ΜΕΤΑΛΛΟ ΘΕΡΑΠΕΥΤΙΚΑ - Ή ΑΝΟΡΓΑΝΑ ΦΑΡΜΑΚΑ . Η ΧΡΗΣΗ ΤΩΝ ΜΕΤΑΛΛΩΝ ΣΤΗΝ ΙΑΤΡΙΚΗ

Δρ. Σ. Κ. Χατζηκακού

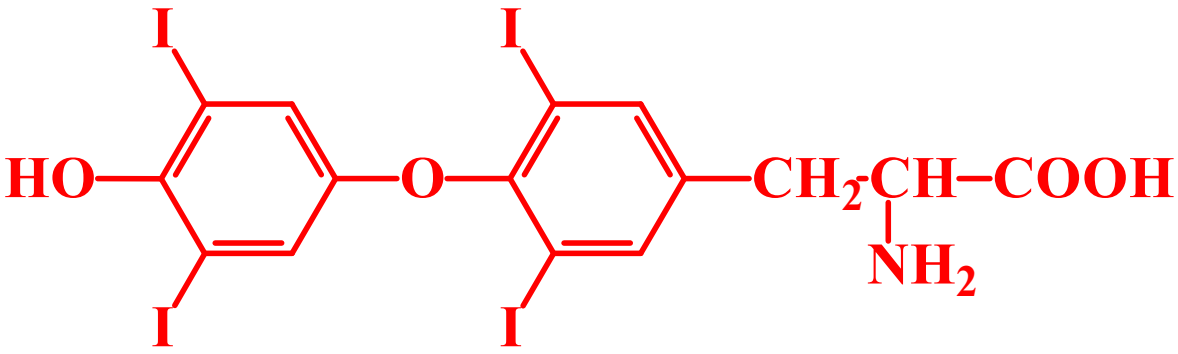
Καθηγητής

It takes twelve years from molecule to medicine

7,000,874 *hours of work*
6,587 *experiments*
423 *researchers*
1 *drug*

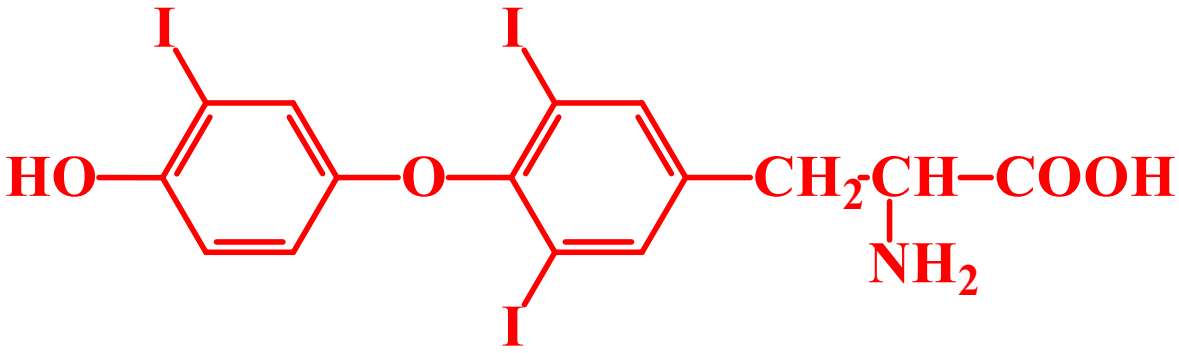
Ενώσεις του Ιωδίου.

THE THYROID HORMONS T4 AND T3



(T4)

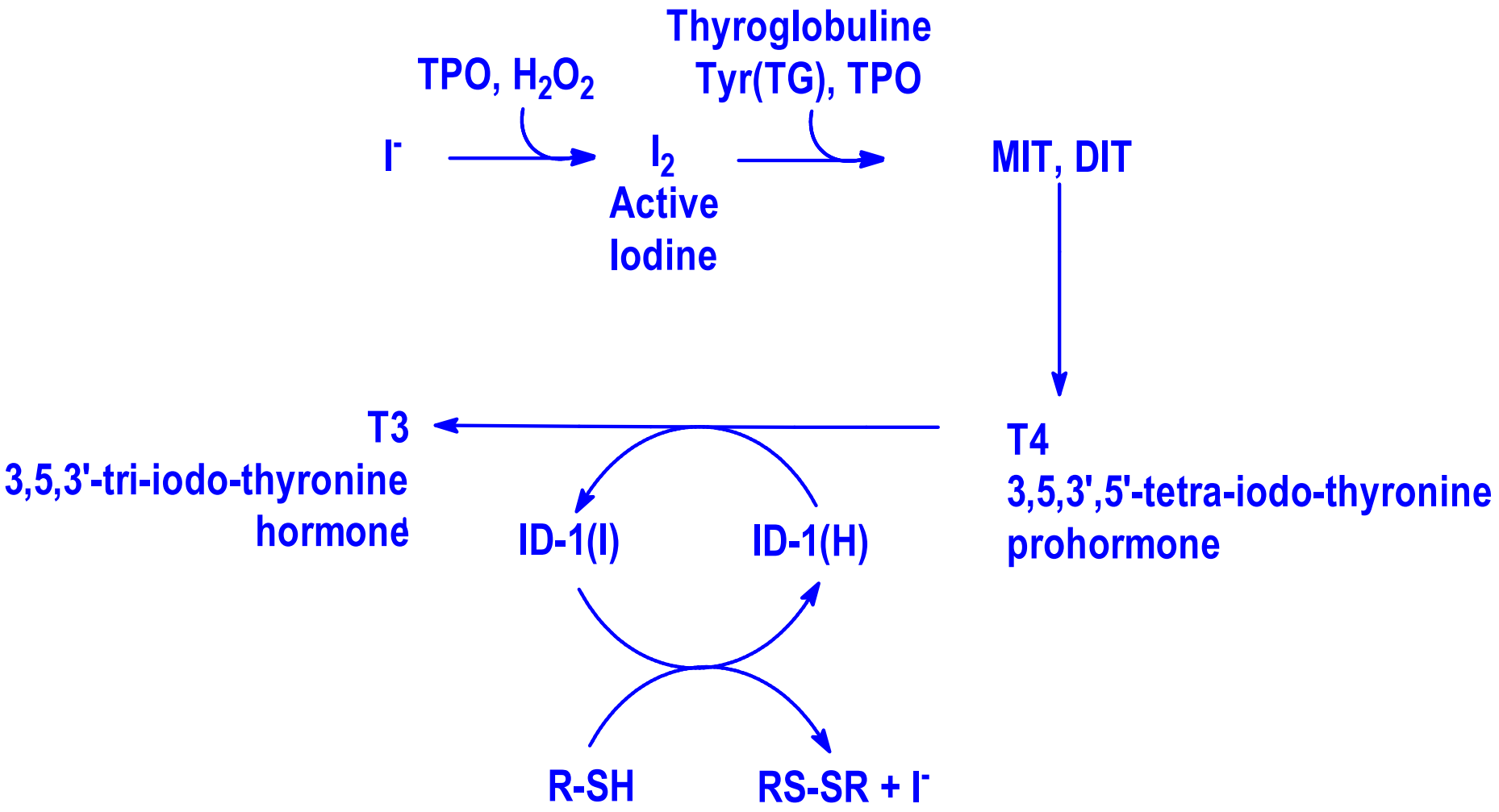
THYROXINE (T4) OR 3,5,3’,5’-TETRA-IODO-THYRONINE



