Syntheses of (S)-5-Substituted 4-Aminopentanoic Acids: A New Class of γ-Aminobutyric Acid Transaminase Inactivators

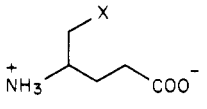
Richard B. Silverman* and Mark A. Levy

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received August 23, 1979

The syntheses of a new class of γ-aminobutyric acid (γ-Abu) transaminase inactivators, the 5-substituted 4-aminopentanoic acids (1), are described. The synthetic route involves the $LiBH_4$ reduction of (S)-5-carbethoxy-2-pyrrolidinone, derived from L-glutamic acid, to (S)-5-(hydroxymethyl)-2-pyrrolidinone (**3a**). The alcohol **3a** is converted to the chloride **3c** or the bromide **3d** with triphenylphosphine and carbon tetrachloride or carbon tetrabromide, respectively. (S)-5-(Fluoromethyl)-2-pyrrolidinone (**3b**) is prepared from the bromide **3d** and silver fluoride. The nitrile **3e** is synthesized from the bromide **3d** with sodium cyanide impregnated alumina. Each of these lactams **3** is hydrolyzed to the corresponding amino acid (1) salt in 1 N aqueous acid. Racemization at the α-carbon of L-glutamate does not occur during the syntheses.

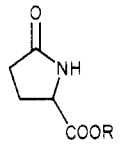
Many convulsive seizures have been shown to be a result of an imbalance in the brain amino acids γ-aminobutyric acid (γ-Abu), an inhibitory neurotransmitter, and glutamate, an excitatory neurotransmitter.[1] When the levels of γ-Abu diminish, convulsive behavior may result; return of normal levels of γ-Abu causes cessation of convulsions. Since γ-Abu does not cross the blood–brain barrier,[2] it itself is not effective as an anticonvulsant. Glutamate and γ-Abu levels are controlled by the enzymes glutamate decarboxylase and γ-Abu transaminase. Inhibition of the transaminase results in increased brain levels of γ-Abu and prevention of convulsive seizures. Thus, compounds which inhibit γ-Abu transaminase are becoming important as anticonvulsants[3] in the treatment of diseases such as epilepsy and Huntington's chorea. We describe here the synthesis of a new class of γ-Abu transaminase inhibitors, the 5-substituted 4-aminopentanoic acids (1).



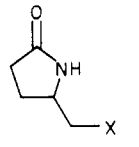
1a, X = OH
b, X = F
c, X = Cl
d, X = Br
e, X = CN

Results and Discussion

The only reported member of this class of compounds is **1a**, prepared by Red-Al[4] reduction of glutamine;[5] however, the product was only observed by TLC and was not isolated.[5] We were unable to prepare **1a** by this method. Because of solubility problems inherent in carrying out organic reactions on amino acids, we chose a different approach to the synthesis of this class of compounds. Protection of glutamic acid to eliminate the zwitterion should increase its solubility in organic solvents; the simplest way to protect both the amino and the γ-carboxyl groups simultaneously is by an internal cyclization to give 5-carbalkoxy-2-pyrrolidinone (**2**). The free carbonyl group then could be reduced to give 5-(hydroxymethyl)-2-pyrrolidinone (**3a**) which could be the common intermediate for the entire series of lactam analogues. Hydrolysis (i.e., deprotection) of these lactams would lead to the amino acids **1**. It also should be noted that when this approach is used, the stereochemistry of the starting glutamic acid should be unaffected during the syntheses. Thus, both stereoisomers of each compound could be obtained, depending upon the stereochemistry of the starting glutamic acid. Radioactively labeled analogues also would be easily accessible from labeled glutamate. Scheme I outlines our routes to the 5-substituted 4-aminopentanoic acids.



