Thermodynamic α-CH acidities of amino acid fragments in five-co-ordinate bicycloazastannoxides in Me_2SO

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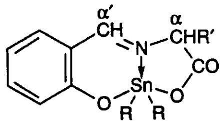
The thermodynamic α-CH acidities of the amino acid moieties in six five-co-ordinate bicycloazastannoxides in Me_2SO have been studied. Their pK_a values are in the range 17.40–18.50. The effects of the bulkiness of the amino acid moieties and the central metal atom (Sn) on the thermodynamic α-CH acidity are interpreted. The crystal structure of one complex was determined, and the formation of its α-carbanion intermediate under the action of 0.1 mol dm^{-3} $NaOCD_3$ has been confirmed by ^1H NMR spectrometry.

In view of the large number of vitamin B_6 related enzymes it is not surprising that pyridoxal phosphate coenzyme derivatives catalyse a variety of chemical reactions *in vivo* (pyridoxal = 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carbaldehyde).[1] One of the important features of the mechanism is the formation of an α carbanion in the presence of a base catalyst. The α position may be the active site of the enzyme.[1a] Most work has focused on mechanistic and spectroscopic properties of the model systems. However, little information on the α-CH acidity and stability of α carbanion has been obtained.[2]

In earlier papers[3] we have demonstrated that the structure of five-co-ordinate bicycloazastannoxides with Schiff bases derived from amino acids is similar to that of the metal–vitamin B_6, chelates.[4] Recently we have also investigated the condensation of bicycloazastannoxides with aldehydes.[5] It was found that the effect of the α-CH acidity and stability of α carbanions on condensation is important. It is thus necessary to find out which factors influence the α-CH acidity and which affect the stability of the carbanion, as well as to elucidate the influence exerted by the nature of the central metal atom (Sn) in five-co-ordinate bicycloazastannoxides.

In this study, we first determined the thermodynamic α-CH acidity (pK_a value) of five-co-ordinate bicycloazastannoxides **1**–**6** with Schiff bases derived from α-amino acids (Gly, Ala, Leu, Phe and Met) by the accurate spectrophotometric method for relative equilibrium acidities of weak carbon acids in dimethyl sulfoxide.[6] The effect of the bulkiness of the amino acid moieties on their α-CH acidities was then interpreted using the Taft equation, and the influence of the central metal atom (Sn) is also discussed. In addition, the single-crystal structure of compound **3** was determined, and the stability of its α-carbanion intermediate investigated by ^1H NMR spectrometry.



	R	R′
1	Ph	H
2	Ph	Me
3	Ph	CH_2Pr^i
4	Ph	CH_2Ph
5	Ph	CH_2CH_2SMe
6	Bu	H

Experimental

General

Melting points were reported with a PHMK melting-point stage the thermometer of which was corrected against a standard. The UV/VIS spectra were obtained with a Beckman DU-8B UV/VIS spectrophotometer.

Anhydrous dimethyl sulfoxide (dmso) and its potassium salt were prepared as described previously;[7] CD_3OD was obtained from Merck-Shuchardt Company. The five-co-ordinate bicycloazastannoxides **1**–**6** with Schiff bases derived from α-amino acids (Gly, Ala, Leu, Phe and Met) and a salicylic aldehyde were synthesised as described.[3c] Characterisation data are given in Table 1.

Proton NMR spectroscopy

The ^1H NMR spectra of complex **3** (3.5×10^{-5} mol) were obtained with a Bruker Ac-P 200 MHz spectrograph in CD_3OD and in 0.1 mol dm^{-3} $NaOCD_3$, respectively. The chemical shifts are reported in ppm with respect to $SiMe_4$ as internal reference. All runs were carried out on homogeneous systems.

