Acknowledgment. Financial support from the National Institutes of Health (Grant No. GM 13453-15) is gratefully acknowledged.

Registry No. **8a**, 75830-06-7; **8b**, 75847-34-6; **8c**, 75830-07-8; **8c**·HCl, 75830-08-9; **8d**, 75830-09-0; **8e**, 75830-10-3; **8f**, 75830-11-4; **8g**, 75830-12-5; **9a**, 75830-13-6; **9b**, 75830-14-7; **9c**, 75830-15-8; **9d**, 75830-16-9; **9e**, 75830-17-0; **9f**, 75830-18-1; **9g**, 75830-19-2; **10a**, 75830-20-5; **10b**, 75830-21-6; **10c**, 75862-66-7; **11a**, 75847-35-7; **11b**, 75830-22-7; **11c**, 75830-23-8; **12a**, 75830-24-9; **12b**, 75830-25-0; **12c**, 75830-26-1; **13a**, 75830-27-2; **13b**, 75830-28-3; **13c**, 75830-29-4; **14a**, 75847-36-8; **14b**, 75830-30-7; **15a**, 75830-31-8; **15b**, 75830-32-9; **16**, 67985-75-5; **18**, 75830-33-0; **19**, 75830-34-1; 2-(isopropoxymethylene)cyclohexanone, 15839-23-3; benzylamine, 100-46-9; *N*-[α-(*tert*-butyloxycarbonyl)glycine]-*N*-benzyl-*N*-(5-hydroxy-4-xanthene)methylamide, 75830-39-6; *N*-benzyl-*N*-(5-hydroxy-4-xanthene)methylamine·HCl, 75830-35-2; 5-nitrosalicylaldehyde, 97-51-8; 5-nitrosalicylaldehyde benzylamine Schiff base, 53848-16-1; *N*-[(*tert*-butoxycarbonyl)-L-valinyl]-*N*-benzyl-*N*-(2-acetoxy-5-nitrobenzyl)amide, 75830-36-3; *N*-(2-hydroxy-5-nitrobenzyl)benzylamine·HCl, 75830-37-4; *N*-(2-hydroxy-5-nitrobenzyl)benzylamine, 75830-38-5; (*tert*-butoxycarbonyl)-L-valine, 13734-41-3.

Carbanions. Electron Transfer vs. Proton Capture. 7. Electron-Transfer Oxidation of an Amino Acid Derived Carbanion

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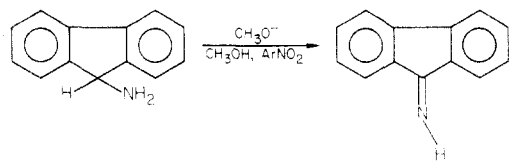
The dimethylamide of phenylalanine, **1**, reacts with potassium *tert*-butoxide and nitrobenzene in *tert*-butyl alcohol at 50 °C in an argon atmosphere. The products are potassium nitrobenzenide ($PhNO_2^-K^+$) and degradative fragments of the amino amide, including ammonia, dimethylamine, potassium benzoate, potassium carbonate, and potassium cyanide. The yields of these isolated degradation products are relatively low when the reaction is run anaerobically but are improved when the reaction is carried out under oxygen. The oxygen-mediated reaction does not produce cyanide or nitrobenzenide but its products are otherwise the same with the addition of oxalate. Conversions are essentially quantitative when the oxygen-mediated reaction is followed by vigorous, acid-catalyzed, hydrolytic workup. The reaction is believed to begin with the one-electron oxidation of the α-amino carbanion, proceeding through a ketimine and/or an enamine which is rapidly oxidized to the eventual products. The rate of oxidation of **1** is approximately the same as its ionization rate but the reaction becomes less efficient if the *N*-pivalyl derivative of **1** is used. Experiments with the dimethylamide of alanine give qualitatively similar results, with potassium formate replacing potassium benzoate in the products.