2a, R = H
b, R = CH_3
c, R = C_2H_5



3a, X = OH
b, X = F
c, X = Cl
d, X = Br
e, X = CN

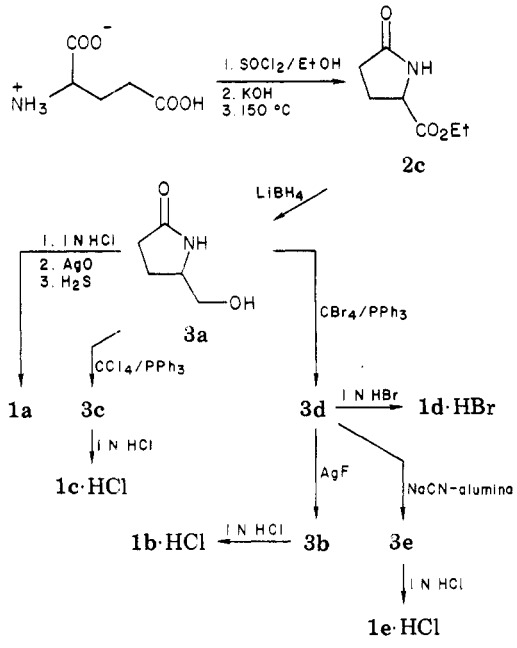
The preparation of **3a** was accomplished by lithium borohydride reduction[6] of **2c**. The physical and spectral properties of this reduction product were in agreement with those reported for the high-pressure catalytic hydrogenation of **2c**.[7] Attempts to reduce the methyl ester **2b**[8] with Red-Al or with diborane resulted in recovery of starting material. Because of the low solubility of **2b** in the aprotic organic solvents used, the ethyl ester **2c** was prepared by a modification of a known procedure.[7] This ester also was not reduced to the desired product by Red-Al.

Compound **3a** was smoothly converted to **3c** and to **3d** with triphenylphosphine and the appropriate carbon tetrahalide.[9] Treatment of **3a** with 1 equiv of thionyl chloride

(1) Roberts, E.; Chase, T. N.; Tower, D. B. "GABA in Nervous System Function"; Raven Press: New York, 1976.
(2) Meldrum, B. S.; Horton, R. W. In "Epilepsy"; Harris, P., Mawdsley, C., Eds.; Churchill Livingstone: Edinburgh, 1974; p 55.
(3) Brezenet, A. M.; Cristiane, F.; Block-Tardy, M.; Gonnard, P. *Biochim. Biophys. Acta* **1978**, *522*, 400.
(4) Red-Al is the Aldrich Chemical Co. tradename for sodium bis(methoxyethoxy)aluminum hydride.
(5) (a) Prasad, B.; Saund, A. K.; Bora, J. M.; Mathur, N. K. *Indian J. Chem.* **1974**, *12*, 290. (b) Mathur, N. K., personal communication.
(6) Bruin, J. W.; de Konig, H.; Huisman, H. O. *Tetrahedron Lett.* **1975**, 4599.
(7) Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 3121.
(8) Blicke, F. F.; Lu, C. Y. *J. Am. Chem. Soc.* **1955**, *77*, 29.
(9) (a) Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466. (b) Gruber, L.; Tömösközi, I.; Radics, L. *Synthesis* **1975**, 708.

0022-3263/80/1945-0815$01.00/0

Scheme I



in chloroform or pyridine gave a white precipitate which decomposed to the starting material (**3a**) upon exposure to moisture. It is likely that this intermediate compound was the imidoyl chloride of the lactam ring.[10] Addition of 2 equiv of thionyl chloride gave a brown-black mixture from which no desired product could be isolated.

The fluoro lactam **3b** was prepared in high yield by treating the bromo lactam **3d** with silver fluoride[11] in acetonitrile in the absence of light. Treatment of **3d** with potassium fluoride and 18-crown-6[12] in refluxing acetonitrile for 5 days yielded little or no detectable (NMR) product. Various attempts at converting **3a** to **3b** failed. Decomposition of **3a** resulted when the mild fluorinating agent diethylaminosulfur trifluoride (DAST)[13] in chloroform or dichloromethane was used. No reaction of **3a** occurred with the following reagents: (1) DAST with 1 equiv of pyridine or triethylamine in chloroform or dichloromethane or in pyridine as solvent; (2) DAST with 1 equiv of triphenylphosphine; (3) difluorotriphenylphosphorane[11,14] in refluxing DMF for 3 days; (4) 2-chloro-1,1,2-trifluorotriethylamine.[11]

The synthesis of (*S*)-(+)-5-(cyanomethyl)-2-pyrrolidinone (**3e**) was accomplished by heating **3d** with sodium cyanide impregnated neutral alumina[15] in dry toluene.

