Experimental Section

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were run with a Varian CFT-80 instrument using tetramethylsilane and dioxane as internal standard, respectively. Mass spectra were recorded with a Kratos-25 instrument as well as with a Hewlett-Packard 5985 B at 70 eV. IR spectra were recorded with a Hitachi 260-10 instrument. Elemental analyses were carried out at the Instituto de Química Bioorgánica del C.S.I.C. (Barcelona).

All commercial α-amino acids and α-hydroxy acids were directly used as received. Fremy's salt was prepared, recrystallized, and stored as reported.[6]

Two buffered solutions[23] were used: sodium carbonate buffer (pH 10) and phosphate buffer (pH 7.2). The phosphate buffer was then appropriately adjusted to the pH needed by adding 0.2 M NaOH.

Oxidation of α-Amino and α-Hydroxy Acids. General Procedure. To a stirred solution of 1 mmol of **1** or **2** in 12 mL of buffer (pH 10), 3 mmol of Fremy's salt were added all at once. Stirring was continued for the time shown. The resulting solution, after acidification with 2 N HCl, was added to a solution of 2,4-dinitrophenylhydrazine (1.2 mmol) in 25 mL of 12 N HCl, previously filtered. The (2,4-dinitrophenyl)hydrazones obtained were recrystallized from ethanol. Their spectroscopic data (IR, NMR, MS) were identical with those of authentic samples.

Preparation of Triazolines 6 and 7. To a stirred solution of Val (1 mmol) in 12 mL of sodium carbonate buffer (pH 10) was added a large excess of Fremy's salt (3 mmol). After 5 days of stirring, a second batch of Fremy's salt (3 mmol) was added. Stirring was continued for another 5 days. The resulting solution was then treated with a filtered solution of 2,4-dinitrophenylhydrazine (2.2 mmol) in 50 mL of 12 N HCl. A precipitate slowly appeared (24 h). Filtration and final recrystallization (twice) from ethanol yielded triazoline **6** in 41% yield as yellow needles, mp 202–203 °C: IR (KBr) 3275, 3100, 2980, 1690, 1610, 1590, 1500, 1410, 1335, 1305, 1260, 1140, 1110, 1075, 915, 860, 830, 740, 710 cm^{-1}; ^1H NMR (Me_2SO-d_6, Me_4Si) 1.60 (6 H, s), 8.05 (1 H, d, J = 9.4 Hz), 8.47 (1 H, dd, J = 9.4 Hz, J = 2.5 Hz), 8.95 (1 H, d, J = 2.5 Hz), 15.50 (1 H, s) ppm; ^{13}C NMR (Me_2SO-d_6, Me_4Si) 25.55, 82.50, 115.60, 122.66, 129.69, 129.96, 138.00, 143.80, 149.50, 158.27 ppm; mass spectrum, m/e (relative intensity) 309 (M^+, 60), 294 (100), 273 (10), 259 (15), 195 (20), 183 (25). Anal. Calcd for $C_{11}H_{11}N_5O_6$: C, 42.72; H, 3.56; N, 22.65. Found: C, 42.64; H, 3.58; N, 22.37.

Identical treatment of Ile (1 mmol) as above yielded triazoline **7** in 38% yield, as yellow prisms: mp 194–195.5 °C; IR (KBr) 3275, 3100, 2975, 1680, 1605, 1595, 1500, 1420, 1330, 1310, 1135, 1110, 1090, 1045, 920, 880, 830, 740, 700 cm^{-1}; ^1H NMR (Me_2SO-d_6, Me_4Si) 1.00 (3 H, t, J = 7.3 Hz), 1.54 (3 H, s), 1.90 (2 H, q, J = 7.3 Hz), 8.05 (1 H, d, J = 9.6 Hz), 8.38 (1 H, dd, J = 9.6 Hz, J = 2.4 Hz), 9.08 (1 H, d, J = 2.4 H), 14.09 (1 H, s) ppm; ^{13}C NMR (Me_2SO-d_6, Me_4Si) 7.38, 23.72, 31.93, 85.56, 115.57, 122.60, 130.02, 130.14, 138.29, 143.82, 149.00, 158.22 ppm; mass spectrum, m/e (relative intensity) 323 (M^+, 19), 294 (100), 273 (24), 183 (21). Anal. Calcd for $C_{12}H_{13}N_5O_6$: C, 44.59; H, 4.05; N, 21.66. Found: C, 44.66; H, 3.86; N, 21.34.

