DALTON COMMUNICATION

Synthesis and characterisation of the first organotin complex of piroxicam. An extended network system *via* non-hydrogen, hydrogen bonding linkages and C–H · · · π contacts

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The organotin complex, $[SnBu_2(pir)]_n$, of the potent and widely used anti-inflammatory drug piroxicam, H_2pir, was obtained and a crystal structure determination showed that in this complex the ligand is doubly deprotonated at the oxygen and amide nitrogen atoms. There are two similar molecules in the asymmetric unit. The isolated molecules of Sn(1) or Sn(2) are arranged in polymers in a head to tail fashion with a stacking of alternate parallel chains. Extended networks of Sn–O–Sn, C–H · · · O and C–H · · · π contacts lead to aggregation and a supramolecular assembly. Real concentration protonation constants for the zwitterionic form (pyridyl group) and the protonated piroxicam (enolic group) were determined spectrophotometrically in pure aqueous solutions of constant ionic strength. It is the first example where piroxicam is proved to act as a doubly deprotonated tridentate ligand.

Piroxicam [4-hydroxy-2-methyl-3-(2-pyridyl carbamoyl)-2*H*-1,2-benzothiazine 1,1-dioxide], H_2pir, is a potent and extensively used non-steroidal anti-inflammatory (NSDA), anti-arthritic drug with a long biological half-life,[1a] which acts by inhibiting enzymes involved in the biosynthesis of prostaglandins. To date, piroxicam is among the top ten NSDAs on the market.[1] The drug, with four donor atoms and several possible isomers,[1] is known to react as a monodentate ligand through the pyridyl nitrogen towards platinum(II) and as a singly deprotonated bidentate chelate ligand, through the pyridyl nitrogen and the amide oxygen, towards copper(II) and cadmium(II).[2] Iron(II), cobalt(II), nickel(II) and zinc(II) almost certainly behave similarly to cadmium(II).[2] Organotin(IV) compounds form an important series of compounds and have been receiving increasing attention in recent years, not only because of their intrinsic interest, but also owing to the importance of tin-based anti-tumour drugs.[3,4] We have developed[5] an interest in the co-ordination chemistry and anti-inflammatory properties of non-steroidal anti-inflammatory drugs, and report here the interaction of $SnBu_2Cl_2$ with piroxicam (H_2pir)† and the crystal structure of the complex $[SnBu_2(pir)]_n$.‡ There are two similar molecules in the asymmetric unit. $[SnBu_2(pir)]_n$ has 1 : 1 Sn : pir stoichiometry and the doubly deprotonated ligand, pir, is coordinated as a tridentate ligand *via* the enolic oxygen O(1), the amide N(2) and pyridyl N(1) nitrogen atoms. The molecular structure is shown in Fig. 1 which includes some selected bond parameters. The very long $Sn–N_{(pyridyl)}$ bonds are readily explic-