The 5-substituted 4-aminopentanoic acids (**1**) were prepared from the corresponding 5-substituted 2-pyrrolidinones (**3**) by hydrolysis in either refluxing 1 N HCl (**3a,b,c,e**) or refluxing 1 N HBr (**3d**) for 2–5 h. The cyano analogue **3e** was heated for 2 h to minimize possible hydrolysis of the nitrile. The alcohol **1a** and the chloride **1c** were further purified by cation-exchange chromatography. Compound **1a**·HCl could not be crystallized and was converted to the free amino acid with silver oxide and hydrogen sulfide. Optical rotation measurements on the lactams **2c** and **3a,c,d,e** and the amino acids **1b,c,d,e** indicated that racemization does not occur in any step of the syntheses.

Preliminary results with a crude enzyme preparation from rat brain indicate that the halo analogues of the series, **1b**, **1c**, and **1d**, are time-dependent, irreversible inactivators of γ-Abu transaminase. The alcohol **1a** and nitrile **1e** are competitive inhibitors, with no observable time-dependent inhibition at concentrations of 8 mM over 20 min. Results of enzymatic studies will be published elsewhere.

Experimental Section

NMR spectra were recorded on either a Varian T-60 or a Hitachi Perkin-Elmer R-20B spectrometer with either internal or external (when D_2O was the solvent) tetramethylsilane (Me_4Si) as standard. IR spectra were obtained on a Perkin-Elmer 283 spectrophotometer. High-voltage electrophoresis was performed with a Gilson Model D high-voltage electrophoretor at 4.2 kV, pH 1.9 (water–95% formic acid–glacial acetic acid, 45:1:4). Melting points were determined with a Thomas-Hoover Unimelt melting point apparatus and are uncorrected.

Dowex 50-X8 (200–400 mesh) in the hydrogen form was used for all cation-exchange chromatography. Silica gel (60–200 mesh, grade 950) was obtained from Grace Davison Chemicals. Acetonitrile, toluene, and methylene chloride were dried by distillation under nitrogen from CaH_2 and were stored under nitrogen. Diglyme (2-methoxyethyl ether) was distilled from CaH_2 under reduced pressure and stored over 4A sieves under nitrogen. Chloroform and carbon tetrachloride were distilled from P_2O_5 under a nitrogen atmosphere and were stored under nitrogen, over molecular sieves. Tetrahydrofuran was freshly distilled under nitrogen from Na immediately before use. All other chemicals and materials were commercially available. Elemental analyses were preformed by either H. Beck, Northwestern University Analytical Services Department, or Microtech Laboratories.

(*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (2c). The procedure of Adkins and Billica[7] was modified as follows: Thirty milliliters (410 mmol) of freshly distilled thionyl chloride was added to a suspension of L-glutamic acid (25.6 g, 175 mmol) in 250 mL of absolute ethanol cooled in an ice bath. The solution was stirred at room temperature for 1 h and heated at reflux for 0.5 h. The product was isolated as described,[7] yielding a colorless oil which solidified on standing to 23.1 g (84%) of a white solid: bp 159–162 °C (2 mm) [lit.[7] bp 152–153 °C (3 mm)]; mp 48–50 °C (lit.[7] mp 51–52 °C); $[\alpha]^{20}_D$ +2.4° (*c* 10, ethanol); NMR ($CDCl_3$) δ 1.3 (3 H, t, *J* = 6 Hz), 2.3 (4 H, m), 4.1 (3 H, m), 7.2 (1 H, br); IR (KBr) 3230 (br), 1740 (s), 1700 (s), 1200 (s), 1100 (m), 1040 (m), 740 (br) cm^{-1}.