Introduction

In a study dealing with the electron-transfer oxidation of 9-substituted fluorenes by base and aromatic nitro compounds, we observed that 9-aminofluorene is cleanly dehydrogenated as shown in eq 1.[1] Evidence was presented that the mechanism involves proton and electron transfer in the sequence $A_{BH}D_{CH} + A_{CA}D_{C\cdot A} + A_{C\cdot A}D_{CA} + A_{BH}D_{NH}$, where A is the electron acceptor and B is a base.[2] An analogous mechanism is possible for flavin-mediated biological oxidations[3] and the connection has been strengthened in a recent study[4] which showed that 9-methoxyfluorenide ion reacts with a model flavin system in a manner analogous to its reaction with nitrobenzene.[5]



(1)

We decided to study the reaction of an amino acid derived carbanion with nitrobenzene. It is obvious that such a remotely analogous system could, at best, provide only permissive evidence for the involvement of carbanion electron transfer in the action of amino acid oxidases. Moreover, a base of the strength found necessary for carbanion formation from **1** is an unlikely resident of an enzyme cavity. One might argue that this fact militates against the proposal of free α-amino carbanions as intermediates in the biological mechanism. The transformation to be described nevertheless represents a new reaction of amino acid derivatives.

Results

The search for an appropriate amino acid derivative started with an attempt to form a carbanion directly from the amino acid. It was found that alanine itself showed no deuterium incorporation after treatment with 0.5 N potassium *tert*-butoxide in *tert*-butyl alcohol-*d* for 4 days at 65 °C. The presence of a carboxylate anion in this substrate apparently makes the energy requirements of the carbanionic charge prohibitive under conditions where we could expect nitrobenzene to survive. Similar results were obtained with Cbz and *t*-Boc derivatives. We were reluctant to experiment with amino acid esters because of the possible complications of transesterification and peptide formation. We therefore settled on the dimethylamide. Most of the work to be described was carried out with the dimethylamide of phenylalanine, **1**.

Anaerobic Reaction. When **1** was treated with potassium *tert*-butoxide in *tert*-butyl alcohol at 50 °C under argon, roughly 4 mol of nitrobenzene were consumed per

(1) Guthrie, R.D.; Wesley, D. P.; Pendygraft, G. W.; Young, A. T. *J. Am. Chem. Soc.* **1976**, *98*, 5870.
(2) For an explanation of the mechanistic code see: Guthrie, R. D. *J. Org. Chem.* **1975**, *40*, 402.
(3) Bruice, T. C. In *Prog. Bioorg. Chem.* **1976**, *4*, 33-40.
(4) Novak, M., Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 8079.
(5) Guthrie, R. D.; Pendygraft, G. W.; Young, A. T. *J. Am. Chem. Soc.* **1976**, *98*, 5877.

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Table I. Products of the Reaction of the Dimethylamide of Phenylalanine, 1, with $PhNO_2$ and KO-*t*-Bu in *t*-BuOH at 50 °C

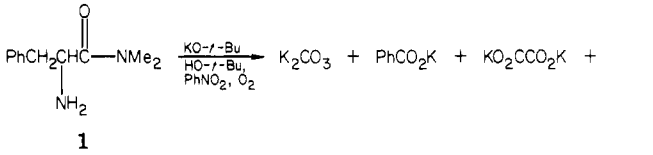
run	[1], M	[$PhNO_2$], M	[KO-*t*-Bu], M	time, h	% yield[a] K_2CO_3	$K_2C_2O_4$	$PhCO_2K$	NH_3	Me_2NH
1	0.298[b]	0.69	0.518	24	23	17	35	26	32
2	0.102	0.21	0.567	70	trace	trace	68	62	63
3	0.125	0.64	0.567	70	trace	trace	61	65	53
4	0.101[e]	0.65	0.493	44	24	25	>95[e]	46[f]	53[g]
5	0.106[e]	0.62	0.567	73	37	45	100[e]	78[h]	83[i]
6	0.101	none	0.493	73	trace	trace	13	5	11
7	0.101[d]	0.60	0.493	4.5	<2	0	30	8	<1

[a] Calculated for 1 mol of product/mol of 1 except for K_2CO_3 which was assumed to give 2 mol/mol of 1. [b] 33% unreacted 1 isolated. [c] 48% unreacted 1 isolated. [d] 46% unreacted 1 isolated. Other runs showed no detectable 1 (<5%). [e] Reaction workup involved acid hydrolysis. [f] 36% yield before hydrolysis. [g] 36% yield before hydrolysis. [h] 58% yield before hydrolysis. [i] 67% yield before hydrolysis.

