrates in the alkylation procedure. In both the IPE and PTC methods, the aldimine ester of alanine (**12**) was readily alkylated a second time ("dialkylation") to yield α-methylphenylalanine (**18**) as the major product after hydrolysis. In contrast, the benzophenone imine ester of alanine (**11**) did not undergo any "dialkylation" in the IPE reaction and only a minor amount of "dialkylation" with the PTC method. In both cases with the benzophenone imine **11**, the major amino acid product, alanine (**17**), resulted from hydrolysis of unreacted starting substrate **11**.

Rates of alkylation of the conjugate bases of **3**, **10**, and their monomethyl derivatives (**11**, **12**) were measured in Me_2SO solution to determine the effect of an α-methyl group on the relative reactivities of the carbanions (see Table III). The rate of reaction of the carbanion derived from **3** with benzyl chloride in pseudo-first-order excess (>10-fold) in Me_2SO was measured by following the disappearance of the anion absorbance at 505 nm. Excellent kinetics were obtained over 3–3.5 half-lives (R^2 values for plots of ln (abs_0/abs_t) vs time were 0.999 or better, k = 2.11 ± 0.02 M^{-1} s^{-1} at 25 °C for three runs with benzyl chloride). Excellent kinetics were obtained for over 3 half-lives for the reaction of the $Ph_2C{=}NC(CH_3)CO_2Et$ anion (**11a**) with benzyl chloride (reaction followed at 530 nm, k = 7.13 ± 0.03 M^{-1} s^{-1} at 25 °C for three runs with benzyl chloride).

Similarly, clean kinetics for at least 90% of the reaction were obtained for the anion derived from 4-$ClC_6H_4CH{=}NCH(CH_3)CO_2Et$ (**12**) with benzyl chloride (reaction followed at 500 nm, k = 8.5 ± 0.2 M^{-1} s^{-1} at 25 °C with benzyl chloride in pseudo-first-order concentrations: 6.3, 14.0, and 14.7 mM). However, poor kinetics were obtained for reaction of the conjugate base of 4-$ClC_6H_4CH{=}NCH_2CO_2Et$ (**10**) with benzyl chloride. This is due to rapid proton transfer between the monoalkylated product (**14**) and the anion derived from **10** (eq 3). The anion derived from **14** can then react to yield dialkylated Schiff base (eq 4). By starting the reactions with large initial concentrations

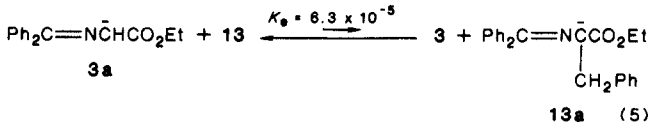


of **10**, the proton-transfer equilibrium (eq 3) is shifted to disfavor the complicating side reaction.[17] Under these conditions good

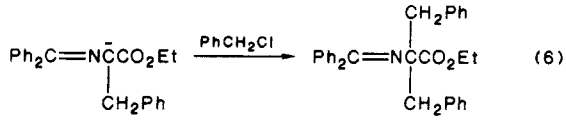
kinetics were obtained for the first half-life, yielding a rate constant of 7.6 ± 0.2 M^{-1} s^{-1}.

Comparison of the rates of benzylation for these four Schiff bases shows that the more sterically hindered α-methyl anions (**11a** and **12a**) react *faster* than their less hindered parent anions (**3a** and **10a**) due to their higher basicities. Similar results have been obtained for the reactions of $ArC(R)CN^-$ and $ArC(R)SO_2Ph^-$ anions with *n*-BuCl in Me_2SO, in which the α-methyl anions (R = CH_3) react 1.3 and 8 times faster that the unsubstituted (R = H) phenylacetonitrile and benzyl phenyl sulfone anions, respectively.[42]

Since the rate constants for S_N2 reaction of α-methyl-substituted carbanions (**11a** and **12a**) are not greatly different from the rate constants for S_N2 reactions of the parent carbanions (**3a** and **10a**), the formation of dialkylated material upon alkylation of **10a**, but not of **3a**, cannot be attributed to differences in steric hindrance in the S_N2 reactions of **3a** and **10a**, but rather to differences in the pK_as of the alkylated products. The alkylated products **12** and **14** (from **10a**) have pK_as only slightly higher than that of **10**, which means that during alkylation of **10a** appreciable concentrations of **12a** (or **14a**) are present and can be alkylated. On the other hand, the alkylation products from **3a** (**11** and **13**) have pK_a values much higher than that of **3**, so that only small concentrations of **11a** (or **13a**) (see eq 5) are present and dialkylation is slow.