(*S*)-(+)-5-(Hydroxymethyl)-2-pyrrolidinone (3a). A mixture of 1.3 g (34.3 mmol) of $NaBH_4$, 15 mL of dry diglyme, and 1.46 g (34.4 mmol) of LiCl was stirred vigorously under nitrogen for 20 min, and 10 mL of dry THF was added. The solid was allowed to settle, and a positive nitrogen pressure was used to filter the supernatant containing the $LiBH_4$ directly into a stirred solution of 5.03 g (32 mmol) of **2c** in 15 mL of dry THF. During filtration, a white solid formed in the second flask and gas evolution was observed. The reaction mixture was stirred for 9 h at room temperature, cooled in an ice bath, and quenched by the slow addition of 30 mL of 20% acetic acid. The THF was evaporated, and the remaining solution was applied to a column of Dowex 50 (60 mL, 1.5 × 34 cm). The column was washed with 150 mL of distilled water, and the combined washes were concentrated to give a yellow semisolid. This residue was distilled under reduced pressure to give 3.24 g (88%) of a colorless oil that solidified upon cooling: bp 147–149 °C (0.06 mm); mp 66–68 °C (lit.[8] mp 65–67 °C); $[\alpha]^{20}_D$ +29° (*c* 5, ethanol); NMR ($CDCl_3$) δ 2.3 (4 H, m), 3.8 (3 H, m), 4.8 (1 H, s), 7.4 (1 H, br); IR (film) 3200 (br), 1680 (s), 1410 (m), 1280 (m), 1110 (m) cm^{-1}.

(*S*)-(−)-5-(Chloromethyl)-2-pyrrolidinone (3c). Triphenylphosphine (6.75 g, 25.7 mmol) in 25 mL of dry carbon tetrachloride was added by syringe to a solution of 1.94 g (16.7 mmol) of **3a** in 15 mL of dry chloroform. After 5 min, the solution became cloudy. The mixture was heated at 55 °C for 6 h and cooled to room temperature, and the solvent was evaporated. The residue was extracted with benzene in a Soxhlet extractor for 15

(10) Ulrich, H. "The Chemistry of Imidoyl Halides"; Plenum Press: New York, 1968; pp 78–80.
(11) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 158–192.
(12) Liona, C. L.; Havir, H. D. *J. Am. Chem. Soc.* **1974**, *96*, 2250.
(13) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(14) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787.
(15) Regen, S. J.; Quici, S.; Liaw, S. J. *J. Org. Chem.* **1979**, *44*, 2029.

h. After the benzene solution was cooled to room temperature, it was filtered and concentrated. The resulting residue was triturated three times with 45 mL of distilled water. The combined aqueous extract was filtered through Celite and the filtrate was concentrated to give 2.39 g of a semisolid. This yellow residue was vacuum distilled to give 1.91 g (86%) of a colorless oil that crystallized to a white solid upon cooling in ice: bp 106.5–107 °C (0.15 mm); mp 53–55 °C; $[\alpha]^{20}_D$ −18° (*c* 2.5, ethanol); NMR ($CDCl_3$) δ 2.2 (4 H, m), 3.5 (2 H, d, *J* = 5 Hz), 4.0 (1 H, m), 7.5 (1 H, br); IR (Nujol) 3200 (br), 1690 (s), 1282 (m), 765 (m, br), 645 (s) cm^{-1}.

Anal. Calcd for C_5H_8ClNO: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.35; H, 6.24; N, 10.36.

(*S*)-(−)-5-(Bromomethyl)-2-pyrrolidinone (3d). A 7.2-g (27.4 mmol) quantity of triphenylphosphine was added to a suspension of 3.0 g (26.1 mmol) of **3a** in 50 mL of dry acetonitrile under nitrogen. The mixture was cooled in an ice bath and 9.1 g (27.4 mmol) of carbon tetrabromide in 25 mL of dry acetonitrile was added dropwise over 15 min. The resulting light yellow solution was stirred at room temperature under a nitrogen atmosphere for 12 h. The solvent was removed by rotary evaporation and 100 mL each of water and hexane were added to the oily residue. This mixture was stirred vigorously until a solid formed. The solid was removed by suction filtration and rinsed with 100 mL of H_2O. The organic and the aqueous layers of the filtrate were separated. The aqueous solution was extracted with seven 100-mL portions of chloroform and with two 50-mL portions of ethyl ether. The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to give 5.8 g of a light yellow oil. This oil was chromatographed on a dry-packed column (3.5 × 35 cm) of silica gel (130 g) and eluted successively with 1:1 chloroform–ethyl acetate (500 mL), 3:7 chloroform–ethyl acetate (500 mL), 1:9 chloroform–ethyl acetate (500 mL), ethyl acetate (300 mL), 1:19 acetone–ethyl acetate (500 mL), and 1:4 acetone–ethyl acetate (1000 mL). Fractions of 15 mL were collected at a rate of 2 mL/min. Product determination was accomplished by combining 15 successive fractions, evaporating the solvent and analyzing any residue by NMR spectroscopy. The desired product, found in fractions 46–195, was obtained as a white solid in a total yield of 3.42 g (74%). An analytical sample was prepared by Kugelrohr distillation to give a colorless oil that solidified to a white solid upon standing at room temperature: bp 102–106 °C (0.1 mm); mp 71–74 °C; $[\alpha]^{20}_D$ −33° (*c* 5, ethanol); NMR ($CDCl_3$) δ 2.3 (4 H, m), 3.4 (2 H, d, *J* = 5 Hz), 3.9 (1 H, m), 7.3 (1 H, br); IR (KBr) 3200 (m), 1695 (s), 1337 (m), 1283 (s), 761 (m, br), 642 (m) cm^{-1}.