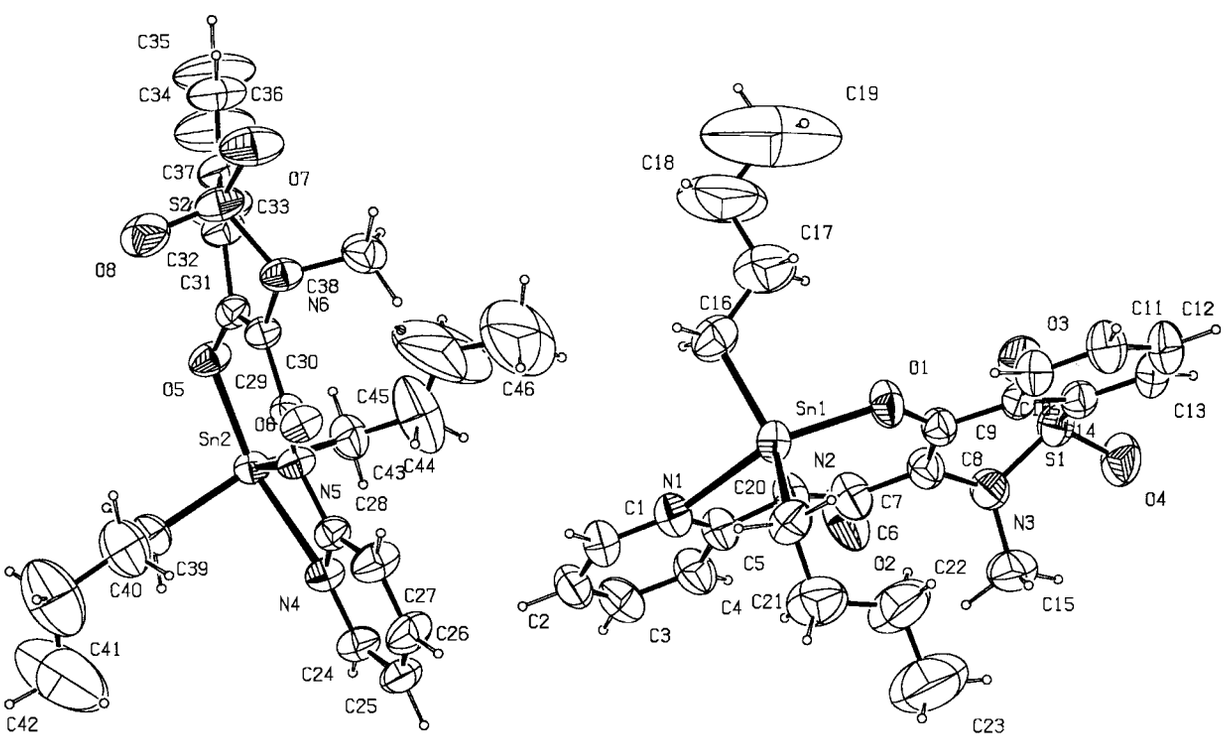

Fig. 1 An ORTEP representation of $[SnBu_2(pir)]_n$ with the atom numbering scheme. Selected bond lengths (Å) [data from the second molecule are in square brackets]; Sn–O 2.083(3) [2.074(2)]; $Sn–N_{(pyridyl)}$ 2.427(3) [2.478(3)]; $Sn–N_{(amide)}$ 2.135(3) [2.176(3)]; Sn(1)–C(16) 2.119(5) [2.120(4)]; Sn(1)–C(20) 2.119(5) [1.238(4)]; C(8)–O(1) 1.313(4) [1.321(4)]; C(6)–O(2) 1.229(5) [1.238(4)]; N(2)–C(5) 1.389(5) [1.388(4)]; N(2)–C(6) 1.375(5) [1.354(4)].

Table 1 Inter-hydrogen bonding, non-hydrogen intermolecular interactions and C–H · · · π interactions in $[SnBu_2(pir)]_n$ in Å and degrees. Cg = ring centroid[a]

Donor (D)	H[a]	Acceptor (A)[b]	D · · · A	H · · · A	D–H · · · A
C(1)	H(1)	O(3)^{i}	3.238(5)	2.5195	132.55
C(20)	H(20B)	O(3)^{i}	3.402(5)	2.4895	145.95
C(36)	H(36)	O(3)^{ii}	3.291(5)	2.5278	137.49
C(38)	H(38B)	O(4)^{i}	3.521(5)	2.4927	169.18
C(43)	H(43A)	O(8)^{iii}	3.354(5)	2.4145	149.72
Sn(1)		O(2)^{i}	3.019(4)		
Sn(2)		O(6)^{iii}	2.611(2)		
Sn(2)		N(6)^{iii}	3.598(3)		
Sn(2)		C(29)^{iii}	3.535(4)		

	H · · · Cg	X · · · Cg	C–H · · · Cg
C(16)–H(16A) · · · Cg(1)	2.772	2.897	86.34
C(21)–H(21A) · · · Cg(1)	2.760	3.315	113.51
C(40)–H(40A) · · · Cg(2)	3.355	3.151	69.83
C(40)–H(40B) · · · Cg(2)	2.697	3.151	106.37
C(44)–H(44B) · · · Cg(2)	2.438	3.170	126.58
C(2)–H(2) · · · Cg(3)	3.283	4.059	140.27
C(35)–H(35) · · · Cg(4)	2.818	3.666	113.51

[a] Cg(1) and Cg(2) are the centroids of the four-membered rings Sn(1)–N(1)–C(5)–N(2) and Sn(2)–N(4)–C(28)–N(5) respectively; Cg(3) and Cg(4) are the six-membered rings N(4)–C(24)–C(25)–C(26)–C(27)–C(28) and C(9)–C(10)–C(11)–C(12)–C(13)–C(14) respectively. [b] Symmetry operations; i, $1/2 - x$, $1/2 + y$, $1/2 - z$; ii, $1 - x$, $-y$, $1 - z$; iii, $3/2 - x$, $-1/2 + y$, $1/2 - z$.