mole of 1 lost. The precipitate which formed was found to contain potassium benzoate, potassium carbonate, the potassium salt of nitrobenzene radical anion (2 mol per mol of 1), and a trace of potassium cyanide. Potassium cyanide was detected in the IR spectrum of the residual solids and derivatized as Prussian Blue. In a reaction which was allowed to proceed for 18 h at 50 °C, a 13% yield of benzoic acid was isolated along with 35% unreacted starting material from 2.9 mmol of 1 and 7.8 mmol of nitrobenzene in 10 mL of 0.5 N potassium *tert*-butoxide in *tert*-butyl alcohol. This experiment also produced 1.09 mmol of K_2CO_3 analyzed as $BaCO_3$. Ammonia, dimethylamine, and azoxybenzene could also be shown to be present.

Because the yields of isolable products were low and difficulties were encountered in separating the other products, it was decided to run the reaction in the presence of molecular oxygen. This had been found to simplify the reaction products in other cases and does not change the course of the reaction of eq 1.[1]

Aerobic Reaction. The reaction of 1 with nitrobenzene and potassium *tert*-butoxide in the presence of molecular oxygen gave the products shown in eq 2 with yields sum-



1 (2)

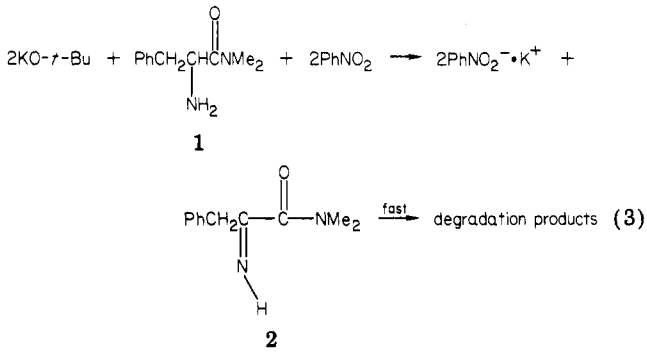
marized in Table I. The half-life for starting material under these reaction conditions appears to have been about 3–6 h (note run 7). The fact that starting material was also recovered from run 1 is probably a result of potassium *tert*-butoxide having been the limiting reagent. A minimum ratio of 4 mol of base/mol of substrate should be maintained for complete reaction. A 2:1 ratio of nitrobenzene to substrate is probably sufficient as indicated by comparing runs 2 and 3. Runs 4 and 5 show the advantages of incorporating acid hydrolysis as a part of the workup procedure (addition of a roughly equal volume of 1 N HCl to the reaction mixture and refluxing for 14 and 24 h, respectively). The recovery of benzoic acid becomes essentially quantitative and the remaining atoms in the starting molecule are probably completely represented within the limits of our analytical procedures. The increased yields observed with a hydrolytic workup suggest that the products present immediately after reaction have the same oxidation state as the final products but lack H_2O. Amides and nitriles are possible candidates.

Run 5 shows that oxygen can serve as an oxidant in the absence of nitrobenzene but is considerably less effective. The initial role of oxygen in the nitrobenzene reaction is to convert nitrobenzene radical anion to nitrobenzene. However it may also, as either O_2, O_2^-, or ROO^-, become involved in oxidative steps following the formation of the initial imine or dehydroamino amide.

A few preliminary runs have been made with the dimethylamide of alanine. The products were qualitatively similar except that potassium formate was obtained in place of potassium benzoate.

Discussion

A series of mechanistic steps consistent with our earlier work suggest the intermediacy of the imine 2 in eq 3. This



imine, 2, or its tautomeric enamine form apparently undergoes a facile further oxidation to give the eventually observed products. In addition to the 2 mol of potassium salt of nitrobenzene radical anion formed in the anaerobic reaction, 0.7 mol of azoxybenzene was also produced. Azoxybenzene is an expected product from the reaction of the radical anion with *tert*-butyl alcohol at 50 °C and this amount would arise from 4.2 mol of radical anion. Thus a minimum of six electrons must be removed from each molecule of 1 to account for the observed products. When the reaction is run in an oxygen atmosphere the first two electrons given up by the substrate are believed to be transferred from nitrobenzene to oxygen in analogy with previous work.[1] Subsequent steps could possibly involve reaction of 2 with oxygen in a more direct way. A recent investigation of the reaction of arylpyruvic acids with base and molecular oxygen identified products which were similar to those of the present study.[6] Some of the mechanistic suggestions contained in that report may be applicable to our system.