Treatment of commercial (Sigma) α-keto isovaleric acid (1 mmol) with Fremy's salt (30 mmol) as indicated for Val yielded triazoline **6** in 58% yield.

Acknowledgment. We thank the Comisiôn Asesora of Spain (Proyecto No. 1240/81) for financial support. We are also grateful to the Universidad Autônoma de Barcelona and the Universidad de Santiago de Compostela for kindly recording our mass spectra.

Registry No. **6**, 104197-46-8; **7**, 104197-47-9; $H_2NCH_2CO_2H$, 56-40-6; $H_2NCH(CH_3)CO_2H$, 56-41-7; $(CH_3)_2CHCH(NH_2)CO_2H$, 72-18-4; $CH_3CH_2CH(CH_3)CH(NH_2)CO_2H$, 73-32-5; $HO_2CCH_2CH_2CH(NH_2)CO_2H$, 56-86-0; $H_2NCH(Ph)CO_2H$, 69-91-0; $PhCONHCH_2CO_2H$, 495-69-2; $PhCONHCH(CH_3)CO_2H$, 2198-64-3; $CH_3CH(OH)CO_2H$, 50-21-5; $PhCH(OH)CO_2H$, 90-64-2; $OHCCO_2H$, 298-12-4; CH_3COCO_2H, 127-17-3; $(CH_3)_2CHCOCO_2H$, 759-05-7; $CH_3CH_2CH(CH_3)COCO_2H$, 1460-34-0; $HO_2CCH_2CH_2COCO_2H$, 328-50-7; $PhCOCO_2H$, 611-73-4; DNP-NHN=CHCO_2H, 3158-42-7; DNP-NHN=C$(CH_3)CO_2H$, 790-12-5; DNP-NHN=C(Pr-i)CO_2H, 6064-65-9; DNP-NH-N=C(Bu-*sec*)CO_2H, 1459-83-2; DNP-NH-N=C$(CH_2CH_2CO_2H)CO_2H$, 1237-47-4; DNP-NH-N=C$(Ph)CO_2H$, 31334-72-2; Fremy's salt, 14293-70-0; oxidase, 9035-73-8; (2,4-dinitrophenyl)hydrazine, 119-26-6.

(23) Perrin, D. D.; Dempsey, B. *Buffers for pH and Metal Ion Control*, Chapman and Hall Laboratory Manual: London, 1974.

An Investigation of the Mode of Formation of the 10-P-5 Protonated Phosphatrane $HP(OCH_2CH_2)_3N^+$

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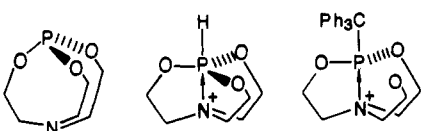
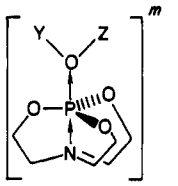
In 1977 it was reported that the unstable phosphite ester amine **1** reacted with Me_3O^+ and Ph_3C^+ to give the first 10-P-5 cations **2** and **3**, respectively.[1] Cation **2** (1-



1 2 3

hydro-2,8,9-trioxa-1-phospha-5-azatricyclor[3.3.3.0]undecane) was shown to possess a TBP structure by X-ray crystallographic means.[2] In contrast to the novel 10-P-5 TBP species such as **4–10** which have been reported from



	Y	Z	m	ref
4:	1p	BF_3	O	3
5:	1p	Et	1+	5
6:	Et	Et	2+	4
7:	1p	Et_3Si	1+	3
8:	Et_3Si	Et_3Si	2+	3
9:	1p	H	1+	4
10:	H	H	2+	4

our laboratories recently, **2** and **3** feature the relatively nonapicophilic proton and triphenylmethyl group, respectively, in the apical position. It is also curious that the hydride–phosphorane cation **2** is the only nonpolymeric product isolated from the reaction of **1** with Me_3OBF_4 (Scheme I) rather than the methyl analogue. In contrast, **3** was reported to form in the analogous reaction with Ph_3CBF_4.[1] Here we show that the unreacted triethanolamine is the source of the protons in the reaction involving Me_3OBF_4. Moreover, we now find that **2** as well as **3** can be formed in the reaction of **1** with Ph_3CBF_4 (Scheme I).