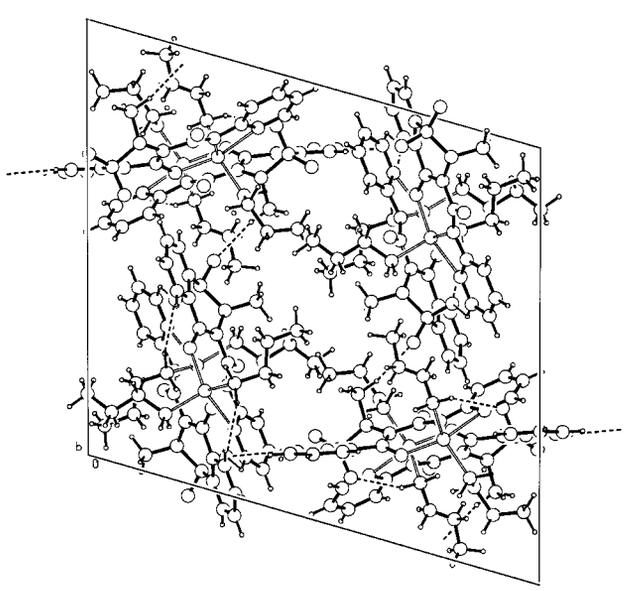

Fig. 2 Packing diagram of the complex $[SnBu_2(pir)]_n$ viewed along the *b* axis of the unit cell, showing intra- and inter-molecular hydrogen bonds.

able in terms of ring strain effects in the four-membered chelate ring and as a result of the low degree of covalent character of the Sn–$N_{(pyridyl)}$ bond. According to Crow *et al.*,[6c] diorganotins with Sn–N bonds longer than 2.39 Å are associated with anti-tumour activity. On this basis, $[SnBu_2(pir)]_n$ should be active.

Analysis of the shape determining angles using the approach of Reedijk and coworkers[7] yields τ ($(\alpha - \beta)/60$) values of 0.01 and 0.13 for Sn(1) and Sn(2) respectively ($\tau = 0.0$ and 1.0 for *SPY* and *TBPY* geometries respectively). The metal co-ordination geometry is therefore described as *SPY* with the N(2) and N(5) occupying the apical positions for Sn(1) and Sn(2) respectively. The donors N(2) and N(5) are chosen as apices by the simple criterion that neither should be any of the four donor atoms which define the two largest angles, α and β.[7] The coordinated part of the ligand is made of three rings, one heterocyclic (I) and two chelates (II and III). The dihedral angles between the planes of the rings I and II, II and III and I and III are 1.5(2), 3.1(2), 4.4(2) and 3.2(2), 5.2(1), 8.0(2)° for Sn(1) and Sn(2) respectively, indicating that the ligand as a whole deviates from planarity, the largest deviations arising from the expected puckering of the sulfonamide rings which contain the pyramidal saturated N atoms, N(3) and N(6). The plane (I) of the first molecule Sn(1) is tilted by 77.92(19)° with respect to the plane (I) of the second one Sn(2). The di-anionic, tridentate ligand has a *EZZ* configuration about the bonds C(5)–N(2), N(2)–C(6) and C(6)–C(7) and the corresponding bonds in molecule (2). This type of ligand configuration was found in the ethanolamine salt of piroxicam[1b] and differs from the *ZZZ* isomer only by a 180° rotation of the pyridyl ring providing an additional internal hydrogen bond of piroxicam. A molecular mechanics analysis[2c] showed that the *ZZZ* configuration is more stable than the *EZZ* one, the deprotonation of amide nitrogen being one of the principal effects which favour *EZZ*. The negative charge of the deprotonated amide is delocalized over the three atom fragment C(6)–N(2)–C(5). This is confirmed by an elongation of the C(6)–N(2) bond to 1.375(5) Å and an elongation of the N(2)–C(5) bond to 1.389(5) Å. The bond distances of the five-atom fragment O(1)–C(8)–C(7)–C(6)–O(2) are consistent with the neutral isomer of piroxicam.[1c] Large thermal parameters are observed in the last two C atoms of the butyl chains; this is considered to arise from disorder in the conformation.