Anal. Calcd for C_5H_8BrNO: C, 33.74; H, 4.53; N, 7.87. Found: C, 34.11; H, 4.66; N, 7.69.

(*S*)-5-(Fluoromethyl)-2-pyrrolidinone (3b). A solution of 1.0 g (5.62 mmol) of **3d** in 10 mL of dry acetonitrile was added dropwise over 10 min to a suspension of 1.6 g (12.69 mmol) of AgF in 20 mL of dry acetonitrile protected from light with aluminum foil. The reaction mixture was stirred at room temperature for 9.5 h and then filtered through a pad of Celite. The brown filtrate was concentrated in vacuo to give a brown oil which was triturated with chloroform; the solid formed was removed by filtration through Celite. The light yellow filtrate was concentrated to a light orange oil which was applied to 25 g of silica gel and eluted with ethyl acetate followed by 50% ethyl acetate–acetone. The product was eluted in the ethyl acetate–acetone eluate, giving 560 mg (85%) of a colorless oil. A sample of this oil was Kugelrohr distilled to give a colorless oil that solidified to a white solid upon standing: bp 73–82 °C (0.1 mm); mp 24–26 °C; NMR ($CDCl_3$) δ 2.3 (4 H, m), 3.9 (1 H, m), 4.3 (2 H, dm, *J* ~ 46 Hz), 7.4 (1 H, br); IR (film) 3220 (br), 1690 (s), 1280 (m), 1015 (m), 970 (m) cm^{-1}.

(*S*)-(−)-5-(Cyanomethyl)-2-pyrrolidinone (3e). To a solution of 1.78 g (10 mmol) of **3d** in 40 mL of dry toluene was added 15 g of sodium cyanide impregnated neutral alumina.[15] The heterogeneous mixture was stirred vigorously at 90–94 °C under a nitrogen atmosphere for 16 h. After the reaction mixture cooled to room temperature, the alumina was removed by suction filtration and washed with four 100-mL portions of ethyl acetate. The filtrate was concentrated to a colorless oil that crystallized upon cooling to give 955 mg (77%) of a white solid. An analytical sample was recrystallized from benzene–ether: mp 81–83 °C; $[\alpha]^{20}_D$ −20° (*c* 5, ethanol); NMR ($CDCl_3$) δ 2.3 (4 H, m), 2.5 (2 H, d, *J* = 5 Hz), 3.9 (1 H, m), 7.4 (1 H, br); IR (KBr) 3280 (s), 2242 (m), 1690 (s), 1274 (m), 1092 (m), 728 (m, br) cm^{-1}.

Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.97; H, 6.50; N, 22.83.