Determination of pK_a of bicycloazastannoxides 1–6

An acid–base equilibrium (1) between the substrate and the

$$HL + in^- \rightleftharpoons Hin + L^- \qquad (1)$$

indicator anion (in^-) is established, where HL is the five-co-ordinate bicycloazastannoxide, and Hin the indicator, the pK_a of which is known. The pK_a values were calculated by means of equations (1) and (2). The acidity of HL was determined by UV irradiation at a wavelength appropriate for its absorbancy relative to Hin.

$$pK_a(HL) = pK_a(Hin) - \log [Hin][L^-]/[HL][in^-] \qquad (2)$$

Crystallography

Crystal data. $C_{25}H_{25}NO_3Sn$ **3**, $M = 506.17$, monoclinic, space group $P2_1/c$, $a = 15.815(4)$, $b = 10.480(2)$, $c = 27.65(1)$ Å, $\beta = 95.30(3)°$, $U = 4563(4)$ Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda = 0.710\,73$ Å), $Z = 8$, $D_c = 1.474$ Mg m^{-3}, $F(000) = 2048$, colourless, crystal dimensions (distance to faces from centre) $0.2 \times 0.3 \times 0.3$ mm, μ(Mo-Kα) = 1.146 mm^{-1}.

Table 1 Characterisation data for bicycloazastannoxides **1**–**6**

Complex	M.p. (°C)[a]	Yield (%)	δ (α-CH)[b]
1	191 (181.5)	78	4.35
2	205 (198–200)	70	4.20
3	207–208 (198)	67	4.20
4	202 (192–194)	75	4.30
5	115–117	87	4.33
6	123.5	80	4.40

[a] Values in parentheses are from ref. 3(*c*). [b] Chemical shift is obtained on a JNMP MX-90 spectrometer in CDCl$_3$, relative to SiMe$_4$.

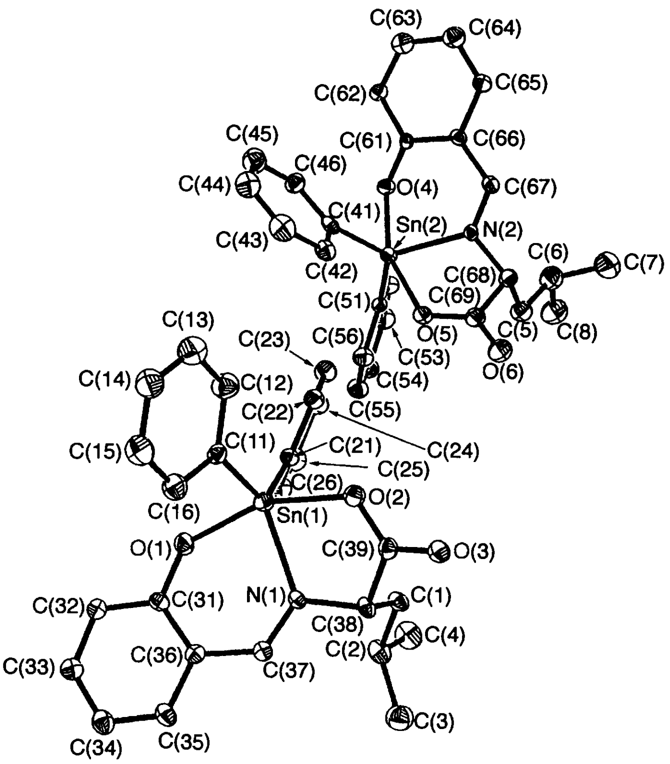


Fig. 1 Crystal structure of complex **3**

Data collection and processing. CAD4 diffractometer, θ_{max} = 23°, ω-scan speed 0.92–5.49 min^{-1}, graphite-monochromated Mo-Kα radiation; 6913 reflections measured (h = −17 to 17, k = 0–11, l = 1–30), 53443 independent reflections [merging R_{int} = 0.023 after absorption correction (maximum, minimum transmission factors = 1.114, 0.854)], giving 2542 with $I > 2\sigma(I)$.

Structure solution and refinement. The structure was solved by direct phase-determination methods (MULTAN 82)[8] and refined by least-squares in a full-matrix anisotropic approximation. Absorption corrections (DIFABS)[9] were applied. Hydrogen atoms were not located. The final refinement (on F^2) gave R = 0.040 (R' = 0.046), $(\Delta/\sigma)_{max}$ = 0.15, S = 0.509; residual peak, hole 0.47, −0.38 e Å^{-3}; w = 1. The calculations were performed on a PDP 11/44 computer with the SDP-PLUS program package.[10]

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/152.

