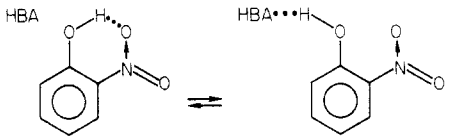
HBA base solvent (constant hypsochromic effect of breaking the internal H bond, smallest bathochromic effect of forming the H bond to solvent) and smaller $\Delta\Delta\nu$ terms for the stronger HBA solvents. As is seen in Table I and Figure 3, however, the converse order is observed. We can rationalize the results in terms of a **3a** ⇄ **3b** equilibrium, with the 2-nitrophenol spectrum a composite of bands arising from *intra*- and *inter*molecularly hydrogen bonded species [the separations between $\nu(\mathbf{3a})_{max}$ and $\nu(\mathbf{3b})_{max}$ are not sufficiently great for the spectrum to show resolution into two bands but lead rather to band broadening]. The



3a 3b

equilibrium is only slightly to the right in the weak HBA base solvent, anisole, and much farther to the right in hexamethylphosphoramide. The farther to the right the equilibrium, the greater is the contribution of **3b** to the composite spectrum and the greater is the hypsochromic shift.

Concluding Remarks. Steric and electronic factors undoubtedly play major roles in the differing hydrogen bonding behavior of **2** and **3**. Formation of a type-B hydrogen bond to HBA solvents would require that either the CH_3NH or NO_2 group of **2** be twisted from planarity, with a consequent decrease in amine → ring → nitro mesomeric interaction, and a significant loss in delocalization energy. The greater HBD acidity of **3** compared with that of **2** may also play a part.

Finally, the relationship between our findings and some interesting observations by Dyall and Kemp[10] deserve mention. These workers found that in weakly basic solvents *N*-methyl-2-nitroaniline (**4**) showed only a single NH stretching peak in the IR, which they attributed to the internally hydrogen bonded species. In the stronger HBA solvents, however, there appeared a low-frequency shoulder, which shifted to increasingly lower frequencies with increasing solvent HBA basicity (and which they resolved graphically into two peaks). In Me_2SO solvent, the lower frequency band was actually the stronger of the two peaks.

They did not conclude from this that the intermolecular hydrogen bond was broken but rather that the single amino hydrogen of **4** *simultaneously* formed an *intra*molelar hydrogen bond to NO_2 and an *inter*molecular hydrogen bond to the solvent, i.e., a *bifurcated* hydrogen bond. To accomplish this, they suggested that the CH_3NH group of **4** twists slightly from planarity.

The findings from the UV-visible and IR spectral studies are not necessarily mutually inconsistent. Dyall and Kemp's picture would be consistent with the present findings if the bathochromic effect of the *inter*molecular portion of the bifurcated hydrogen bond were offset by a slight decrease in the bathochromic effect of the (probably slightly weaker) internal hydrogen bond, and/or by a possible hypsochromic effect of twisting the CH_3NH group slightly from planarity.

Acknowledgment. The work by R.W.T. was supported in part by a grant from the Public Health Service. The work by M.J.K. was done under Naval Surface Weapons Center Independent Research Task IR-210.

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Effect of α-Amino Substituents on Rates of Formation of sp^2-Hybridized Carbanions[1]

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Received October 6, 1981

Kinetics of the sodium methoxide catalyzed deuterium exchange of the methyl esters of *N,N*-dimethylglycine, *N*-methylproline, isovaleric acid, and *cis*- and *trans*-2-methylcyclopentanecarboxylic acid have been studied in methanol-*O*-*d* at 35 °C. The results are taken as additional evidence for destabilizing repulsions between unshared electron pairs as an important factor in decreasing reactivity in carbanion formation. Such repulsions can be minimized by rotation around the bond between the substituent and the carbanion center.