(1) Milbrath, D. S.; Verkade, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 6607 and references therein.
(2) Clardy, J. C.; Milbrath, D. S.; Springer, J. P.; Verkade, J. G. *J. Am. Chem. Soc.* **1976** *98*, 623.
(3) Carpenter, L. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1985**, *107*, 7084.
(4) Carpenter, L. E.; de Ruiter, B.; van Aken, D.; Buck, H. M.; Verkade, J. G. *J. Am. Chem. Soc.*, in press.
(5) van Aken, D.; Merkelbach, I. I.; Koster, A. S.; Buck, H. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1045.

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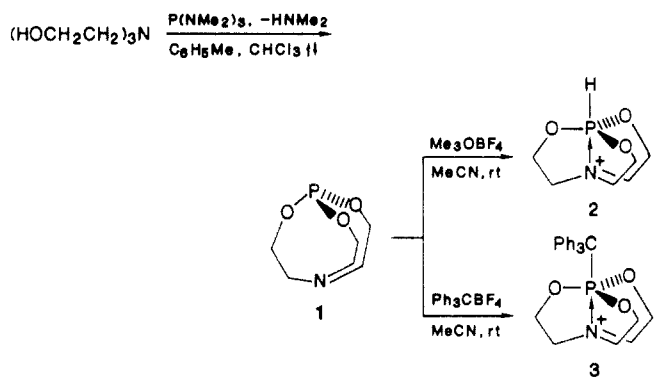
Scheme I



Results and Discussion

In the synthesis of **2**, $CHCl_3$ is used as a cosolvent to solubilize the $(HOCH_2CH_2)_3N$.[1] Using $CDCl_3$ as a substitute cosolvent we isolate only **2** in the same yield (6%), thus ruling out $CHCl_3$ as the proton source. The other cosolvent, toluene, is another potential proton source, since alkylation of aromatics by carbenium ions involves proton release.[6] However, substitution of heptane for the toluene consolvent gave only **2**, although in somewhat lower yield (4%). Repetitions of the synthesis with $Et_3OBF_4/C_6H_5Me/CHCl_3$, $MeOS(O)_2CF_3/C_6H_5Me/CHCl_3$, $MeOS(O)_2CF_3/C_6H_5Me/CDCl_3$, or $MeOS(O)_2CF_3$/heptane/$CHCl_3$ also gave only **2** in comparable yields (ca. 6%). Although these alkylating agents are unlikely sources of protons, $CD_3OS(O)_2CF_3$ was synthesized[6] and reacted with **1** using C_6H_5Me and $CHCl_3$ as cosolvents. Again, **2** was formed in 6% yield. We believe it unlikely that adventitious water could be present in sufficient quantity to lead to the formation of **2** in 6% yield, especially in view of the rather stringent precautions that were taken to insure anhydrous conditions.[1,3] Moreover, the yield of **1** is consistently about 6% using Me_3OBF_4, Et_3OBF_4, $MeOS(O)_2CF_3$, and $CD_3OS(O)_2CF_3$. It would be fortuitous if the amount of adventitious water were also so constant. Substitution of D_3CCN for MeCN as a solvent for the alkylating agent again gave only **2**.