An interesting sidelight of the present work is the fact that the *N*-pivalyl derivative of 1 does not undergo oxidation under these conditions, despite the fact that the kinetic acidity of its α-hydrogen is considerably greater than that for 1. An estimate of the half-life for ionization of 1 under the conditions of the reactions in Table I can

(6) Jefford, C. W.; Knopfel, W.; Cadby, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 6432.

be obtained by comparing the rate of hydrogen–deuterium exchange of 1 in *tert*-butyl alcohol-*d*[7] and making an approximate correction for solvent isotope effect. This procedure suggests that 1 is being oxidized at an ionization-limited rate. Possibly the effect of an *N*-pivalyl group is to increase the stability of the carbanion relative to the radical, making electron transfer less competitive with carbanion reprotonation.

Experimental Section

DL-*N*-(Carbobenzoxy)phenylalanine *p*-Nitrophenyl Ester. This compound was prepared from DL-phenylalanine, using procedures analogous to those in the literature.[8,9]

DL-*N*-Carbobenzoxyphenylalanine Dimethylamide. DL-*N*-(Carbobenzoxy)phenylalanine *p*-nitrophenyl ester (28.8 g, 68.5 mmol) was dissolved in 250 mL of $CHCl_3$ and dimethylamine (6.16 g, 137 mmol) was bubbled through the solution. The reaction mixture was allowed to stand for 0.5 h at room temperature and the yellow solids were removed by filtration. The filtrate was washed with three 50-mL portions of 2 N NaOH. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and the solvent removed by rotary evaporation to give 19.8 g of product: 89%; mp 125–126.5 °C; ^1H NMR ($CDCl_3$) δ 2.6–2.8 (2 s, 6 H), 2.9–3.2 (d, 2 H), 4.7–5.0 (m, 1 H), 5.1 (s, 2 H), 5.8 (br, 1 H), 7.2 (s, 5 H), 7.3 (s, 5 H).

DL-Phenylalanine Dimethylamide. DL-(Carbobenzoxy)-phenylalanine dimethylamide (8.90 g, 27.3 mmol) was dissolved in 250 mL of absolute ethanol and 0.74 g of 10% Pd on carbon was added. The mixture was shaken under 4 atm of hydrogen for 22 h. The mixture was filtered through Celite and the solvent removed by rotary evaporation. A second such hydrogenation was carried out. The combined products were dissolved in ca. 50 mL of CH_2Cl_2 and extracted with four 25-mL portions of 10% NaOH and 50 mL of water. The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 and the solvent removed by rotary evaporation. Distillation gave 6.58 g, 63% of clear liquid: bp 145–150 °C (0.8 torr); ^1H NMR ($CDCl_3$) δ 1.6 (s, 2 H), 2.6–3.0 (d, 2 s, 8 H), 3.9 (t, 1 H), 7.2 (s, 5 H); mass spectrum (no parent ion), *m/e* 120, 101, and 91 are main peaks at 70 eV, *m/e* 143, and 162 show up at 12 eV. The L derivative was also prepared by the same method from commercially available L-*N*-(carbobenzoxy)phenylalanine *p*-nitrophenyl ester and had identical spectral properties. The L isomer is a low-melting (ca. 40 °C), hygroscopic solid. The elemental analysis for the L isomer follows.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.85; H, 8.51; N, 14.44.