The effect of α-fluoro and α-alkoxy substituents on rates of formation of sp^2-hybridized carbanions has been studied previously by this research group. Rates of sodium methoxide catalyzed deuterium exchange in methanol-*O*-*d* were determined for methyl esters of fluoroacetic, methoxyacetic, tetrahydrofuran-2-carboxylic, 1,3-dioxolane-2-carboxylic, and several reference acids.[2,3] The results were discussed in terms of repulsions between unshared pairs of electrons and the electronegativities of fluorine and oxygen as well as simple steric and polar effects. Amino substituents differ from fluoro and alkoxy substituents in that they have only one unshared pair of electrons. Hence an α-amino substituent on a carbanion can orient itself (if rotation around the bond joining it to the carbanion system is feasible) so that all its unshared electrons are in an

(1) (a) Supported in part by Grant CHE 79 26319 from the National Science Foundation. Part 23 in the series "Structural Effects on Rates and Equilibria". (b) For part 22, see Hine, J.; Linden, S.-M. *J. Org. Chem.* **1981**, *46*, 1635-8.

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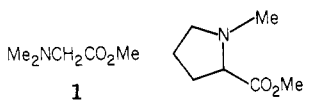
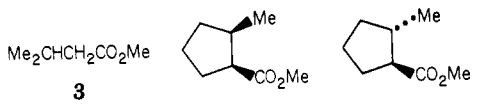
0022-3263/82/1947-1738$01.25/0

orbital that is orthogonal to the orbitals containing the unshared carbanion electrons. For this reason we have studied the exchange of the methyl ester of *N,N*-dimethylglycine (1). (With a primary or secondary amino group, base-catalyzed aminolysis of the ester would have been a probable serious complication.) To have a case in which rotation around the bond between the amino group and the carbanion center is constrained, we studied methyl hygrate (2), the methyl ester of *N*-methylproline. To



1 2

provide models for the steric effects that might be seen with 1 and 2, we also studied methyl isovalerate (3) and the methyl esters of *cis*- and *trans*-2-methylcyclopentanecarboxylic acid (4 and 5).

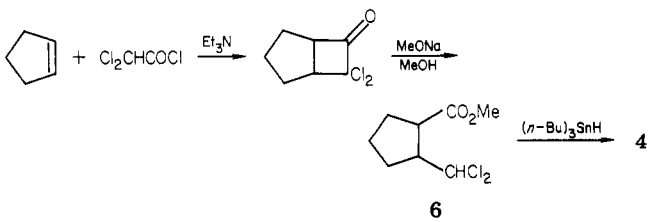


3 4 5

Garst and co-workers have studied the effects of α-amino and α-amido substituents on carbanion formation by unsymmetrical ketones. Enolates formed under both kinetic and thermodynamic conditions were captured and analyzed as trialkylsilyl ethers.[4] This work, including a discussion of earlier literature data, gave valuable information concerning α-amino substituent effects on carbanion formation. However, in not all cases were data on isosteric nitrogen-free ketones available for comparison purposes. Furthermore, the method provides a comparison of only two things (the two sides of the ketone) at a time. Hence, for example, we cannot tell whether the tendency of 3-pyrrolidinones to form carbanions to a greater extent at carbon 4 than at carbon 2 is a result of activation at carbon 4 or deactivation at carbon 2 (or both). It is plausible that repulsions involving the unshared electron pair of the α-amino group could slow reaction at carbon 2, but it is also plausible that the same factors that cause a β-methoxy substituent to increase the rate of carbanion formation by a methyl ester by 160-fold[2] could cause the β-amino substituent to increase the reactivity at carbon 4 substantially.

Results and Discussion

Compounds 1–3 were prepared by minor modifications of known procedures. The known adduct of cyclopentene and dichloroketene[5] was methanolized in a manner analogous to that reported for similar compounds[5,6] to give ester 6, which was reduced to 4. Although the preparation