(T3)

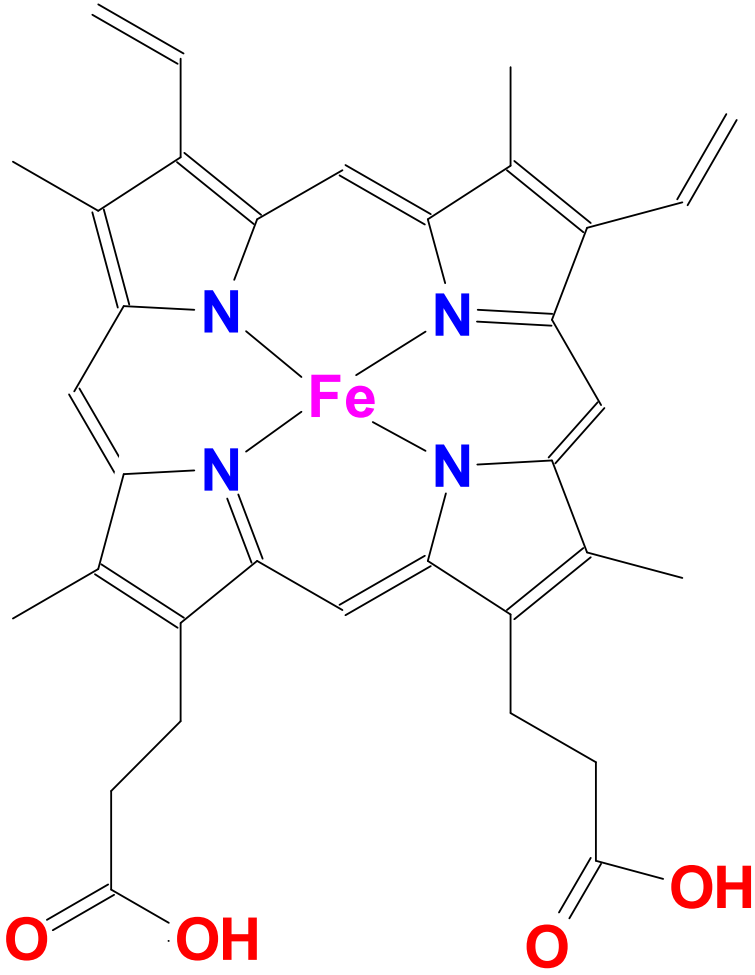
HORMONE (T_3) OR 3,5,3’-TRI-IODO-THYRONINE

SYNTHESIS OF T4 AND T3 HORMONS



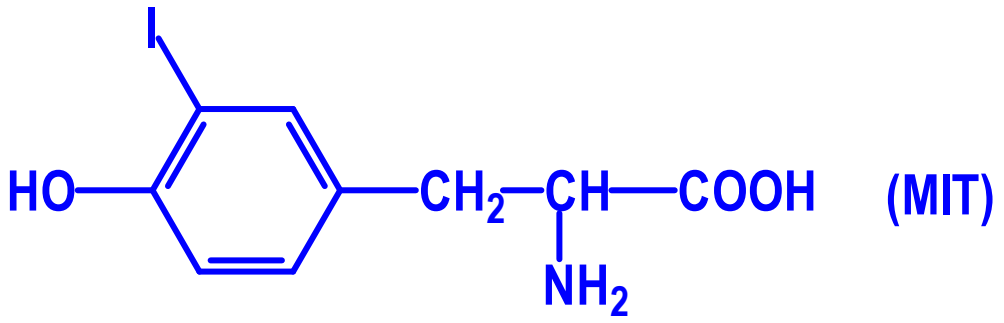
(1) S.Hadjikakou, et.al., *Eur. J. Inorg Chem.,* 2003, 1635-1640
(2) M.C. Aragoni, et.al., *J Am. Chem. Soc.,* 2002, 124, 4538-4539
(3) W.W. du Mont, et.al., *Angew. Chem. Int. Ed*. 2001, *40*, 2486-2489

THYROID PEROXIDASE (TPO)