3a **13a** (5)



(6)

13a

These results suggest that one should be able to anticipate the extent of competition to be expected between mono- and dialkylation of anions of weak acids from a knowledge of the acidities of the parent acid and its monoalkyl derivative. Information of this kind is available for a number of carbon acids. α-Methylation is known to increase the acidities of nitroalkanes, but decreases the acidities of most other carbon acids. The decrease is 0.6 unit from acetone to 3-pentanone and 1.1 from the latter to 2,4-dimethyl-3-pentanone. Such relatively small changes are typical of ketones and account for the well-known competition between monoalkylation and dialkylation for most enolate ion alkylations. The problem of dialkylation is of course exacerbated by the presence of α- and α′-hydrogen atoms in many ketones. 3-Methylpentane-2,4-dione is 1.7 units less acidic than pentane-2,4-dione, so the problem is alleviated somewhat in alkylation of the former. The acidities of nitriles and sulfones appear to be decreased by over 2 units by α-substitution. It is not surprising then to find that alkylation of these weak acids gives primarily monoalkylation.[11b]

Experimental Section

Instruments and Analyses. Melting points are uncorrected. Proton NMR spectra were determined on a Varian EM-390 spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Product samples were analyzed by HPLC with a C18 HPLC column (Waters μBondapak, P/N 27324) and 70:30 MeOH/H_2O (v/v) containing $NaHCO_3$ (0.1 g per each 1000 mL of mixed solvent) as the mobile phase at a flow rate of 2.0 mL/min and UV detection at 254 nm. Elemental analyses were performed by Midwest Microlab, Ltd. of Indianapolis, IN. High-resolution mass spectra were conducted at Eli Lilly and Co. in Indianapolis. Amino acid analyses were performed in the laboratory of Dr. R. Roeske at the Indiana University School of Medicine on a Beckman 119CL amino acid analyzer.

Materials and Syntheses. General Data. All reagents were commercially available reagent-grade chemicals unless otherwise noted. Purity of pK_a samples was ascertained by HPLC, TLC, NMR, IR, and melting point or boiling point, whenever applicable. The preparation and properties of Schiff bases **3**, **4**, **11**, **13**, and **15** have been reported.[43]

Equilibrium acidity measurements were carried out by the method described earlier.[21]

Kinetics. Rates of reactions in Me_2SO were determined spectrophotometrically, as previously described.[40]

***N*-(Diphenylmethylene)benzenemethanamine[44] (6).** Equimolar amounts of benzophenone and benzylamine in toluene containing BF_3·Et_2O were refluxed with azeotropic removal of water.[11] A normal aqueous workup was followed by recrystallization from ether/hexane. **6**: mp 58–9 °C (lit.[45] mp 55–60 °C); NMR δ 4.5 (2 H, s), 7.0–7.8 (15 H, m).

***N*-(Phenylmethylene)benzenemethanamine.[46]** Equimolar amounts (0.05 mol) of benzaldehyde, benzylamine, and $MgSO_4$ were stirred in CH_2Cl_2 (100 mL) for 2 h at room temperature. The suspension was filtered and washed with cold water (3 × 30 mL), 2 M aqueous sodium hydroxide containing NH_2OH·HCl (2 g/100 mL of solution) (1 × 30 mL), 1% aqueous $NaHCO_3$ (1 × 30 mL), and brine (1 × 30 mL). The organic solution was dried ($MgSO_4$) and filtered, and the solvent was removed to yield a clear oil, which was ≥99% pure by HPLC; NMR δ 4.6 (2 H, s), 7.0–7.9 (10 H, m), 8.1 (1 H, s).

***N*-(4-Pyridinylmethylene)benzenemethanamine[1e]** was prepared from 4-pyridinecarboxaldehyde and benzylamine by the procedure described above for *N*-(phenylmethylene)benzenemethanamine; mp 56–7 °C (lit.[1e] mp 56–8 °C); NMR δ 4.8 (2 H, s), 7.3 (5 H, s), 7.5 (2 H, d), 8.3 (1 H, s), 8.6 (2 H, d).

***N*-(9*H*-Fluoren-9-ylidene)benzenemethanamine[47] (7).** By analogy with our previously described procedure,[43] benzylamine (0.5 g, 4.7 mmol) and fluorenone imine hydrochloride[48] (1.0 g, 4.6 mmol) were stirred overnight at room temperature in CH_2Cl_2 (15 mL). Normal workup gave an oil which was recrystallized from ether/hexane. **7**: mp 78–9 °C; NMR δ 5.2 (2 H, s), 7.0–7.9 (13 H, m); IR (KBr) 1635 cm^{-1}. Anal. Calcd for $C_{20}H_{15}N$: C, 89.19; H, 5.61; N, 5.20. Found: C, 89.39; H, 5.73; N, 5.37.