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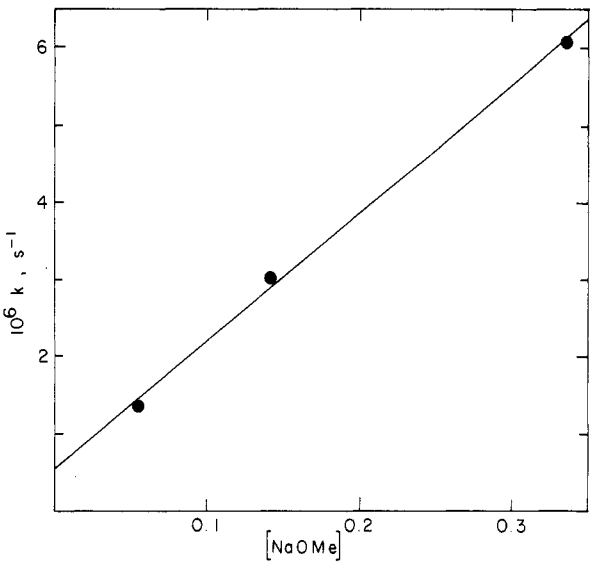
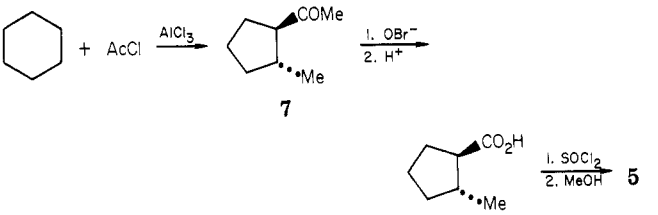


Figure 1. Plot of first-order rate constants for deuterium exchange of methyl hygrate (2) vs. sodium methoxide concentration.

of 5 from 3-methylcyclohexanone has been reported,[7] we made it by the following reaction sequence:



The ketone 7[8] prepared in this way has been reported to be 83% trans and 17% cis.[9] The 5 we obtained contained 12% 4, which was reduced to 7% by preparative VPC.

First-order rate constants per exchangeable hydrogen atom (k_{obsd}) were obtained at sodium methoxide concentrations varying over a range of at least 2.5-fold. If there is a first-order exchange reaction and a base-catalyzed reaction, the k_{obsd} values should fit eq 1. With none of

$$k_{obsd} = k_1 + k_2[\text{NaOMe}] \quad (1)$$

the esters studied previously[2,3] was a detectable k_1 value found, but with amino substituents a new possibility arises. The amino esters will be in equilibrium with the corresponding ammonium ions (eq 2). Sodium methoxide

$$Me_2NCH_2CO_2Me + MeOH \rightleftharpoons Me_2N^+HCH_2CO_2Me + MeO^- \quad (2)$$

catalyzed exchange of the ammonium ion will be kinetically equivalent to uncatalyzed exchange of the free amine. In addition, since the amine concentrations used in the various runs were not varied greatly, catalysis of exchange by the amino groups of other ester molecules would also contribute to the first-order pathway. For methyl hygrate (2) a plot of k_{obsd} against the sodium methoxide concentration (Figure 1) gives an intercept that we believe is significantly larger than zero. The resulting k_1 value is 5.4×10^{-7} s^{-1}. For none of the other esters, including 1, was the intercept significantly larger than zero.

The average k_2 values obtained from the individual runs for 1, 3, 4, and 5 and the value for 2 obtained from the slope of the line in Figure 1 are listed in Table I. Also

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Table I. Rate Constants for NaOMe-Catalyzed Exchange of Esters in MeOD at 35 °C

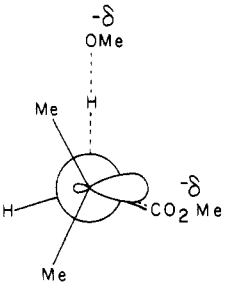
ester	$10^5 k_2$, M^{-1} s^{-1}	k^a/k_{ref}
$Me_2NCH_2CO_2Me$ (1)	127	32
$Me_2CHCH_2CO_2Me$ (3)	4.0	
methyl hygrate (2)	1.67[b]	2.6[c]
methyl *cis*-2-methylcyclopentanecarboxylate (4)	1.89	
methyl *trans*-2-methylcyclopentanecarboxylate (5)	0.51	
$MeOCH_2CO_2Me$	92[d]	7
$MeCH_2CH_2CO_2Me$	12.9[d]	
methyl tetrahydrofuran-2-carboxylate	6.7[e]	2.7
methyl cyclopentanecarboxylate	2.5[e]	
$MeCH_2CO_2Me$	16.4[d]	
HCH_2CO_2Me	126[d]	