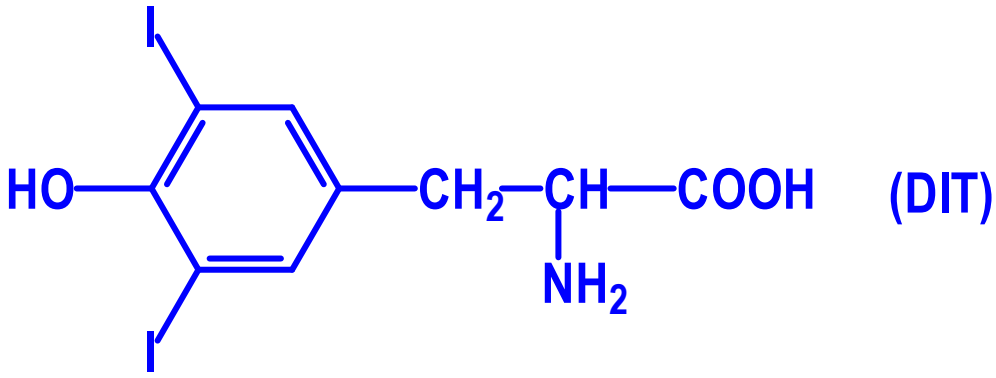


TPO-active site

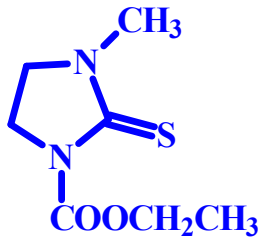
MONO-IODO-TYROSINE (MIT)



DI-IODO-TYROSINE (DIT)

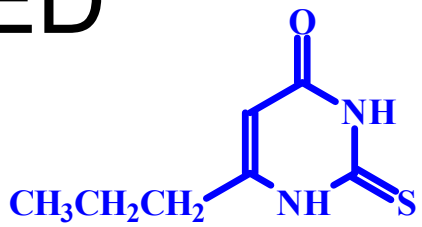


DRUGS AND ANTI-THYROID AGENTS USED

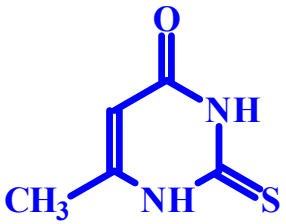


Carbimazole
3-methyl-2-thioxo-4-imidazoline-1-carboxylate

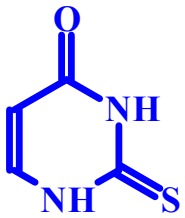
methyl-imidazoline-2-thione
methymazole (MMI)



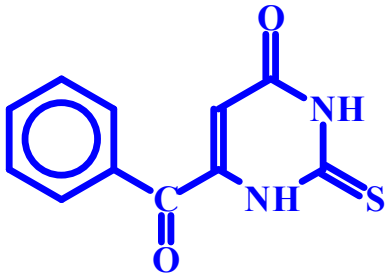
6-propyl-thiouracil (PTU)



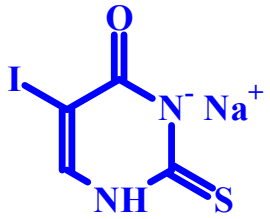
methyl-thiouracil



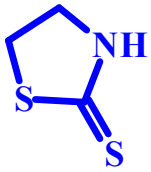
thiouracil



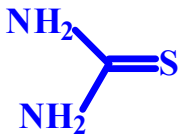
Benzyl-thiouracile



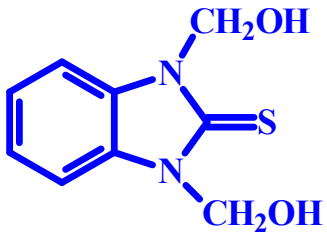
Iodo-thiouracil sodium



mercapto-thiazoline
(TZD)



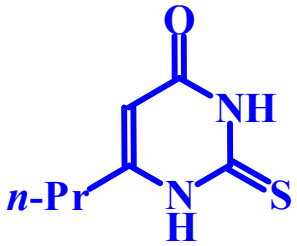
Thiourea



bis(hydroxymethyl)
benzimidazoline-2-thione

Martidale *The Extra Pharmacopoeia*, 28th edition, The pharmaceutical press, London 1982

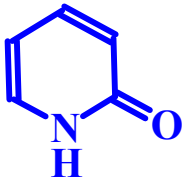
LIGANDS USED IN OUR WORK



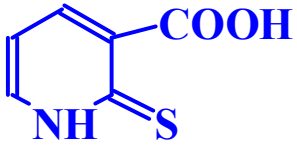
6-*n*-propyl-thiouracil (PTU)

pyrimidine-2-thione (PMT)

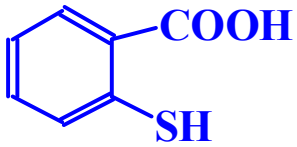
pyridine-2-thione (PYSH)



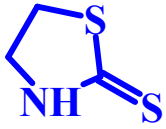
pyridine-2-one (PYOH)



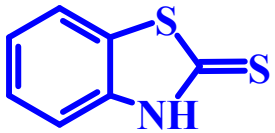
2-mercapto-nicotinic acid (MNA)



2-mercapto-Benzoic acid (MBA)

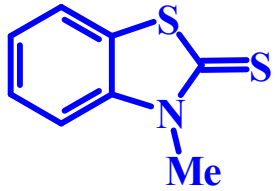


thiazolidine-2-thione (TZD)



benzothiazole-2-thione (BZT)