Ethyl *N*-(ethoxyphenylmethylene)glycinate[49] (8) was prepared according to the procedure of Tarzia et al.[50] **8**: bp 107–9 °C (0.25 mm) [lit.[50] bp 124–6 °C (1.3 mm)]; NMR δ 1.2 (3 H, t), 1.3 (3 H, t), 4.1 (2 H, s), 4.15 (2 H, q), 4.35 (2 H, q), 7.4 (5 H, s).

2-Phenyl-5(4*H*)-oxazolone[51] was prepared according to the procedure given in ref 51: mp 85–6 °C (lit.[51] mp 89–92 °C); NMR δ 4.4 (2 H, s), 7.4–8.1 (5 H, m).

Ethyl *N*-[(Dimethylamino)phenylmethylene]glycinate. Dimethylamine (10 mL, 0.15 mol) in MeOH (40 mL) was added dropwise to a stirred, ice-cold solution of the imidate **8** (5.0 g, 21.2 mmol) and dimethylamine hydrochloride in MeOH (60 mL). Following the addition, the solution was allowed to come to room temperature and stirring was continued for 2 h. The solution was filtered, most of the MeOH was removed, and CH_2Cl_2 (100 mL) was added to the concentrated mixture. The organic solution was washed with 3 × 50 mL of saturated aqueous K_2CO_3, 3 × 50 mL of H_2O, and 1 × 50 mL of brine, dried ($MgSO_4$), and filtered, and the solvent was removed to yield a gold oil containing a fine solid suspension. Dry ether (100 mL) was added, the solution was filtered, and the solvent was removed. The resulting oil was distilled; bp 99–101 °C (0.05 mm); NMR δ 1.2 (3 H, t), 2.8 (6 H, s), 3.6 (2 H, s), 4.0 (2 H, q), 7.0–7.5 (5 H, m); MS (high resolution), *m/e* 234.1350 (M^+) ($C_{13}H_{18}N_2O_2$ requires 234.1368).

Ethyl *N*-[(dimethylamino)methylene]glycinate[52] was prepared according to the procedure of Fitt and Gschwend;[3b] bp 72 °C (0.05 mm) [lit.[52] bp 75 °C (0.001 mm)]; NMR δ 1.25 (3 H, t), 2.8 (6 H, s), 3.8 (2 H, s), 4.1 (2 H, q). 7.2 (1 H, s).

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(51) Vandenberg, G. E.; Harrison, J. B.; Carter, H. E.; Magerlein, B. J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 946–8.

(52) Kantlehner, W.; Wagner, F.; Bredereck, H. *Liebigs Ann. Chem.* **1980**, 344–357.

Ethyl *N*-(phenylmethylene)glycinate[53] **(9)** was prepared from benzaldehyde and glycine ethyl ester hydrochloride according to the procedure of Stork et al.[54] The CH_2Cl_2 containing the product was washed with 3 × 30 mL of cold water, 1 × 30 mL of 1% $NaHCO_3$, and 1 × 30 mL of brine, dried ($MgSO_4$), and filtered to give a clear oil. **9**: NMR δ 1.3 (3 H, t), 4.3 (2 H, q), 4.5 (2 H, s), 7.4–8.0 (5 H, m), 8.3 (1 H, s).

Ethyl *N*-[(4-chlorophenyl)methylene]glycinate (10) was prepared from 4-chlorobenzaldehyde and glycine ethyl ester hydrochloride according to the procedure described above for **9**. **10**: mp 31–2 °C; NMR δ 1.3 (3 H, t), 4.15 (2 H, q), 4.25 (2 H, s), 7.5 (4 H, AB quartet, J = 9 Hz, $\Delta\nu$ = 29 Hz), 8.1 (1 H, s); IR (KBr) 1745, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 58.57; H, 5.33; Cl, 15.76; N, 6.47.

Ethyl *N*-[(4-nitrophenyl)methylene]glycinate[55] was prepared from 4-nitrobenzaldehyde and glycine ethyl ester hydrochloride according to the procedure described above for **9**; mp 86–7 °C (lit.[55] mp 87 °C); NMR δ 1.3 (3 H, t), 4.2 (2 H, q), 4.45 (2 H, s), 8.1 (4 H, AB quartet, J = 9 Hz, $\Delta\nu$ = 29 Hz), 8.4 (1 H, s).