[a] k_{ref} is the rate constant for the isosteric ester in which the ether oxygen has been replaced by a methylene group or the amino nitrogen by a methinyl group. [b] There is also a first-order path, with $k_1 = 5.4 \times 10^{-7}$ s^{-1}. [c] Calculated as described in the text. [d] From ref 2. [e] From ref 3.

listed are values for some of the compounds studied previously. Let us approximate the steric effects of oxygen and nitrogen as those of CH_2 and CH, respectively, an approximation that should be better for nitrogen than for oxygen. If it is accepted that the polar substituent effect in solution is the same for all saturated alkyl groups,[10-12] then comparison of methoxy with ethyl and dimethylamino with isopropyl keeps the polar effect of the reference substituent constant and roughly corrects for simple steric hindrance. On this basis we note from Table I that the appropriate ratio of k_2 values to estimate the nonsteric effect for methoxy ($MeOCH_2CO_2Me/MeCH_2CH_2CO_2Me$) is 7 and the ratio for dimethylamino (1/3) is 32.

With the five-membered-ring compounds, methyl tetrahydrofuran-2-carboxylate is compared with methyl cyclopentanecarboxylate and a ratio of 2.7 is obtained. Inversion at the nitrogen atom of **2** gives two conformers, one analogous to **4** and the other analogous to **5**. **4** and **5** were equilibrated by use of sodium methoxide in methanol to estimate the relative abundance of these two conformers. The equilibrium constant for transformation of **4** to **5** was found to be 9.4 (which is somewhat larger than the value (6) found for the dimethyl cyclopentane-1,2-dicarboxylates in methanol at 50 °C[13]). Accordingly, the reference for **2** was taken to be a mixture of 90% **5** and 10% **4**, whose rate constant for carbanion formation is (0.9) (0.51×10^{-5}) + (0.1) (1.89×10^{-5}) or 0.65×10^{-5} M^{-1} s^{-1}. Thus, the nonsteric effect of a ring α-amino group is a rate enhancement of (1.67/0.65) or 2.6-fold, essentially the same as the ring α-alkoxy effect of 2.7-fold. This contrasts with the effects seen in acyclic esters, where the activating nonsteric effect is 32/7 or 4.6 times as large for the α-amino as for the α-alkoxy substituent. We believe that the difference between the relative effects of α-amino and α-alkoxy substituents in cyclic and in acyclic compounds arises from repulsion between the unshared electron pairs of the substitutent and the π electrons of the carbanion.

Such repulsions could be minimized in carbanion formation of **1** if the bond to the dimethylamino group were rotated so that the unshared electron pair was in an orbital orthogonal to the orbital on the α-carbon atom in which an unshared pair of electrons is being generated in the transition state (cf. **8**). However, there may be more steric hindrance in transition-state **8** than in the transition state derived from the reference compound, **3**. In addition, such



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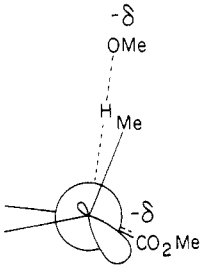
a restriction on the torsional angle between the dimethylamine group and the rest of the molecule would have an unfavorable effect on the entropy of activation. Thus for both steric and entropic reasons the average transition state for reaction of **1** probably has some repulsion between unshared pairs of electrons. In transition states derived from **2**, ring strain keeps the unshared pair of electrons on the amino group from getting very near to perpendicular to the π electrons of the incipient carbanion. Nevertheless, plausible transition states for carbanion formation from **2**, especially from the transoid conformer of **2**, could give amounts of repulsion between unshared electron pairs that are far from maximal, as illustrated in transition state **9**. Thus, the difference between the ste-



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rically corrected α-amino effect in acylic esters (32-fold) and that in cyclic esters (2.6-fold) measures the difference between a small amount of repulsion between unshared electron pairs and a larger amount of such repulsion.