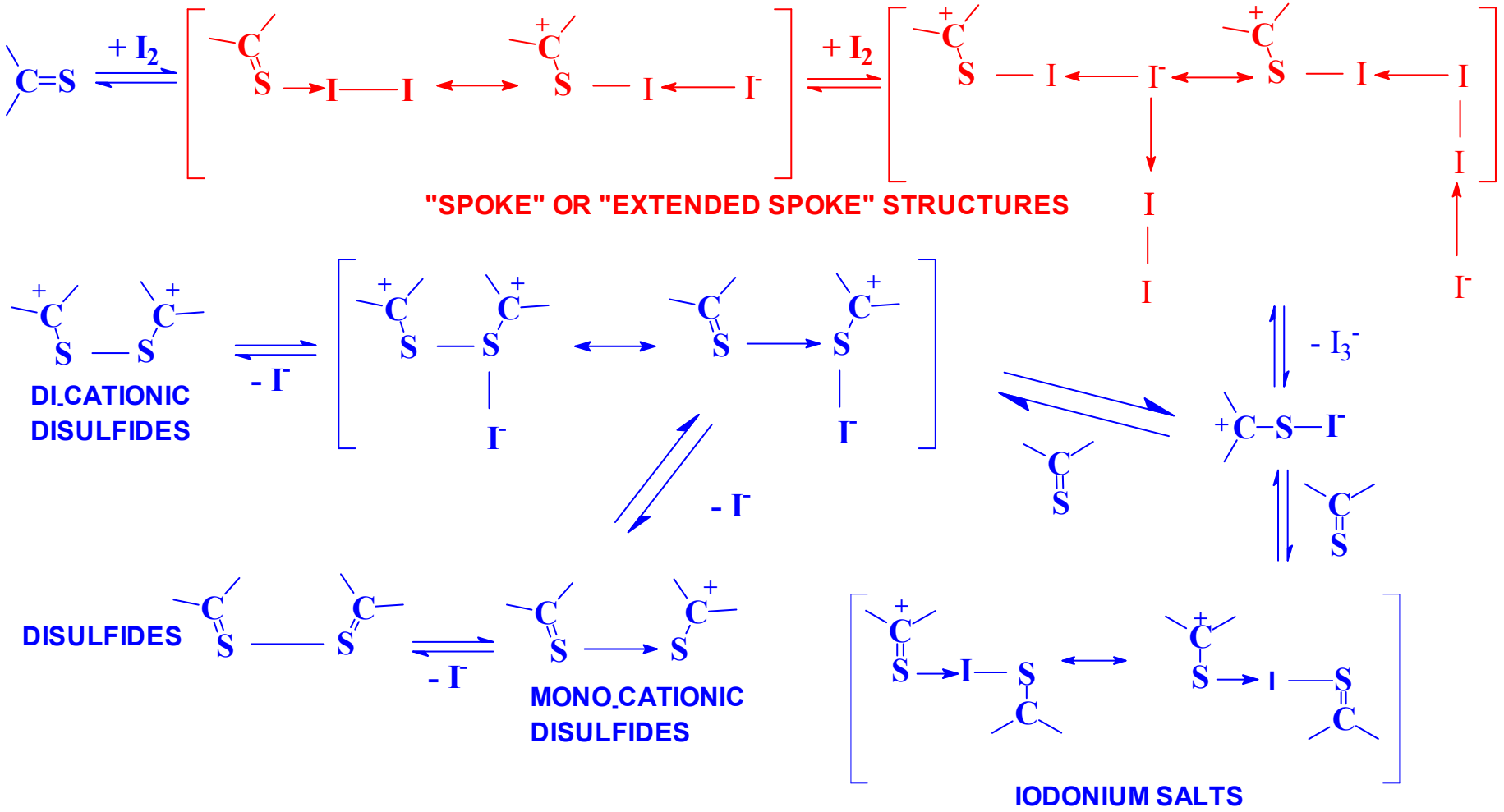
5-chloro-benzothiazole-2-thione (CMBZT)



N-Methyl-benzothiazole-2-thione (NMBZT)

benzimidazole-2-thione (BZIM)

SYNTHESIS OF THIOAMIDE-DIIODINE COMPLEXES



(a) S..K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2002, 1718-1728

(b) S..K. Hadjikakou, et.al, *Spectrochimica Acta Part A*, 58 (2002) 2725–2735

(c) S.K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2003, 1635-1640

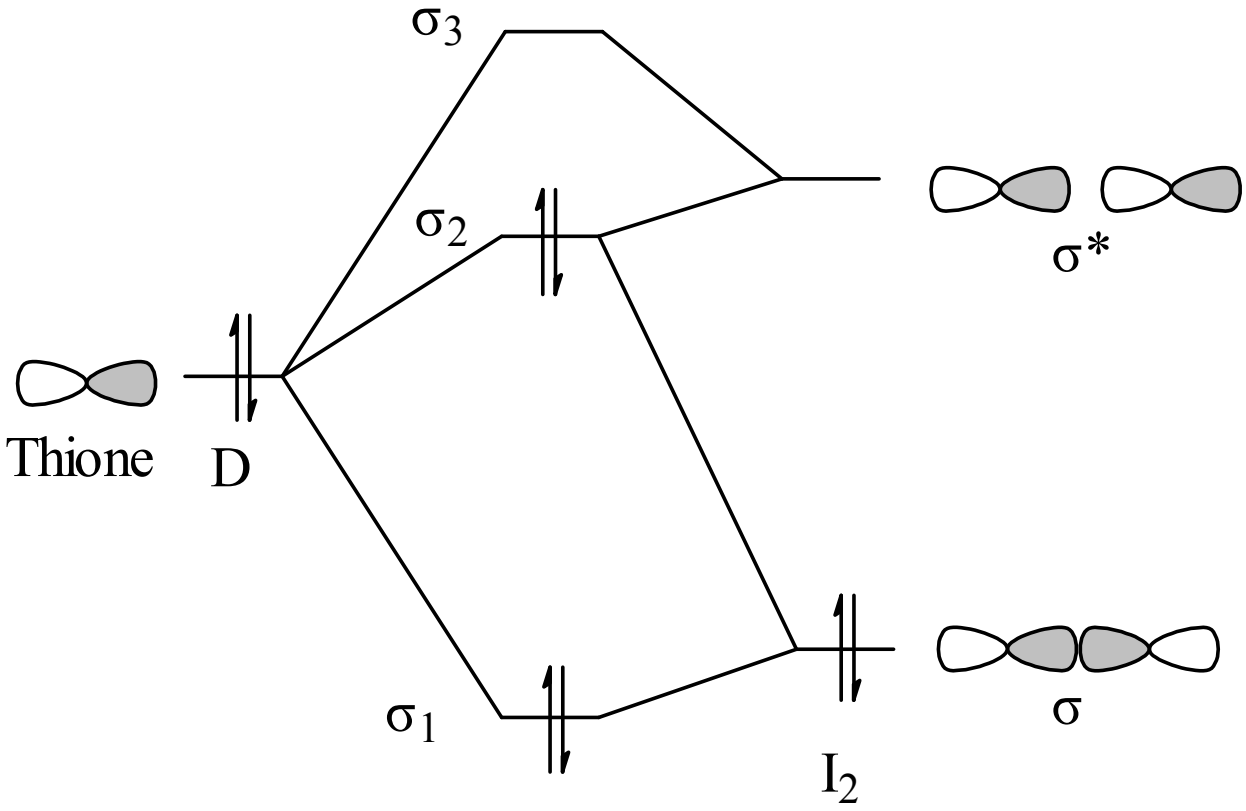
(d) S.K. Hadjikakou, et.al, *Eur. J. Inorg Chem.*, 2004, 4324-4329