Solvents, Solutions, and Reagents. Preparation and/or purification of all of these have been described previously.[10,11]

Anaerobic Reaction Procedure. The substrate (usually 2.5–3.0 mmol) and nitrobenzene (or nitrobenzene and an internal standard for GC analysis) were placed in a glass centrifuge tube containing a small magnetic stirring bar. The mixture was degassed (freeze–thaw) and treated with 10.0 mL of degassed potassium *tert*-butoxide in *tert*-butyl alcohol under O_2-free argon. After the specified time at 50 °C, the tube was subjected to centrifugation and the supernatant solution drawn off in a gas-tight syringe. The solids were washed with 10 mL of *tert*-butyl alcohol (using the stirring bar) and the reaction supernatant plus washings treated with 1.0 mL of 11.4 N HNO_3. The precipitated KNO_3 was separated by centrifugation and the filtrate concentrated by rotary evaporation. The KNO_3 precipitate contained some dimethylammonium nitrate (NMR).

The material obtained from the reaction liquids contained nitrobenzene and azoxybenzene as components which were soluble in pentane and ether. The insoluble portion was soluble in $CDCl_3$. It was found to contain some NH_4NO_3 as determined by analysis of an aqueous extract with $Na_3CO(NO_2)_6$ using the procedure of Wagner, Brown, and Peters.[12] The resulting ammonia complex was identified by IR comparison with authentic material. This fraction also contained unreacted starting compound as its HNO_3 salt which could be separated by neutralization and extraction. Other unidentified components were also present in the $CHCl_3$ solution.

The solids which precipitated from the reaction mixture contained the potassium salt of nitrobenzene anion radical $PhNO_2^-\cdot K^+$, which was analyzed for in the following way. From reaction of 1 (205.8 mg, 1.07 mmol) and nitrobenzene (747.4 mg, 6.07 mol) in the presence of 100.4 mg of hexadecane with 10.0 mL of 0.729 N potassium *tert*-butoxide in *tert*-butyl alcohol for 41 h at 50 °C was obtained a copious red-brown precipitate. After two 10-mL washes with *tert*-butyl alcohol and two 10-mL washes with THF (all solvents dry and degassed), the resultant solids were slurried in 10.0 mL of Me_2SO and 1.0 mL was removed for ESR analysis. After a 100-fold dilution with Me_2SO, the solution gave an ESR spectrum of nitrobenzenide: $a^N = 9.9$, $a_o^H = 3.3$, $a_p^H = 4.0$, $a_m^H = 1.07$ G (lit.[13] $a^N = 10.10$, $a_o^H = 3.39$, $a_p^H = 3.94$, $a_m^H = 1.01$ G). By comparing the (peak intensity) (width)^2 of the peaks of this spectrum with those of standard nitroxide solutions (correcting for multiplicity differences), it was ascertained that the 1.0-mL aliquot contained 0.04 mmol of $PhNO_2^-\cdot K^+$. The remaining 9 mL of Me_2SO slurry was treated with a measured amount of dicyclohexyl and a stream of O_2 gas allowed to bubble through for about 10 min. The resultant solution, after workup, was found (by GC comparison with standard mixtures) to contain 2.0 mmol of $PhNO_2$. This clearly arose from $PhNO_2^-\cdot K^+$ because only traces of hexadecane were present. The washes of the solids were combined and worked up in ether–water. GC analysis showed 2.25 mmol of $PhNO_2$ and 0.74 mmol of azoxybenzene.

Acidification of the aqueous solution from workup of the oxygenated reaction solids produced CO_2 (identified by IR as $BaCO_3$). Potassium cyanide was also shown to be present by conversion to Prussian Blue. Extraction of the acidified aqueous material with CH_2Cl_2 gave benzoic acid, identified by comparison with authentic material.

Aerobic Reaction Procedure. Substrate (usually 1.5–3.0 mmol), nitrobenzene (4–12 mmol) and solvent–base solution (20 mL) were stirred in a reaction vessel into which a slow flow of oxygen gas was introduced through a syringe needle. The effluent gases were passed through a 12-in. column packed with glass helices into a gas-bubbler trap containing acetic anhydride and an internal standard (naphthalene or 4-bromochlorobenzene). After completion of the reaction, the contents of the trap were analyzed directly on a Varian Aerograph Model 90P gas chromatograph using a 5 ft × 0.25 in. column of 20% Carbowax 20M with 2% NaOH on Chromosorb P (45/60 mesh).[14] Amounts of acetamide and *N,N*-dimethylacetamide were determined after correction for response ratios using standard mixtures.