Molecules of the same numbering, related by the 2_1 symmetry axis, are joined into chains by intermolecular bonds between tin and the neighbouring ketonic oxygen atom, with distances Sn(1) · · · O(2)^{i} 3.019(4) and Sn(2) · · · O(6)^{iii} 2.611(2) Å respectively. The range of intermolecular distances, Sn · · · O of 2.61–3.02 Å have been confidently reported for intra-molecular bonds, indicate Sn–O bonding.[6b] Other close interactions, which may cross-link the chains and ensure crystal cohesion, include the possibility of C–H · · · O and C–H · · · π hydrogen bonds.[8a] These interactions are listed in Table 1 and are shown in the packing diagram in Fig. 2.

The isolated molecules of Sn(1) or Sn(2) are arranged in polymers in a head to tail fashion with a stacking of alternate parallel chains. Crystal cohesion is ensured by the hydrogen bonds in and between the two chains. The monomers of Sn(1) are linked through intermolecular hydrogen bonds of C–H · · · O type,[8a] O(3)axial · · · H–C(1) and O(3)axial · · · H–C(20), while the monomers of Sn(2) are linked through O(8)axial · · · H–C(43). Each polymer $Sn(1)_n$ is hydrogen bonded to two neighbouring chains of $Sn(2)_n$ by C(36)–H · · · O(3)axial and C(38)–H · · · O(4)eq respectively, leading to the formation of corrugated layers which are directed along the *ac* diagonal of the unit cell. Further, C–H · · · π interactions[8b] and intramolecular bonds stabilize this structure.

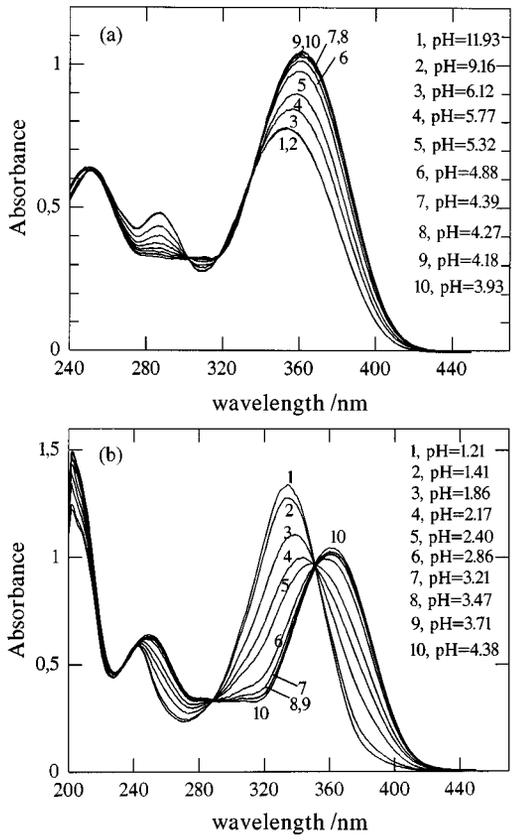

Fig. 3 (*a*) Absorption spectra for piroxicam at 25 °C in the high pH region, where the species $Hpir^-$ (λ_{max} = 356 nm) and H_2pir (λ_{max} = 361 nm) are present; (*b*) absorption spectra for piroxicam at 25 °C in the low pH region, where the species H_2pir (λ_{max} = 361 nm) and H_3pir^+ (λ_{max} = 335 nm) are present.

Although it is remarkable that there are so many contacts, and of so many different types, the interactions themselves are consistent with known guidelines for hydrogen bond formation.[8c] In this case molecular recognition of the hydrogen bonds leads to aggregation and a supramolecular assembly.

The concentration protonation constants of piroxicam, K_{a1} and K_{a2}, were determined§ and the 95% confidence limits of their logarithms were found to be equal to 5.61 ± 0.01 and 1.97 ± 0.01 (n = 7) with relative standard deviations 0.16% and 0.64%, respectively. The low solubility of piroxicam and its low K_{a2} value is the reason for using spectrophotometry to find the protonation constants of the molecule. In aqueous solutions with pH values between 1 and 12 only three independent species of piroxicam ($Hpir^-$, H_2pir and H_3pir^+) become visible as shown by the absorption spectra in Fig. 3.