(*S*)-4-Amino-5-hydroxypentanoic Acid (1a). A solution of 766 mg (6.67 mmol) of **3a** in 10 mL of 1 N HCl was heated at reflux for 4 h, cooled to room temperature, and concentrated in vacuo to give a colorless oil. This residue was dissolved in water and was applied to a column (1.5 × 11 cm) of Dowex 50 (H^+ form). The column was washed with H_2O until the eluate was neutral, and the amino acid was eluted with 2 N aqueous NH_3. The fractions giving a positive ninhydrin test were combined and evaporated in vacuo to give a colorless oil. Ethanol was added to this residue and evaporated to give 738 mg of a white solid. High-voltage electrophoresis of this solid for 25 min at pH 1.9, 4.2 kV, followed by ninhydrin visualization showed three spots at 14.5, 22.0, and 28.5 cm toward the cathode. A 420-mg sample of this solid was applied to a column (60 mL, 1.5 × 34 cm) of Dowex 50 (H^+ form), preequilibrated with 0.05 N HCl. The column was eluted at 1 mL/min with a linear gradient of HCl from 0.05 to 0.5 N concentration in a total volume of 2000 mL, collecting 3-mL fractions. Fractions 375–520 were positive with ninhydrin; fractions 416–520 showed only one component by high-voltage electrophoresis. These fractions (416–520) were combined and concentrated in vacuo to give a colorless oil which was reevaporated from water several times. The residue was dissolved in 40 mL of water, protected from light, and solid Ag_2O was added. The silver salts were removed by filtration through Celite, and H_2S was bubbled through the filtrate in the absence of light. Excess H_2S was allowed to dissipate in the hood overnight. The Ag_2S formed was removed by filtration through powdered cellulose and Celite. The resulting colorless filtrate gave an oil upon concentration in vacuo. Swirling this residue in absolute ethanol gave 243 mg of a white solid which was then washed three times with 2-propanol: mp 147–148 °C; NMR (D_2O) δ 1.8 (2 H, m), 2.2 (2 H, m), 3.5 (1 H, m), 3.7 (2 H, t, *J* = 4 Hz), 4.6 (4 H, s, HDO); IR (KBr) 3100 (br), 1570 (s), 1410 (s), 1380 (s), 1240 (m), 1100 (m).

Anal. Calcd for $C_5H_{11}NO_3 \cdot {}^2/_3H_2O$: C, 41.36; H, 8.56; N, 9.66. Found: C, 41.14; H, 8.46; N, 10.10.

(*S*)-(+)-4-Amino-5-fluoropentanoic Acid Hydrochloride (1b·HCl). A solution of 400 mg (3.41 mmol) of **3b** in 10 mL of 1 N HCl was refluxed for 6 h. The reaction was cooled to room temperature and the solvent was evaporated in vacuo at 30 °C to give a white solid. This solid was dried overnight in a vacuum desiccator, giving 553 mg (95%) of a product which was recrystallized from acetic acid–ethyl acetate, yielding shiny white plates: mp 170–171 °C; $[\alpha]^{20}_D$ +11° (*c* 2.5, 1 N HCl); NMR (D_2O) δ 2.0 (2 H, t, *J* = 7 Hz), 2.5 (2 H, m), 3.6 (1 H, m), 4.6 (4 H, s, HDO), 4.7 (2 H, dm, *J* = 48 Hz); IR (KBr) 3000 (br), 1720 (s), 1600 (m), 1192 (s), 1020 (m), 832 (m) cm^{-1}.

Anal. Calcd for $C_5H_{10}FNO_2 \cdot HCl$: C, 35.00; H, 6.46; N, 8.16; F, 11.07; Cl, 20.66. Found: C, 35.11; H, 6.28; N, 7.88; F, 11.32; Cl, 20.55.