Results and Discussion

Table 2 Selected bond lengths (Å) and angles (°) for compound **3**

Sn(1)–O(1)	2.082(5)	Sn(1)–O(2)	2.137(4)
Sn(1)–N(1)	2.135(6)	Sn(1)–C(11)	2.082(6)
Sn(1)–C(21)	2.111(6)	O(1)–C(31)	1.338(7)
O(2)–C(39)	1.285(7)	O(3)–C(39)	1.245(7)
N(1)–C(37)	1.300(8)	N(1)–C(38)	1.505(7)
C(1)–C(2)	1.538(9)	C(1)–C(38)	1.580(8)
C(2)–C(3)	1.55(2)	C(2)–C(4)	1.56(1)
C(11)–C(12)	1.41(2)	C(11)–C(16)	1.370(9)
C(12)–C(13)	1.44(2)	C(13)–C(14)	1.37(1)
C(14)–C(15)	1.36(1)	C(15)–C(16)	1.47(2)
C(21)–C(22)	1.381(8)	C(21)–C(26)	1.380(9)
C(22)–C(23)	1.392(9)	C(23)–C(24)	1.41(2)
C(24)–C(25)	1.37(2)	C(25)–C(26)	1.44(1)
C(31)–C(32)	1.436(9)	C(31)–C(36)	1.413(9)
C(32)–C(33)	1.384(9)	C(33)–C(34)	1.40(2)
C(34)–C(35)	1.427(9)	C(35)–C(36)	1.420(9)
C(36)–C(37)	1.470(9)	C(38)–C(39)	1.510(9)
O(1)–Sn(1)–O(2)	157.6(2)	Sn(1)–N(1)–C(38)	115.7(4)
O(1)–Sn(1)–N(1)	83.4(2)	C(37)–N(1)–C(38)	115.3(5)
O(1)–Sn(1)–C(11)	95.5(2)	O(1)–Sn(1)–C(21)	96.1(2)
O(2)–Sn(1)–N(1)	75.1(2)	O(2)–Sn(1)–C(11)	91.1(2)
C(2)–C(1)–C(38)	113.6(5)	O(2)–Sn(1)–C(21)	98.2(2)
C(1)–C(2)–C(3)	112.1(6)	C(1)–C(2)–C(4)	107.0(6)
C(3)–C(2)–C(4)	110.5(7)	N(1)–Sn(1)–C(11)	122.3(2)
N(1)–Sn(1)–C(21)	114.5(2)	C(11)–Sn(1)–C(21)	122.9(3)
Sn(1)–C(11)–C(12)	119.8(5)	Sn(1)–C(11)–C(16)	120.9(6)
C(12)–C(11)–C(16)	119.4(6)	C(11)–C(12)–C(13)	119.9(8)
C(12)–C(13)–C(14)	120.5(9)	C(13)–C(14)–C(15)	119.6(9)
C(14)–C(15)–C(16)	121.7(8)	Sn(1)–O(1)–C(31)	132.0(4)
C(11)–C(16)–C(15)	118.9(8)	Sn(1)–O(2)–C(39)	118.1(5)
Sn(1)–C(21)–C(22)	121.7(6)	Sn(1)–C(21)–C(26)	117.6(6)
C(22)–C(21)–C(26)	120.6(7)	Sn(1)–N(1)–C(37)	128.5(4)
C(21)–C(22)–C(23)	122.7(7)	C(22)–C(23)–C(24)	116.8(7)
C(23)–C(24)–C(25)	121.9(8)	C(24)–C(25)–C(26)	119.9(8)
C(21)–C(26)–C(25)	118.0(7)	O(1)–C(31)–C(32)	117.0(7)
O(1)–C(31)–C(36)	120.7(7)	C(32)–C(31)–C(36)	122.4(6)
C(31)–C(32)–C(33)	116.4(7)	C(32)–C(33)–C(34)	123.9(8)
C(33)–C(34)–C(35)	118.5(8)	C(34)–C(35)–C(36)	120.2(7)
C(31)–C(36)–C(35)	118.6(7)	C(31)–C(36)–C(37)	125.8(7)
C(35)–C(36)–C(37)	115.6(7)	N(1)–C(37)–C(36)	123.9(7)
N(1)–C(38)–C(1)	108.3(5)	N(1)–C(38)–C(39)	104.7(5)
C(1)–C(38)–C(39)	105.1(5)	O(2)–C(39)–O(3)	123.1(7)
O(2)–C(39)–C(38)	119.6(6)	O(3)–C(39)–C(38)	117.3(7)

Table 3 Proton NMR data for complex **3** and its α-carbanion

	δ				
System	α'-CH=N	α'-CHNC*	Aryl	α-CH	CH$_2$Pr^i
3–CD$_3$OD	8.82	—	7.0–8.15	4.52	1.0–2.0
3–NaOCD$_3$	8.60	8.42	6.75–8.17	—	0.81–2.21

* The α-carbanion intermediate.