(e) S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

(f) S..K. Hadjikakou, et.al, *Inorg. Chem.,* 2005*, 44*, 8617-8627

(g) Hadjikakou S.K., et.al., *unpublished results*

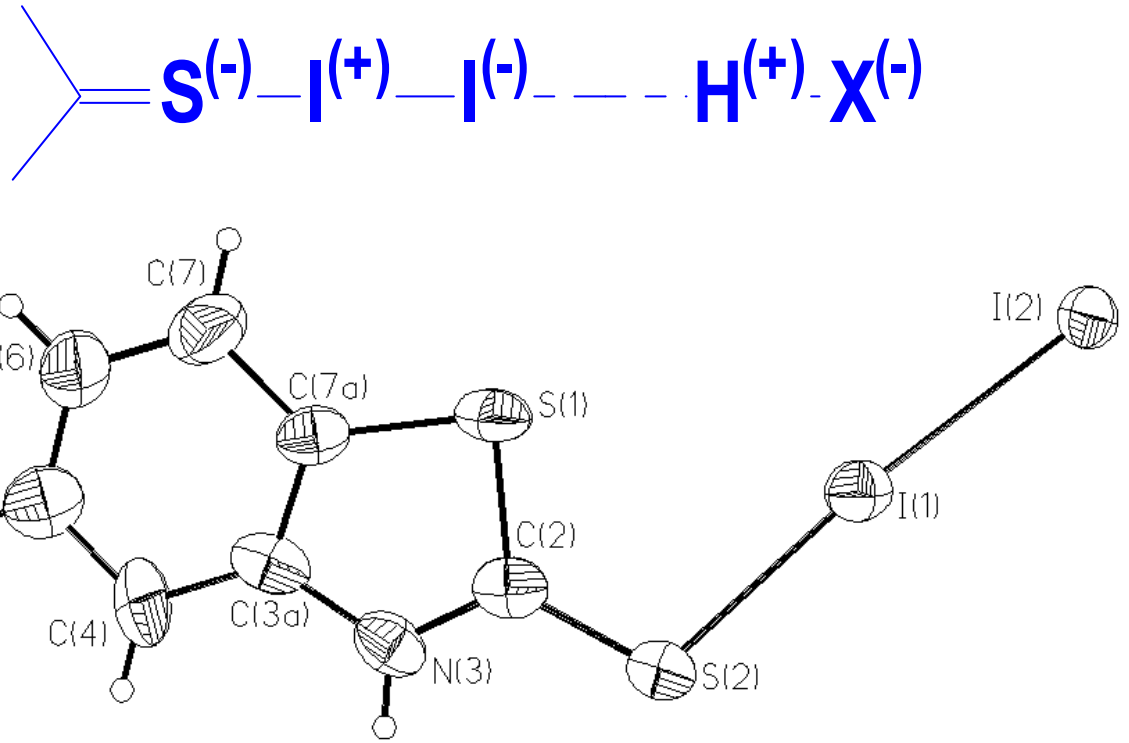
FRONTIER MO'S DIAGRAM OF D-I_2 ADDUCTS SHOWING THE CONTRIBUTION OF THE σ* MO.



CRYSTAL STRUCTURE OF [(BZT)I_2] BZT= 2-MERCAPTO-BENZOTHIAZOLE

I(1)-I(2)= 3.077(2)
I(1)-S(2)= 2.728(6)
N(3)···I(2)^{I}= 3.597(18)

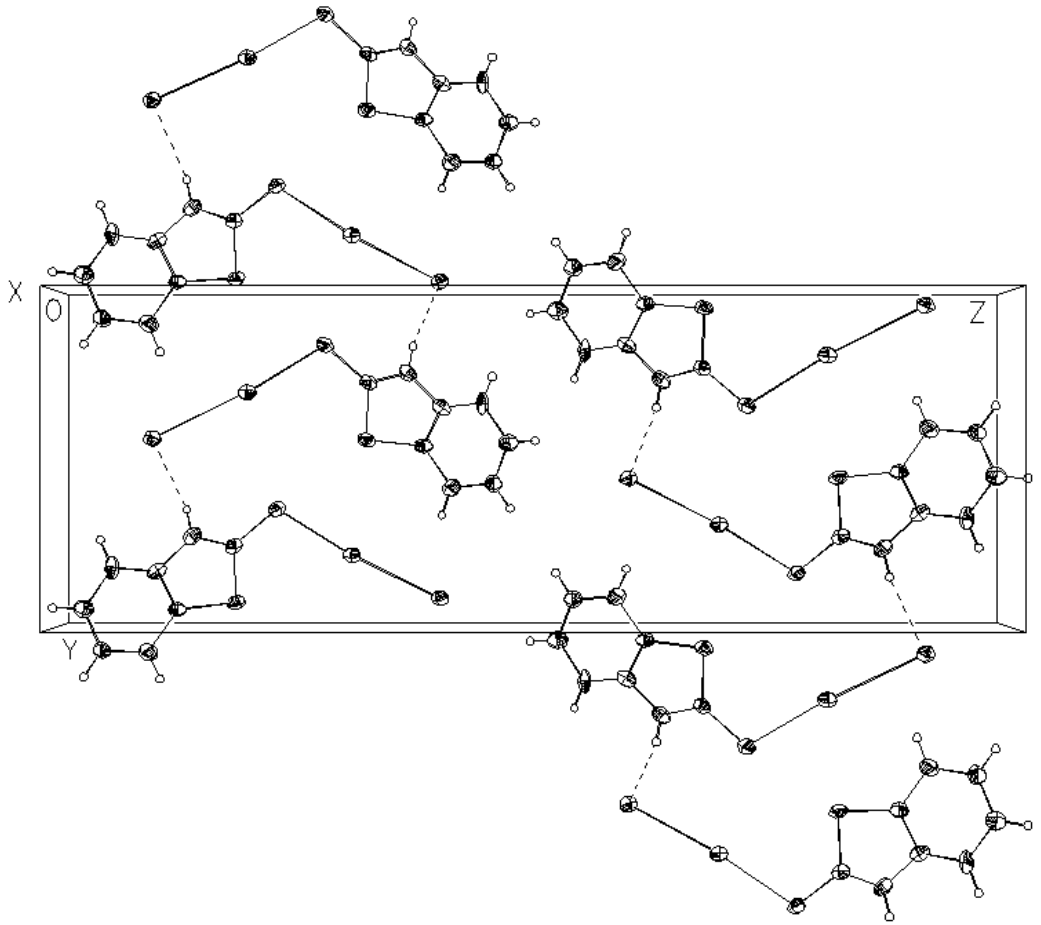
S(2)-I(1)-I(2)= 174.18(14)
C(2)-S(2)-I(1)= 109.2(7)
N(3)-H(3)···I(2)^{I}= 158