Acknowledgements

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Notes and references

† A suspension of H_2pir (0.166 g, 0.5 mmol) in methanol (6 cm^3) was treated with a standard aqueous 0.1 mol dm^{-3} KOH solution (1 cm^3, 1.0 mmol). The resulting colourless solution was stirred while a solution of $SnBu_2Cl_2$ (0.152 g, 0.5 mmol) in methanol (6 cm^3) was added to give a colourless solution. A quantity of distilled water was added (10 cm^3) and the reaction mixture was stirred for 15 min. The white powder was filtered off, washed with 2–3 ml of cold distilled water and dried *in vacuo* over silica gel. Crystals of $[SnBu_2(pir)]_n$ suitable for X-ray analysis were obtained by slow evaporation of a fresh MeOH–MeCN solution. Anal. Calc. for $SnC_{23}H_{29}N_3O_4S$: C, 49.14; H, 5.19; O, 11.38; N, 7.47; S, 5.70. Found: C, 49.95; H, 5.00; O, 11.40; N, 7.94; S, 5.66%. IR (–CO–NH–) ν(C=O) 1590s, ν(C=N) 1522s, $\nu(SO_2)_{as}$ 1340s, $\nu(SO_2)_{sym}$ 1180s.

‡ *Crystal data* for $C_{23}H_{29}N_3O_4SSn$: M = 562.28, monoclinic, space group $P2_1/n$ (no. 14), a = 19.696(7), b = 12.650(3), c = 21.066(7) Å, β = 106.010(10)°, U = 5045(5) $Å^3$, Z = 8, T = 291 K, D_c = 1.480 g cm^{-3}, crystal dimensions 0.30 × 0.41 × 0.89, $F(000)$ = 2296, Mo-Kα radiation, λ = 0.71073 Å, μ(Mo-Kα) = 1.13 mm^{-1}. 10854 unique reflections were measured (R_{int} = 0.013), 8169 observed ($F_o > 3.0\sigma(F_o)$) with R and R_w 0.037 and 0.050 respectively. CCDC reference number 186/1319. See http://www.rsc.org/suppdata/dt/1999/663/ for crystallographic files in .cif format.

§ Aqueous piroxicam solutions of constant ionic strength were used to determine protonation constants. All solutions were prepared using distilled water obtained from a borosilicate autostill (Jencons Ltd.). 5×10^{-5} M working piroxicam solutions having different hydrogen ion concentrations and constant ionic strength (μ = 0.1) were then prepared using standard HCl or KOH and KCl solutions; all measurements were made at 25 °C and the absorption spectra were collected in the range 240–440 nm. A rearrangement[9] of the well known equation

$$K_{a1} = [H_3O^+]\frac{\varepsilon_{(H_2pir)} - \varepsilon_o}{\varepsilon_o - \varepsilon_{(Hpir^-)}} \quad (1)$$

or

$$K_{a2} = [H_3O^+]\frac{\varepsilon_{(H_3pir^+)} - \varepsilon_o}{\varepsilon_o - \varepsilon_{(H_2pir)}} \quad (2)$$

(where ε_o, $\varepsilon_{(H_2pir)}$ and $\varepsilon_{(H_3pir^+)}$ are the molar absorption coefficients of the observed solution, negative ionized, molecular and positive charged species, respectively) in the form of

$$\varepsilon_o = \varepsilon_{(H_2pir)} - K_{a1}\frac{\varepsilon_o - \varepsilon_{(Hpir^-)}}{[H_3O^+]} \quad (3)$$

or

$$\varepsilon_o = \varepsilon_{(H_3pir^+)} - K_{a2}\frac{\varepsilon_o - \varepsilon_{(H_2pir)}}{[H_3O^+]} \quad (4)$$

was used to determine K_{a1} and $\varepsilon_{(Hpir^-)}$ values from (3) as well as K_{a2} and $\varepsilon_{(H_3pir^+)}$ values from (4). The $\varepsilon_{(Hpir^-)}$ value can be securely obtained from the absorption spectra of piroxicam that completely coincide with each other with pH > 8. By making use of eqn. (1) and (2) only relatively low errors accompany the $\varepsilon_{(H_2pir)}$ and K_{a1}, but much larger errors result for the $\varepsilon_{(H_3pir^+)}$ and K_{a2} values, that have to be determined in very strongly acid solutions.