From the X-ray data for complex **3** (Fig. 1, Table 2), the Schiff-base ligand ring is planar. The Sn atom is situated at the centre of a pseudo-trigonal bipyramid, with one N and two C atoms of the phenyl groups at the equatorial positions. Two O atoms lie below and above the triangular plane, respectively.

The ^{1}H NMR data for complex **3** (Table 3) show that in 0.1 mol dm^{-3} NaOCD$_3$ the α-CH resonance (near δ 4.5) disappears completely, and two peaks at δ 8.3 and 8.6 appear. According to Martell and co-workers,[11] the new peak at δ 8.3 is assigned to the α'-CH resonance in the α-carbanion intermediate. The reason may be due to the increasing negative charge at the α position as the α-proton is dissociated.[12] Thus, it is assumed that the α-carbanion intermediate is an important species in the K(CH$_2$OMe) system.

The pK_a values of complexes **1**–**3** are 17.63, 18.09 and 18.50, respectively (Table 4). The difference in acidity corresponds to the bulkiness of the amino acid moiety. With the change in substituent from H to Bu^i, an enhancement in electron-donating ability takes place. As a result the stability of the α

Table 4 The pK_a values of compounds **1**–**6** (two determinations in each case)

Complex	pK_a	Hin	λ^a/nm
1	17.63 ± 0.03	*b*	545
2	18.09 ± 0.00	*c*	607
3	18.50 ± 0.20	*c*	607
4	17.73 ± 0.12	*b*	545
5	17.68 ± 0.20	*b*	545
6	17.40 ± 0.10	*b*	545

[a] The wavelength at which the data were recorded. [b] 9-Phenylfluorene. [c] 4-Chloro-2-nitroaniline.

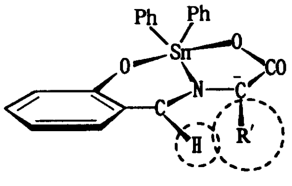


Fig. 2 Schematic representation of the intramolecular steric interaction between the alkyl group of the amino acid moiety and the aldimine proton in the α-carbanion intermediate of five-co-ordinate bicycloazastannoxides

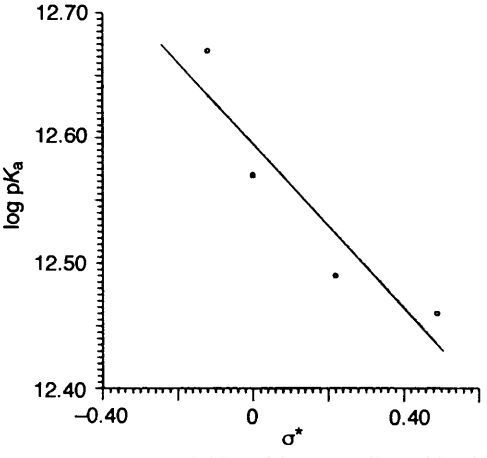
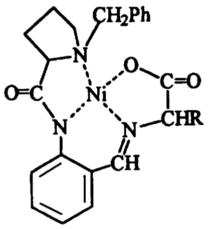


Fig. 3 Taft plot of α-CH acidities of five-co-ordinate bicycloazastannoxides

carbanion is decreased and its α-CH acidity becomes weaker. According to the crystal structure (Fig. 1) the formation of the α-carbanion intermediate requires an energetically unfavourable eclipsed arrangement of the alkyl group of the amino acid fragment and of the aldimine proton of the same ligand (Fig. 2). Further the C=N bond is shorter than any of the C–C bonds. This enhances the intramolecular steric effect. The bulkiness of the amino acid moieties leads to severe repulsive steric interactions between the alkyl group of the amino acid fragment and the aldimine proton. This explains why the α-CH acidity is negatively related to the bulkiness of the amino acid fragments.