(*S*)-(+)-4-Amino-5-chloropentanoic Acid Hydrochloride (1c·HCl). A solution of 493 mg (3.69 mmol) of **3c** in 10 mL of 1 N HCl was heated at reflux for 5 h. After the solution was cooled to room temperature, the solvent was removed in vacuo to give a light yellow oil. This oil was dissolved twice in 20 mL of glacial acetic acid and the solvent was removed in vacuo to give 495 mg of a white solid. High-voltage electrophoresis, pH 1.9, 4.2 kV, for 25 min followed by ninhydrin visualization showed two minor spots at 14.5 and 25 cm and one major spot at 21.5 cm toward the cathode. The solid (390 mg) was applied to a column (1.5 × 21 cm) of Dowex 50 (H^+ form) preequilibrated with 0.1 N HCl. The column was eluted with a linear gradient of HCl from 0.1 to 0.5 N concentration over 2000 mL at a rate of 1 mL/min, collecting 3-mL fractions. Fractions 345–455 gave positive ninhydrin tests, and contained only one component by high-voltage electrophoresis (21 cm toward the cathode for 25 min). These fractions were combined and concentrated in vacuo to give a clear, colorless oil. Water was added and evaporated three times and the residue was dried under vacuum to give a white solid. Recrystallization of this solid from acetic acid–ethyl acetate gave 280 mg of white plates: mp 131.5–132.5 °C; $[\alpha]^{20}_D$ +16° (*c* 2.5, 1 N HCl); NMR (D_2O) δ 1.7 (2 H, td, *J* = 10 Hz), 2.1 (2 H, m), 3.5 (3 H, m), 4.5 (4 H, s, HDO); IR (KBr) 3130 (br), 1730 (s), 1610

(m), 1420 (m), 1180 (s), 750 (m) cm^{-1}.

Anal. Calcd for $C_5H_{10}ClNO_2 \cdot HCl$: C, 31.94; H, 5.90; N, 7.45; Cl, 37.71. Found: C, 31.60; H, 6.07; N, 7.30; Cl, 37.27.

(*S*)-(+)-4-Amino-5-bromopentanoic Acid Hydrobromide (1d·HBr). A solution of 330 mg (1.85 mmol) of **3d** in 10 mL of 1 N HBr was heated at reflux for 5 h. The reaction solution was cooled to room temperature and the solvent was removed in vacuo. The resulting dark oil was dissolved in 2 mL of H_2O and applied to a column (1 × 10 cm) of Dowex 50 (H^+ form). The column was washed with distilled water until the eluate was neutral, and the amino acid was eluted with 1 N HBr. The acidic fractions that gave a positive ninhydrin test were combined and concentrated in vacuo to a light yellow oil. Acetic acid was added and evaporated (2×). The oil was crystallized and recrystallized from acetic acid–ethyl acetate to give 230 mg of a white solid. Electrophoresis of this solid at 4.2 kV, pH 1.9, for 20 min showed one component at 18 cm toward the cathode as detected by ninhydrin: mp 137–138 °C; $[\alpha]^{20}_D$ +14.3° (*c* 10, 1 N HBr); NMR (D_2O) δ 1.9 (2 H, m), 2.4 (2 H, m), 3.6 (3 H, m), 4.6 (4 H, s, HDO); IR (KBr) 3120 (br), 1728 (s), 1605 (m), 1497 (s), 1175 (m), 620 (m) cm^{-1}.

Anal. Calcd for $C_5H_{10}BrNO_2 \cdot HBr$: C, 21.68; H, 4.00; N, 5.06. Found: C, 22.01; H, 4.03; N, 4.70.

(*S*)-(+)-4-Amino-5-cyanopentanoic Acid Hydrochloride (1e·HCl). A solution of 124 mg (1.0 mmol) of **3e** in 5 mL of 1 N HCl was heated at reflux for 2 h. After the solution was cooled to room temperature, the solvent was removed in vacuo to give a gummy solid. Water (0.5 mL) was added and evaporated (2×). The residue was dissolved in 10 mL of absolute ethanol, cooled to 0 °C, and filtered through a sintered-glass funnel. The filtrate was concentrated and the residue was crystallized from ethanol–ethyl acetate to give 97 mg of fluffy white crystals. Electrophoresis for 20 min showed one spot at 17.5 cm toward the cathode as detected by ninhydrin: mp 147.5–149 °C; $[\alpha]^{20}_D$ +8° (*c* 2.5, 1 N HCl); NMR (D_2O) δ 0.9 (~1.5 H, t, J = 7 Hz), 1.9 (2 H, td, J = 7 Hz), 2.3 (2 H, m), 2.75 (2 H, d, J = 6 Hz), 3.5 (~1.5 H, m), 4.5 (~4.5 H, s, HDO); IR (KBr) 3100 (s, br), 2244 (w), 1723 (s), 1580 (m), 1496 (s), 1180 (s), 793 (m) cm^{-1}.