Ethyl *N*-[(4-chlorophenyl)methylene]-DL-alanate (12) was prepared from 4-chlorobenzaldehyde and DL-alanine ethyl ester hydrochloride according to the procedure described above for **9**. **12**: oil; NMR δ 1.3 (3 H, t), 1.4 (3 H, d), 4.0–4.4 (3 H, m), 7.5 (4 H, AB quartet, J = 9 Hz, $\Delta\nu$ = 32 Hz), 8.3 (1 H, s); IR (KBr) 1740, 1635 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; Cl, 14.79; N, 5.84. Found: C, 60.27; H, 6.01; Cl, 14.68; N, 5.89.

Ethyl *N*-[(4-chlorophenyl)methylene]-DL-phenylalanate (14) was prepared from 4-chlorobenzaldehyde and DL-phenylalanine ethyl ester hydrochloride according to the procedure described above for **9**. **14**: oil; NMR δ 1.2 (3 H, t), 2.8–4.35 (5 H, m), 7.1–7.75 (9 H, m), 7.85 (1 H, s); IR (KBr) 1740, 1645 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; Cl, 11.23; N, 4.44. Found: C, 68.63; H, 6.00; Cl, 11.24; N, 4.70.

Ethyl α-[[(4-chlorophenyl)methylene]amino]-DL-benzeneacetate (16) was prepared from 4-chlorobenzaldehyde and DL-phenylglycine ethyl ester hydrochloride according to the procedure described above for **9**. **16**: oil; NMR δ 1.15 (3 H, t), 4.1 (2 H, q), 5.15 (1 H, s), 7.2–7.8 (9 H, m), 8.2 (1 H, s); IR (KBr) 1740, 1640 cm^{-1}. Anal. Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; Cl, 11.75; N, 4.64. Found: C, 67.36; H, 5.39; Cl, 11.74; N, 4.64.

Determination of Equilibrium Concentrations of Tautomers by NMR. Compound **6** (ca. 20 mg) was dissolved in DMSO (0.5 mL). A NMR tube was fitted with a septum cap and, by means of syringe needles, purged with argon. The DMSO solution of **6** was added to the tube and a NMR spectrum was taken. At the NMR machine, ca. 2 drops of a solution of *t*-BuOK in DMSO (ca. 70 mM) was added to the above solution. The solution was mixed and returned to the NMR. Spectra were then taken at frequent time intervals to observe any change in composition of the species in the tube. After approximately 30 min no further change in the spectrum was observed and the experiment was terminated. From a comparison of the peak heights assigned to the benzylic hydrogens in **6** (δ 4.5, 2 H) and the benzylic hydrogen in **6′** (δ 5.7, 1 H), the relative equilibrium composition of the mixture was determined: 33% **6** and 67% **6′**. Similar experiments using 1,3,3-triphenylpropene, **3**, **4**, and **10** as starting compound gave the results discussed in the text.

Product Studies: Alkylation of 11 or 12 with Benzyl Bromide by Ion-Pair Extraction or Phase-Transfer Catalysis. (a) Alkylation of 11 with Benzyl Bromide by Ion-Pair Extraction. A mixture of **11** (1.05 g, 3.75 mmol) and benzyl bromide (0.77 g, 4.5 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL) was added rapidly to a magnetically stirred solution of 10% aqueous sodium hydroxide (3.75 g, 9.38 mmol, 2.5 equiv) and tetrabutylammonium hydrogen sulfate (1.27 g, 3.76 mmol, 1.0 equiv) and stirring was continued at 23 °C for 3 h. HPLC analysis of the reaction mixture after 3 h showed (normalized raw area, retention time) the following: **11** (58%, 4.8 min) and two other products, AA (40%, 7.8 min, presumed to be the benzophenone Schiff base benzyl ester of **17**) and AB (2%, 13.5 min, unknown product). The layers were separated, the organic layer was reduced in vacuo to an oil, ether (30 mL) was added, and the precipitated salts were filtered. The ethereal solution was washed with water (2 × 20 mL) and saturated aqueous sodium chloride (20 mL) and dried ($MgSO_4$), and the solvent was removed to yield crude product (1.45 g). This product was dissolved in ether (5 mL) and stirred with 1 N aqueous HCl (6 mL, 6 mmol) at 23 °C for 24 h. The layers were separated, and the aqueous layer was washed with ether (2 × 10 mL). Concentrated HCl (6 mL, 72 mmol) was added to the aqueous layer and the solution was refluxed for 12 h. After cooling and removal of the solvent, the solid residue was taken up in water (70 mL) and stirred overnight with strongly acidic cation-exchange resin (Amberlite IR-120+, 20 cm^3). The resin was collected on a Buchner funnel and washed with distilled water until the filtrate showed a negative test for chloride ion ($AgNO_3$). The resin was then stirred overnight with 6 N NH_4OH (50 mL) and filtered, and the water was removed in vacuo to yield 0.32 g of product; amino acid analysis: 82% alanine (**17**), 0% α-methylphenylalanine (**18**). Anal. Calcd for $C_3H_7NO_2$ (alanine): C, 40.44; H, 7.92; N, 15.72. Calcd for $C_{10}H_{13}NO_2$ (α-methylphenylalanine): C, 67.02; H, 7.31; N, 7.82. Found: C, 41.06; H, 7.93; N, 14.94; residue, 0.53; weight loss at 120 °C, 0.68.