Because of the two unshared electron pairs on oxygen, repulsions between unshared electrons can not be minimized nearly as much in the transition state derived from methyl tetrahydrofuran-2-carboxylate as in the transition state (**9**) derived from **2**. Rotation around the bond to the methoxy group in methyl methoxyacetate can give a transition state with less repulsion between unshared electrons than in the transition state derived from methyl tetrahydrofuran-2-carboxylate, but substantial repulsions will have to remain. The difference between such repulsions in the acyclic transition state and the cyclic transition state is smaller in the alkoxy than in the amino case. The sterically corrected α-alkoxy activating rate effect increases from 2.7-fold in the cyclic case but only to 7-fold in the acyclic case.

The fact that k_1 is observable with methyl hygrate (**2**) and not with the glycine derivative, **1**, shows that the ratio k_1/k_2 is larger for **2** than for **1**. This is presumably because k_2 is decreased by repulsions between unshared electrons that are harder to avoid with **2** than with **1**. There are no unshared electrons on nitrogen in the reactions governed by k_1.

The present rate data reflects stabilities of transition states leading to carbanions, not the stabilities of car-

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banions themselves. For example, although α-methyl substituents have been observed to decrease the rate of formation of a carbanion α to a carbonyl group,[2,14] they can increase the equilibrium constants,[15] just as with carbanions α to nitro groups.[16] Similarly, equilibrium measurements on acetophenone derivatives have shown that α-methoxy substituents stabilize carbanions substantially relative to α-methyl or α-hydrogen.[17] the comparison of α-methoxy with α-methyl is the same as seen in our rate data on ester; the comparison with α-hydrogen is not. Thus, carbanion stability must be an important factor in determining rates of carbanion formation, but it is not the only significant factor. Carbanion stability must be evaluated by equilibrium measurements, not rate measurements. The effect of α-amino substituents on equilibrium constants for carbanion formation by acetophenone derivatives in dimethyl sulfoxide solution has been studied by Bordwell and co-workers.[18]

Experimental Section

Minor modifications of literature procedures were used for the preparation of $Me_2NCH_2CO_2Me$ (1)[19] and methyl hygrate (2).[20] A general esterification procedure[21] was used to make $Me_2CHCH_2CO_2Me$ (3).[22]

Methyl *cis*-2-(Dichloromethyl)cyclopentanecarboxylate (6). A solution of 1.3 g (24 mmol) of NaOMe in 10 mL of MeOH was added dropwise to a mixture of 3.3 g (18 mmol) of 7,7-dichlorobicyclo[3.2.0]heptan-6-one[5] and 5 mL of MeOH at −5 to −20 °C. After removal of methanol, the residue was extracted with ether. After evaporation of the ether, distillation gave 2.4 g (62%) of 6: bp 73–74 °C (0.7 mm); NMR (CCl_4) δ 6.00 (d, 1, J = 9 Hz, $CHCl_2$), 3.65 (s, 3, OCH_3), 2.90 (m, 2, CHCH), 2.3–1.8 (m, 6, $CH_2CH_2CH_2$).

Anal. Calcd for $C_8H_{12}O_2Cl_2$: C, 45.52; H, 5.73; Cl, 33.59. Found: C, 45.76; H, 5.74; Cl, 33.09.

Methyl *cis*-2-Methylcyclopentanecarboxylate (4). Dropwise addition of 2.3 g (11 mol) of 6 to 9 g (26 mmol) of tri-*n*-butyltin hydride in 40 mL of *n*-hexane and a little 2-azobis(isobutyronitrile) at reflux was followed by 1 h of additional refluxing. Distillation gave 0.9 g (57%) of 4: bp 28–29 °C (1 mm): NMR (CCl_4) δ 3.60 (s, 3, OCH_3), 2.76 (m, 1, $CHCO_2$), 2.30 (m, 1, $CHCH_3$), 1.70 (m, 6, $CH_2CH_2CH_2$), 0.90 (d, 3, J = 6 Hz, $CHCH_3$). A small amount of 5 present as an impurity was removed by preparative VPC.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.24; H, 9.91.