$D + I_2 \longrightarrow DI_2$

S..K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2002, 1718-1728

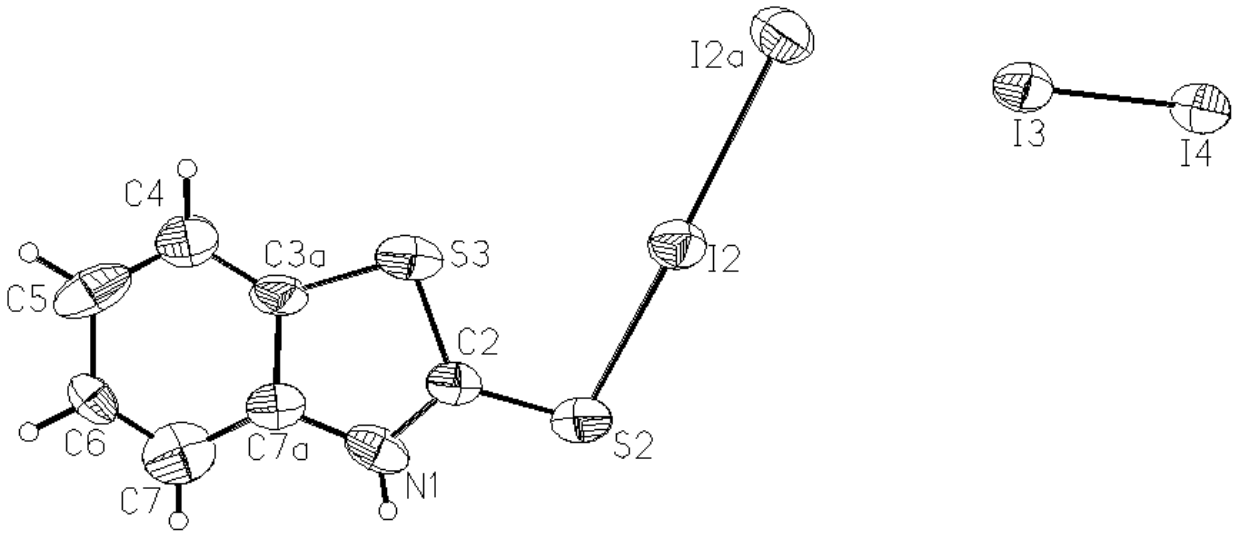
UNIT CELL OF [(BZT)I_2]



CRYSTAL STRUCTURE OF [{(BZT)I_2}·I_2]
BZT= 2-MERCAPTO-BENZOTHIAZOLE

I(3)-I(4)= 2.7504(18)
I(2)-I(2A)= 2.969(2)
S(2)-I(2)= 2.587(5)
N(1)···I(3)^{I}= 3.76(2)