(b) Alkylation of 12 with Benzyl Bromide by Ion-Pair Extraction. The procedure followed was analogous to that for product study (a), with **12** (0.90 g, 3.8 mmol). After 3 h of reaction, HPLC showed the following: **12** and/or benzyl bromide (overlap) (1.5%, 3.3 min) and two additional products, AC (90%, 9.6 min, presumed to be the 4-chlorobenzaldehyde Schiff base ethyl ester of product **18**) and AD (8.5%, 18.2 min, presumed to be the 4-chlorobenzaldehyde Schiff base benzyl ester of product **18**). Workup as before gave 1.28 g of crude product. The two-step hydrolysis procedure and ion-exchange yielded 0.56 g of product; amino acid analysis: 5% alanine (**17**), 91% α-methylphenylalanine (**18**). Anal. Calcd for $C_3H_7NO_2$ (alanine): C, 40.44; H, 7.92; N, 15.72. Anal. Calcd for $C_{10}H_{13}NO_2$ (α-methylphenylalanine): C, 67.02; H, 7.31; N, 7.82. Found: C, 65.35; H, 7.30; N, 7.52; residue, none; weight loss at 120 °C, 0.80.

(c) Alkylation of 11 with Benzyl Bromide by Phase-Transfer Catalysis. A heterogeneous mixture of **11** (1.05 g, 3.75 mmol), benzyl bromide (0.77 g, 4.5 mmol), tetrabutylammonium bromide (0.12 g, 0.4 mmol), finely ground technical-grade potassium carbonate (1.56 g, 11.3 mmol), and acetonitrile (30 mL) was refluxed with stirring for 48 h. HPLC analysis of the reaction mixture showed the following: starting imine **11** (86%, 4.85 min) and two other minor products, AA (3%, 8.1 min) and AB (11% 14.0 min), which were identical by coinjection with the products from product study a. The mixture was cooled and filtered, the solvent was removed in vacuo. The residue was dissolved in ether (30 mL), filtered, washed with water (2 × 20 mL) and saturated aqueous NaCl (20 mL), and dried ($MgSO_4$), and the solvent was removed to yield 1.73 g of crude product. The further steps in the hydrolysis and ion-exchange procedure described earlier for product study a were followed to yield 0.32 g of product; amino acid analysis: 63% alanine (**17**), 23.5% α-methylphenylalanine (**18**). Anal. Calcd for $C_3H_7NO_2$ (alanine): C, 40.44; H, 7.92; N, 15.72. Anal. Calcd for $C_{10}H_{13}NO_2$ (α-methylphenylalanine): C, 67.02; H, 7.31; N, 7.82. Found: C, 42.81; H, 7.18; N, 12.68; residue, 6.10; weight loss at 120 °C, 0.72.

(d) Alkylation of 12 with Benzyl Bromide by Phase-Transfer Catalysis. The procedure is analogous to that for product study (c), with **12** (0.90 g, 3.8 mmol). After 48 h of reaction, HPLC showed the following: starting imine or benzyl bromide (overlap) (1%, 3.3 min) and one major product, AC (99%, 9.8 min, identical with the product formed in product study b). Workup as in product study c gave 1.33 g of crude product. The two-step hydrolysis procedure and ion-exchange yielded 0.51 g of product; amino acid analysis: 7% alanine (**17**), 94% α-methylphenylalanine (**18**). Anal. Calcd for $C_3H_7NO_2$ (alanine): C, 40.44; H, 7.92; N, 15.72. Anal. Calcd for $C_{10}H_{13}NO_2$ (α-methylphenylalanine): C, 67.02; H, 7.31; N, 7.82. Found: C, 64.90; H, 7.15; N, 7.71; residue, 1.29; weight loss at 120 °C, 0.35.

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