Methyl *trans*-2-Methylcyclopentanecarboxylate (5). Dropwise addition of 6.62 g (45 mmol) of 2-methylcyclopentanecarbonyl chloride[8] to 1.45 g (45 mmol) of methanol at 0 °C was followed by 1 h of stirring at room temperature. The mixture was poured into water and the organic layer was washed with sodium bicarbonate solution, dried over magnesium sulfate, and distilled to give 6 g (93%) of ester: bp 28–33 °C (0.5 mm); NMR (CCl_4) δ 3.60 (s, 3, OCH_3), 2.3–1.5 (m, 8, $CHCH_2CH_2CH_2CH$), 1.00 (d, 3, J = 6 Hz, $CHCH_3$) plus the peaks for 4, which VPC on a 6-ft 10% polyphenyl ether column showed to be present to the extent of about 12% as a more slowly eluted but partly overlapping peak. Preparative VPC gave a mixture of 93% 5 and 7% 4, which was used for the kinetic studies.

Kinetic Procedure. The reaction kinetics were followed, as described previously,[2,3] by IR measurements of the concentration of MeOH being formed. With the 0.05-mm Irtran-2 cell used the extinction coefficient was 107.4 M^{-1} cm^{-1}. The sodium methoxide concentration was determined at various times during each run. Although the concentration usually decreased slightly during the course of a run, in never deviated by more than 3% from the average value except in the run with 1 and 0.0298 M average [NaOMe], where deviations were as large as 8%. Initial ester concentrations were in the range 0.24–0.66 M. In the kinetic studies on 5 the presence of about 7% 4 was corrected for, using the rate constant obtained from studies on pure 4. All the other esters were at least 99% pure.

Equilibrium between 4 and 5. A solution of 0.4 g of a mixture of 12% 4 and 88% 5 in 6 mL of 1.4 M NaOMe was kept at 35.0 ± 0.1 °C for 34 days. After neutralization with 0.7 M HCl and extraction with ether, the ether was largely evaporated and the residue found by VPC analysis on a 6 ft-10% polyphenyl ether column at 85 °C to contain 9.4 times as much 5 as 4. The rate constant for approach to equilibrium (the sum of the forward and reverse rate constants for isomerization) may be shown to be between the rate constants for formation of the common carbanion by 4 and 5. If these rate constants are the same in CH_3OH as in CH_3OD, the half-time for equilibration under the present conditions will be between 8 and 29 h.

Registry No. 1, 7148-06-3; 2, 27957-91-1; 3, 556-24-1; 4, 80926-05-2; 5, 63649-24-1; 6, 80926-06-3.

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Hydrolysis of Medium-Ring Phosphates. Mechanism of Rate Acceleration by an Amino Group

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Received September 21, 1981

A series of 2-oxo-2-(*p*-nitrophenoxy)-1,3-dioxa-2-phosphacyclooctane derivatives (1–5) having either a nitrogen or a sulfur atom placed transannularly in the ring were synthesized, and their rates of hydrolysis were examined. The pH–rate profile shows that while 1 undergoes hydrolysis over a wide pH range, others are hydrolyzed at a significant rate only in basic medium, thus implicating the amino function for rate enhancement. By comparison with rates obtained with 2 and 3 and the quarternary derivative 4, a mechanism involving rate-determining proton transfer from nitrogen to phosphoryl oxygen has been proposed for the hydrolysis of 1 at an acidic pH. The enhancement in the rate of spontaneous hydrolysis of the same compound, however, is explained by a combination of intramolecular general-base and nucleophilic catalysis.

The question of rate acceleration by neighboring carboxyl[1,2], hydroxyl[3], or amide[4] functions in phosphate ester hydrolysis has been the subject of several investigations. Of particular interest to our present problem are the

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