1 (*a*) G. A. Ando and J. G. Lombardino, *Eur. J. Reumatol. Inflam.*, 1983, **6**, 3; (*b*) J. Bordner, P. D. Hammen and E. B. Whipple, *J. Am. Chem. Soc.*, 1989, **111**, 6572; (*c*) J. Bordner, J. A. Richards, P. Weeks and E .B. Whipple, *Acta Crystallogr.*, *Sect. C*, 1984, **40**, 989.
2 (*a*) R. Cini, *J. Chem. Soc.*, *Dalton Trans.*, 1996, 111; (*b*) D. Di Leo, F. Berrettini and R. Cini, *J. Chem. Soc.*, *Dalton Trans.*, 1998, 1993; (*c*) R. Cini, R. Basosi, A. Donati, C. Rossi, L. Sabadini, L. Rollo, S. Lorenzini, R. Gelli and R. Marcolongo, *Met. Bas. Drugs*, 1995, **2**, 43; (*d*) R. Cini, G. Giorgi, A. Cinquantini, C. Rossi and M. Sabat, *Inorg. Chem.*, 1990, **29**, 5197.
3 (*a*) C. J. Evans and S. Karpel, *Organotin Compounds in Modern Technology*, J. Organomet. Chem. Library vol. 16, Elsevier, New York, 1985; (*b*) A. J. Crow, in *Metal-Based Antitumour Drugs*, ed. M. Gielen, Freund, London, 1989, vol. 1, pp. 103–149.
4 (*a*) P. Tauridou, U. Russo, G. Valle and D. Kovala-Demertzi, *J. Organomet. Chem.*, 1993, **44**, C16; (*b*) D. Kovala-Demertzi, P. Tauridou, J. M. Tsangaris and A. Moukarika, *Main Group Met. Chem.*, 1993, **16**, 315; (*c*) P. Tauridou, U. Russo, D. Marton, G. Valle and D. Kovala-Demertzi, *Inorg. Chim. Acta*, 1995, **231**, 139; (*d*) D. Kovala-Demertzi, P. Tauridou, A. Moukarika, J. M. Tsangaris, C. P. Raptopoulou and A. Terzis, *J. Chem. Soc.*, *Dalton Trans.*, 1995, 123; (*e*) D. Kovala-Demertzi, P. Tauridou, U. Russo and M. Gielen, *Inorg. Chim. Acta*, 1995, **239**, 177; (*f*) N. Kourkoumelis, A. Hatzidimitriou and D. Kovala-Demertzi, *J. Organomet. Chem.*, 1996, **514**, 163.
5 (*a*) D. Kovala-Demertzi, A. Theodorou, M. A. Demertzis, C. Raptopoulou and A. Terzis, *J. Inorg. Biochem.*, 1997, **6**, 151; (*b*) D. Kovala-Demertzi, D. Mentzafos and A. Terzis, *Polyhedron*, 1993, **11**, 1361; (*c*) D. Kovala-Demertzi, S. K. Hadjikakou, M. A. Demertzis and Y. Deligiannakis, *J. Inorg. Biochem.*, 1998, **69**, 223; (*d*) M. Konstandinidou, A. Kourounakis, M. Yiangou, L. Hadjipetrou, D. Kovala-Demertzi, S. K. Hadjikakou and M. A. Demertzis, *J. Inorg. Biochem.*, 1998, **70**, 63.
6 (*a*) K. C. Molloy, T. G. Purcell, K. Quill and I. W. Nowell, *J. Organomet. Chem.*, 1984, **267**, 237; (*b*) A. R. Forrester, S. J. Garden, R. A. Howie and J. L. Wardell, *J. Chem. Soc.*, *Dalton Trans.*,

1992, 2615; (*c*) A. J. Crow, P. J. Smith, C. J. Cardin, H. E. Parge and F. E. Smith, *Canc. Lett.*, 1984, **24**, 45.
7 A. Addison, R. T. Nageswara, J. Reedijk, J. Van Rijn and G. C. Verschoor, *J. Chem. Soc.*, *Dalton Trans.*, 1984, 1349.
8 (*a*) T. Steiner, B. Lutz, J. van der Maas, A. M. M. Schreurs, J. Kroon and M. Tamm, *Chem. Commun.*, 1998, 171; (*b*) T. Steiner, M. Tamm, A. Grzegorzewski, N. Schulte, N. Veldman, A. M. M. Schreurs, J. Kroon, J. van der Maas and B. Lutz, *J. Chem. Soc.*, *Perkin Trans. 2*, 1996, 2441; (*c*) M. C. Etter, *Acc. Chem. Res.*, 1990, **23**, 120; G. R. Desiraju, *Acc. Chem. Res.*, 1991, **24**, 290.
9 R.W. Ramette, *Chemical Equilibrium and Analysis*, Addison-Wesley Publishing Company, London, 1981, p. 432.

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