Direct Product Analysis of Aerobic Reaction. The solid precipitate which formed during the reaction was separated by filtration, washed with 10 mL of *tert*-butyl alcohol, and dried in air. The filtrate was treated as described above in the anaerobic reaction procedure. It contained mostly nitrobenzene and any starting compound which remained unreacted. A sample of the reaction solids was dissolved in 5 mL of water and sufficient 5% $CaCl_2$ solution was added to complete precipitation. The precipitate was separated by filtration and benzoic acid was recovered from the filtrate as described above. The calcium salts were digested in aqueous HCl and the evolved gases passed through a saturated solution of $Ba(OH)_2$. $BaCO_3$ was separated by filtration, weighed, and identified by IR comparison. The filtrate from this procedure gave a precipitate of calcium oxalate after neutralization with NaOH and treatment with 5% $CaCl_2$ solution. Calcium oxalate was identified by IR comparison with an authentic sample.

Analysis of Aerobic Reaction Products after Hydrolysis. After the specified reaction time, the acetic anhydride trap was replaced with a $Ba(OH)_2$ trap and 15 mL of 1 N HCl was injected

(7) Work of R. D. Guthrie and E. C. Nicolas to be published subsequently.
(8) Bergman, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1197.
(9) Manning, M.; duVigneaud, V. *Biochemistry* **1976**, *4*, 1884.
(10) *tert*-Butyl alcohol was purified by the method of Guthrie, Burdon, and Lovell (*J. Org. Chem.* **1973**, *38*, 3114).
(11) Nitrobenzene was purified by the method of Guthrie and Wesley, (*J. Am. Chem. Soc.* **1970**, *92*, 4057).
(12) Wagner, C. D.; Brown, R. H.; Peters, E. D. *J. Am. Chem. Soc.* **1947**, *69*, 2611.
(13) Russell, G. A.; Weiner, S. A. *J. Org. Chem.* **1966**, *31*, 248.
(14) A similar column was described by O'Donnell and Mann (*Anal. Chem.* **1964**, *36*, 2097).

into the reaction vessel. Oxygen bubbling was resumed for 15–30 min. $BaCO_3$ was collected as before. The reaction mixture was then heated at 88 °C for the specified time. Extraction with CH_2Cl_2 gave benzoic acid and nitrobenzene which were separated by extraction with NaOH. The aqueous hydrolysate was neutralized with NaOH and more ammonia and dimethylamine were trapped in acetic anhydride. The final aqueous solution was neutralized with dilute HCl and calcium oxalate was precipitated with $CaCl_2$ solution as described above.

Preparation of DL-Alanine Dimethylamide. The L form of this compound had been prepared earlier by Freudenberg and Nickolai.[15] The DL derivative was prepared by a procedure very similar to the one described above for the phenylalanine case. The *N*-carbobenzoxy precursor was a crystalline solid: mp 80.5–82.5 °C from ether–hexane; ^1H NMR ($CDCl_3$) δ 1.25–1.35 (d, 3 H), 2.95–3.05 (d, 6 H), 4.7 (m, 1 H), 5.15 (s, 2 H), 5.9 (br, 1 H), 7.4 (s, 5 H).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.61; H, 7.27; N, 11.45.

DL-Alanine dimethylamide was prepared from this material by hydrogenation in essentially quantitative yield: ^1H NMR δ 1.2–1.3 (d, 3 H), 2.3 (br, 2 H), 2.95–3.05 (2 s, 6 H), 3.85 (m, 1 H).

Anaerobic Reaction of DL-Alanine Dimethylamide with Nitrobenzene and Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. The amino amide (186 mg, 1.60 mmol) was treated with nitrobenzene (438 mg, 3.55 mmol) and 5.0 mL of 0.52 N potassium *tert*-butoxide in *tert*-butyl alcohol in a septum-covered centrifuge tube at 50 °C for 44 h as described above. The precipitated solids were washed with ether and weighed, 242 mg. Extraction with degassed Me_2SO left 157 mg of solids after washing with ether. The Me_2SO solution gave a strong nitrobenzenide ESR spectrum. The residual solids showed no significant NMR absorption except for that due to formate. Analysis of these solids for formate (by NMR—adding known amounts of HCO_2Na) indicated a 20% yield of potassium formate. Gravimetric analysis for carbonate showed a 28% yield of this material as potassium carbonate. The balance of the solids may have been potassium oxalate but an analysis for this product was not carried out. Workup of the reaction solution showed no NMR evidence for organic compounds other than starting materials.