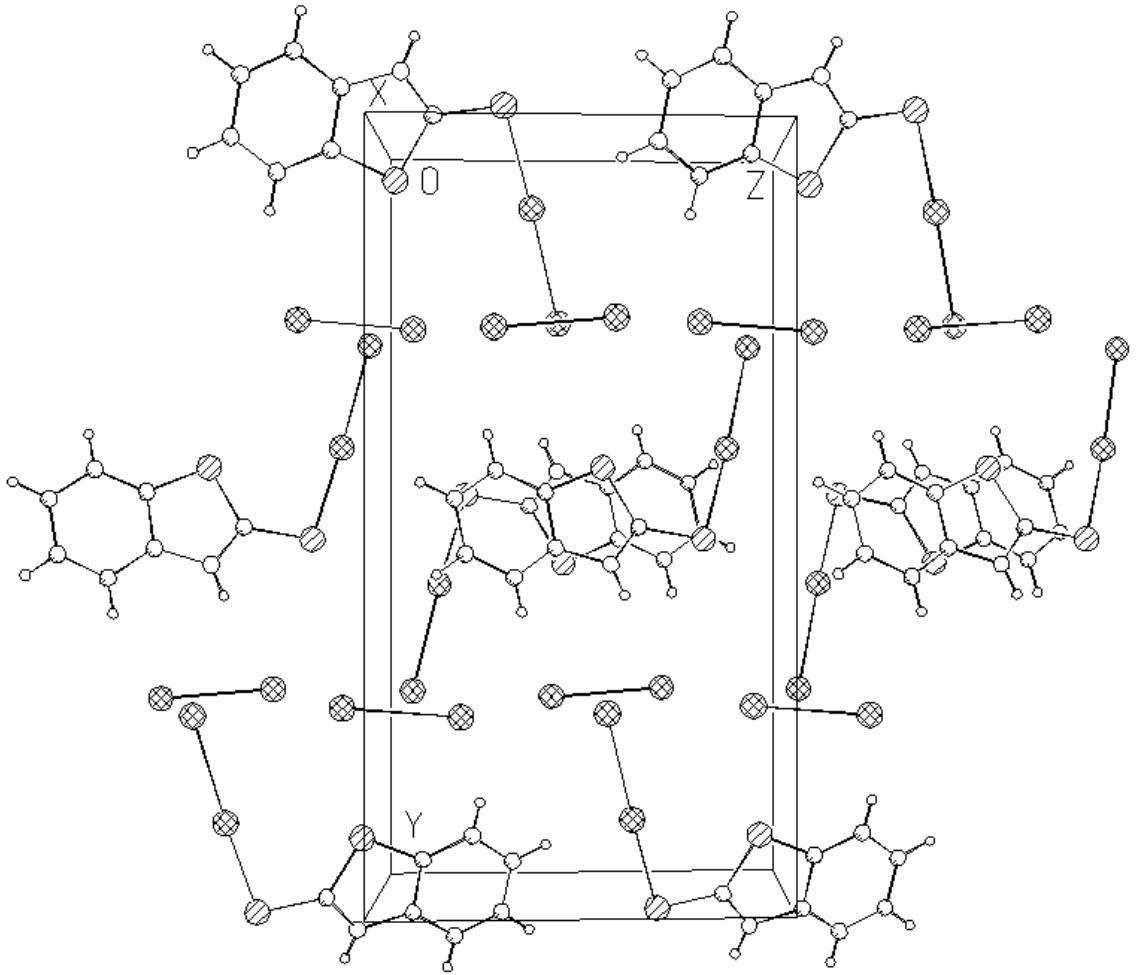
C(2)-S(2)-I(2)= 101.4(6)
S(2)-I(2)-I(2A)= 177.78(13)
N(1)-H(1)···I(3)^{I}= 145



$$D + 2I_2 \longrightarrow DI_2 \cdot I_2$$

S..K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2002, 1718-1728

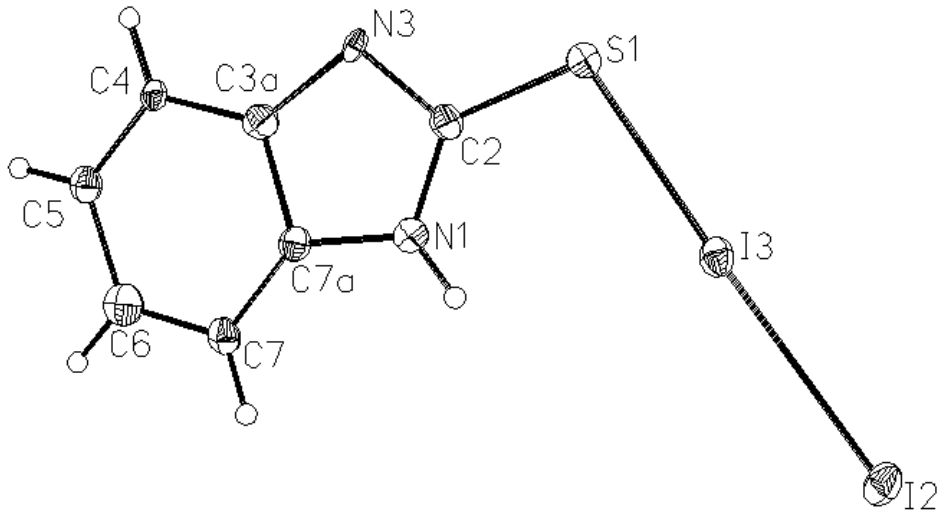
UNIT CELL OF [{(BZT)I_2}·I_2]

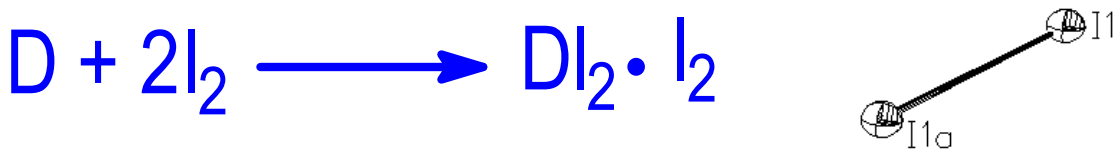


CRYSTAL STRUCTURE OF $[\{(BZIM)I_2\}_2 \cdot I_2 \cdot 2H_2O]$
BZIM= 2-MERCAPTO-BENZIMIDAZOLE

I(1)-I(1A)= 2.767(3)
I(2)-I(3)= 2.989(2)
I(3)-S(1)= 2.571(6)
N(1)···I(3) = 3..471(8)
O(1)W···O(1)W^{ii}= 2.78(2)
O(1)W···N(3)^{iii}= 2.77(3)