The yield of **2** is low owing to the rather low yield of **1** (ca. 10%). Furthermore, intermediate **1** is unstable with respect to polymerization[7] and must be derivatized in situ.[1] In the course of repeatedly synthesizing **1**, we noticed that its yield is maximized at ca. 10% by slowly adding the reactants simultaneously over a 24-h period (even though the evolution of $HNMe_2$ is not complete at this time) and by maintaining a 1:1 molar ratio of reactants. The lack of complete $HNMe_2$ evolution indicates that $(HOCH_2CH_2)_3N$ is also not entirely consumed when the alkylating agent is added. We conclude, therefore, that alkylation of the alcohol groups accurs with proton release for the formation of **2** (as well as for the protonation of any unalkylated $HNMe_2$ present in solution).

In a previous publication we reported that **3** is formed when Ph_3CBF_4 is reacted with **1** (Scheme I). We now find that this reaction is erratic, giving either **3** or **4** or a mixture of these two products. The competition of OH groups for Ph_3C^+ is expected to be weaker than for Me_3O^+, thus accounting for the formation of **3** in the former case. The factors influencing the variable nature of the reaction of **1** with Ph_3C^+ have not been identified.

Experimental Section

Phosphatrane **1** was synthesized by a modification[8] of the route given earlier.[1] To the room-temperature reaction mixture were added the alkylating agents dropwise (in 100 mL of MeCN) in 20% molar excess over the $(HOCH_2CH_2)_3N$ used in the preceding reaction. The resulting crude **2** which precipitated was filtered and extracted with 2 × 25 mL of hot MeCH, and the solvent was removed under vacuum. After washing the residue with 30 mL of Me_2CO, further purification was accomplished as described earlier.[1]

Acknowledgment. J.G.V. is grateful to the National Science Foundation for a grant in support of this research. We thank Xi Shikang for experimental assistance.

Registry No. **1**, 36712-66-0; **2**·BF_4, 58418-99-8; $(HOCH_2CH_2)_3N$, 102-71-6; $P(NMe_2)_3$, 1608-26-0.

(6) van Aken, D.; Castelijns, A. M. C. F.; Verkade, J. G.; Buck, H. M. *Recl. Trav. Chim. Pas-Bas* **1979**, *98*, 12.
(7) Booth, B. L.; Hazeldine, R. N.; Laali, K. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2887.
(8) The polymerization that **1** undergoes may be similar to the ring-opening polymerization observed for a cyclic aminophosphine derivative of a furanoside (Penczek, S.; Baran, J.; Pretula, J.; Tapienis, G. *Proc. IUPAC Macromol. Symp. 28th* **1982**, 203; *Chem. Abstr.* **1983**, *98*, 89802g).

Proton NMR Studies of Self-Association in the Civet Constituent (+)-(*S*,*S*)-(*cis*-β-Methyltetrahydropyran-2-yl)-acetic acid

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Introduction

Self-association in carboxylic acid solutions has been extensively investigated,[1] as the nature, energetics, and geometry of the association complex formed is of great interest, particularly in the case of biologically produced carboxylic acids.

Dimerization of simple carboxylic acids in solution have been studied by ^1H NMR spectroscopy, but invariably such investigations were based upon changes in the chemical shifts of the acidic protons alone.[2] Chemical shifts of these protons, however, are highly dependent on trace impurities, and reproducible results are often difficult to achieve, even following careful purification of both solvent and substrate.

A particularly interesting case of self-association is that of (+)-(*S*,*S*)-(*cis*-β-methyltetrahydropyran-2-yl)acetic acid (**1**) a naturally occurring heterocyclic acid found in trace quantitites in Civet,[3] a perfume material secreted by a scent gland of the civet cat (*Viverra civetta*). We have recently completed its total synthesis[4] by taking advantage of the enantiomerically pure (*S*)-(+)-5-chloropentan-2-ol which was obtained from enzymatic reduction of the corresponding ketone with *Thermoanaerobium brockii* alcoholdehydrogenase (TBADH)[4,5] (Scheme I).

Interestingly, we observed strong concentration and temperature dependencies in the ^1H NMR spectrum of both the synthetic material **1** and an authentic sample.[6] These findings may explain the wide diversity in chemical shifts reported in the literature for synthetic samples of **1** prepared by various authors.[7] Chemical shift values

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‡ Incumbent of Charls H. Revson Career Development Chair.

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