Anal. Calcd for $C_6H_{10}N_2O_2 \cdot HCl \cdot {}^1/_2C_2H_5OH$: C, 41.81; H, 6.98; N, 13.87. Found: C, 42.09; H, 7.02; N, 14.25.

A sample of this solid that was recrystallized from ethanol–ethyl acetate (3×) was twice dissolved in 5 mL of distilled H_2O and was lyophilized. The resulting fluffy white solid was further dried under vacuum over P_2O_5, mp 149–151 °C.

Anal. Calcd for $C_6H_{10}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$: C, 38.41; H, 6.45; N, 14.93. Found: C, 38.47; H, 6.14; N, 15.30.

Acknowledgment. We are grateful for support of this research by the National Institutes of Health (Grant NS 15703), DHEW.

Registry No. 1a, 72478-99-0; **1b**·HCl, 72522-16-8; **1c**·HCl, 72479-00-6; **1d**·HBr, 72479-01-7; **1e**·HCl, 72479-02-8; **2c**, 7149-65-7; **3a**, 17342-08-4; **3b**, 72479-03-9; **3c**, 72479-04-0; **3d**, 72479-05-1; **3e**, 72479-06-2; L-glutamic acid, 56-86-0.

Theoretical Approach to Substituent Effects. Phenols and Phenoxide Ions

Addy Pross,*[1a-c] Leo Radom,*[1a,c] and Robert W. Taft*[1c]

Research School of Chemistry, Australian National University, Canberra, ACT 2600, Australia, Department of Chemistry, Ben Gurion University of the Negev, Beer Sheva, Israel, and Department of Chemistry, University of California, Irvine, California 92717

Received August 6, 1979

Ab initio molecular orbital calculations on substituent interactions in substituted phenols and phenoxide ions have been performed. Theoretical gas-phase acidities are generally in satisfactory agreement with available gas-phase experimental data. The effects of substituents on acidity are largely determined by effects in the phenoxide anion and only to a slight extent by those in the corresponding neutral phenol. Substituents which interact favorably in the meta position of phenol generally act unfavorably at the para position and vice versa. Both σ and π charge transfer are found to be of importance in determining energies of interaction. The σ acceptance by a substituent stabilizes OH and O^- more effectively at the para position than at the meta position by a π-inductive mechanism. Direct π interactions are also more important for para substituents and result in stabilization by π acceptors and destabilization by π donors. The net results for the π-donating and σ-accepting groups (NH_2, OH, and F) are an increase in acidity at the meta position and a decrease in acidity (with the exception of the strongly σ-accepting F substituent) at the para position. For the σ- and π-accepting groups (NO_2, CN, CHO, and CF_3), both meta and para substitution lead to enhanced acidity, with a larger effect at the para position.

With the advent of both experimental and theoretical techniques for studying gas-phase chemical reactions, research on substituent effects has made significant recent progress. Specifically, the separation of intrinsic molecular effects from solution effects has become possible, enabling a clearer understanding of both to be obtained.[2]

The interaction of a large number of neutral substituents with an aromatic ring has recently been studied by using ab initio molecular orbital theory.[3] This paper extends that study first by the comparison of a neutral substituent (OH) with a charged one (O^-) and second by examining the interaction of each of these two groups with a series of additional substituents.[4] The results also provide theoretical estimates of the relative acidities of substituted phenols and enable the separation of the effect of the substituent on acidity into components due to the neutral phenol on the one hand and to the charged phenoxide ion on the other. Such a separation is at present not accessible

(1) (a) Research School of Chemistry, Australian National University, Canberra, ACT 2600, Australia; (b) Department of Chemistry, Ben Gurion University of the Negev, Beer Sheva, Israel; (c) Department of Chemistry, University of California, Irvine, CA 92717.

(2) See, for example, R. W. Taft, *NATO Adv. Study Inst. Ser., Ser. B*, **40**, 271 (1979).

(3) W. J. Hehre, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 1496 (1972).

(4) A paper utilizing ab initio calculations to assess torsional barriers in para-substituted phenols has appeared: L. Radom, W. J. Hehre, J. A. Pople, G. L. Carlson, and W. G. Fateley, *J. Chem. Soc., Chem. Commun.*, 308 (1972).

0022-3263/80/1945-0818$01.00/0