The influence of the various side-chains of the amino acid fragments on their α-CH acidities can be elucidated from the Taft equation. Conventionally, inductive and steric effects may be separated by utilising Taft σ* parameters to measure the inductive or polarising effect of a group. The parameters of several of the amino acids under discussion[1] are: Gly, +0.49; Phe, +0.22, Ala, 0.0; Leu, −0.12.[13] The relationship between the Taft σ* parameters and the α-CH acidities is depicted in Fig. 3.

It has been reported that the pK_a values of nickel(II) complexes **7**–**9** in dmso, the amino acid moieties of which are Gly, Ala and Val, are 18.8, 19.2 and 19.5, respectively.[2] This trend is stronger than in complexes **1**–**3** because of the greater strength of the Ni–O and Ni–N bonds compared with corresponding bonds in organotin(IV) complexes. According to the crystal data for complexes **3** and **9**, the Sn–O and Sn–N bonds are longer than the Ni–O and Ni–N bonds: **9**, Ni–O 1.866, Ni–N 1.855;[14] **3**, Sn–O 2.105, Sn–N 2.135 Å. It is a logical consequence that the bond strength will increase with decrease in bond length. Such an increase in bond strength would make the chelate rings more rigid and render the intramolecular steric non-bonding interactions more severe. The higher acidity in the organotin(IV) complex results from the lability of the α-CH bonding.



	R
7	H
8	Me
9	Pr^i

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References

1 (*a*) A. E. Martell, *Acc. Chem. Res.*, 1989, **22**, 115; (*b*) K. Jitsukawa, T. Yamamoto, T. Atsumi, H. Masuda and H. Einaga, *J. Chem. Soc., Chem. Commun.*, 1994, 2335; (*c*) V. A. Soloshonok, Yu. N. Belokon, N. A. Kuzmina, V. I. Maleev, N. Yu. Svistunova, V. A. Solodenko and V. P. Kukhar, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1525; (*d*) Yu. N. Belokon, *Pure Appl. Chem.*, 1992, 1917.
2 M. I. Terehova, Yu. N. Belokon, V. I. Maleev, W. I. Chernoglazova, K. A. Kochetkov, V. M. Belikov and E. G. Petro, *Izv. Akad. Nauk. SSSR., Ser. Khim.*, 1986, 905.
3 (*a*) J. Wang, F. Lui and Y. Zhang, *J. Organomet. Chem.*, 1989, **371**, 35; (*b*) J. Wang, F. Lui and Y. Zhang, *J. Organomet. Chem.*, 1989, **375**, 173; (*c*) J. Wang, Y. Zhang, Y. Xu and Z. Wang, *Heteroatom Chem.*, 1992, 599.
4 A. E. Martell, *Proceedings of Symposium on Chemical and Biological Aspects of Pyridoxal Catalysis, Rome 1962*, Pergamon, London, 1963, pp. 13–28.
5 J. Wang and X. Yang, *Heteroatom Chem.*, 1996, **7**, 211.
6 R. W. Taft and F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 463.
7 W. S. Matthews, J. E. Bare, J. E. Baretmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. S. McCallum, G. J. McCallum and N. R. Vanier, *J. Am. Chem. Soc.*, 1975, **97**, 7006.
8 MULTAN 82, SDP PLUS, B. A. Frenz and Associates, College Station, TX and Enraf-Nonius, Delft, 1982.
9 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.
10 SDP Structure Determination Package, Enraf-Nonius, Delft, 1985.
11 K. Tatsumoto, R. P. Reddy and A. E. Martell, *Can. J. Chem.*, 1986, **64**, 2050.
12 P. A. Taylor and A. E. Martell, *Inorg. Chim. Acta.*, 1988, **152**, 181.
13 D. Hopgood, *J. Chem. Soc., Dalton Trans.*, 1972, 482.
14 Yu. N. Belokon, V. I. Maleyev, S. V. Vitt, M. G. Ryzhov, Yu. D. Kondrashov, S. N. Golubev, Yu. P. Vauchskii, A. I. Kazika, M. I. Novikova, P. A. Krasutaskii, A. G. Yurchenko, I. L. Dubchak, V. E. Shklover, Y. T. Struchkov, V. I. Bakhmutov and V. M. Belikov, *J. Chem. Soc., Dalton Trans.*, 1985, 17.

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