(15) Freudenberg, K.; Nikolai, F. *Justus* Liebigs Ann. Chem. **1934**, *510*, 223.

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Registry No. DL-1, 3705-50-8; L-1, 29618-17-5; DL-*N*-carbobenzoxyphenylalanine dimethylamide, 75768-06-8; DL-*N*-(carbobenzoxy)phenylalanine *p*-nitrophenyl ester, 2578-86-1; L-*N*-(carbobenzoxy)phenylalanine *p*-nitrophenyl ester, 2578-84-9; potassium nitrobenzenide, 34480-35-8; DL-*N*-carbobenzoxyalanine dimethylamide, 75801-52-4; DL-alanine dimethylamide, 75768-07-9; potassium formate, 590-29-4; $PhNO_2$, 98-95-3; KO-*t*-Bu, 865-47-4; K_2CO_3, 584-08-7; $K_2C_2O_4$, 583-52-8; $PhCO_2K$, 582-25-2; NH_3, 7664-41-7; Me_2NH, 124-40-3.

Conformational Analysis of Fused-Ring 1,2-Diazetidines by Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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A series of 1,2-diazetidines with alkyl and carbonyl substituents on nitrogen has been synthesized, and conformational changes observed for these compounds have been examined by variable-temperature ^{13}C NMR spectroscopy. All compounds exhibit conformational changes involving nitrogen inversion, and those with carbonyl substituents have barriers to inversion 2–3 kcal/mol lower than those of alkylated analogues. Differences in activation parameters are discussed in terms of steric and electronic effects.

Introduction

Three processes have been described[1] to explain conformational changes observed by dynamic nuclear magnetic resonance spectroscopy for cyclic hydrazines of various ring sizes: (1) ring reversal, (2) nitrogen inversion, and (3) rotations about amide bonds. In many examples, more than one of these processes can occur, rendering the unambiguous assignment of the conformational change difficult. This problem is nowhere more apparent than in the study of four-membered-ring hydrazines, 1,2-diazetidines. For example, temperature-dependent ^1H NMR spectral changes observed for N,N-dialkylated 1,2-diazetidines have been interpreted as involving nitrogen inversion.[2] Spectral changes exhibited by diethyl tetramethoxy-1,2-diazetidine-1,2-dicarboxylate are consistent with a conformational change involving rotations about amide bonds.[3] Temperature-dependent ^{19}F spectra of 1,2-bis(trifluoromethyl)tetrafluoro-1,2-diazetidine[4] and diethyl tetrafluoro-1,2-diazetidine-1,2-dicarboxylate[5] have been interpreted as involving either ring reversal[6] or nitrogen inversion.[4,5]

We have prepared a series of 1,2-diazetidines in which ring torsion has been minimized in order to study "torsion-free" nitrogen inversion and/or amide rotations in 1,2-diazetidines. We now report conformational changes and corresponding activation energies as a function of nitrogen substituent in a series of fused-ring 1,2-diazetidines.

(1) For reviews, see: (a) S. F. Nelsen, *Acc. Chem. Res.*, **11**, 14 (1978); (b) Y. Shvo, "Chemistry of Hydrazo, Azo, and Azoxy Groups", S. Patai, Ed., Wiley, New York, 1975, Part 2, pp 1017–1095; (c) J. M. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1971).
(2) J. H. Hall and W. S. Bigard, *J. Org. Chem.*, **43**, 2785 (1978).
(3) H. Carlson, A. P. Schaap, and M. Raban, *J. Org. Chem.*, **38**, 1605 (1973).
(4) P. Ogden, *J. Chem. Soc. D*, 1084 (1969).
(5) W. D. Phillips, "Determination of Organic Structures by Physical Methods", F. C. Nachod and W. D. Phillips, Eds., Academic Press, New York, 1962, p 455.
(6) B. Price, I. O. Sutherland, and F. G. Williamson, *Tetrahedron Lett.*, 1603 (1967).

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