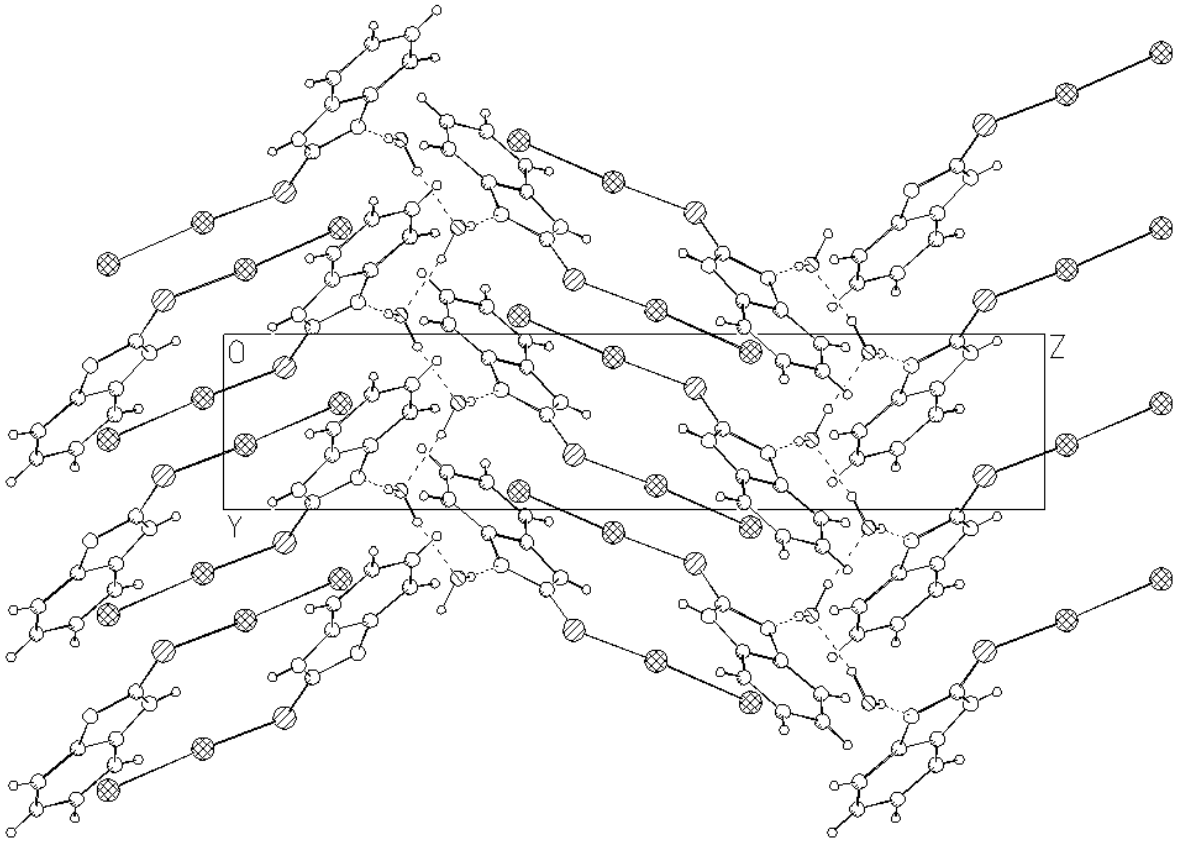
S(1)-I(3)-I(2)= 176.76(14)
C(2)-S(1)-I(3)= 102.3(8)
N(1)-H(1)···I(3)= 119





S.K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2002, 1718-1728

UNIT CELL OF $[\{(BZIM)I_2\}_2 \cdot I_2 \cdot 2H_2O]$



CRYSTAL STRUCTURE OF [(PTU)I_2]
PTU= 6-*n*-PROPYL-THIOURACIL

I(21)-I(22)= 2.8264(4),

S(2)-I(21)= 2.7805(10), **weak interaction**

C(2)-S(2)= 1.696(4),

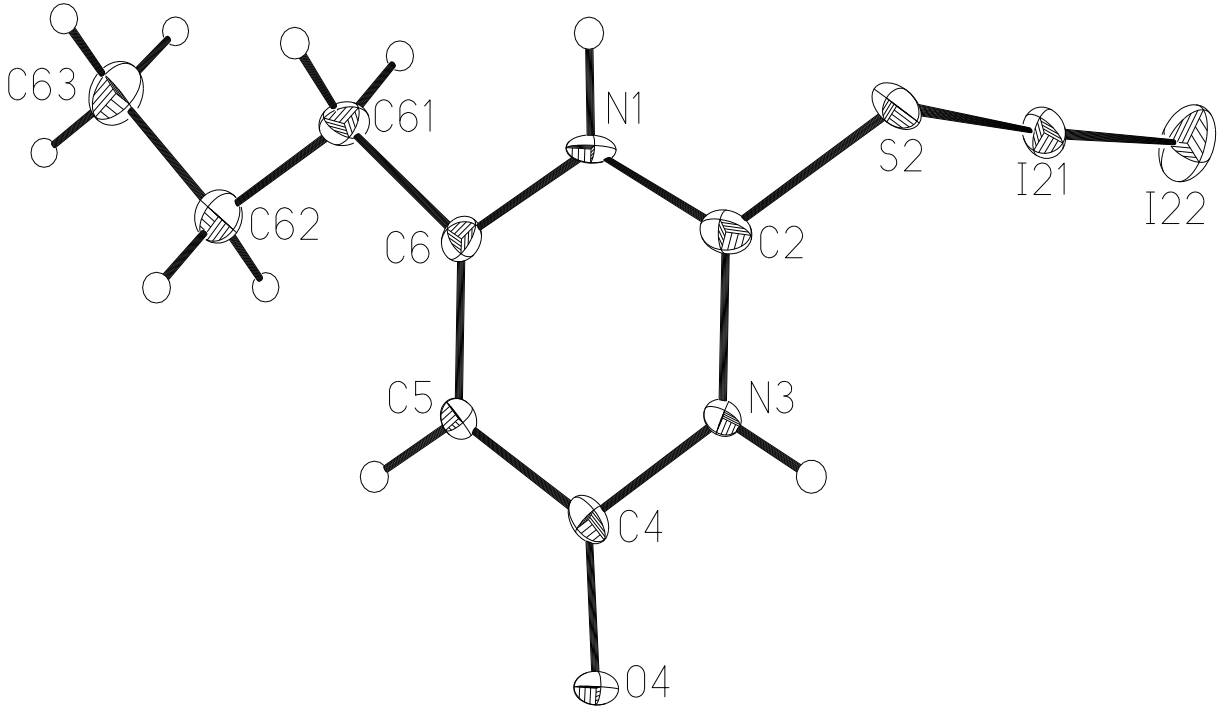
C(2)-S(2)-I(21)= 96.05(12),

S(2)-I(21)-I(22)= 175.85(2),

N(3)-C(2)-S(2)-I(21)= 85.0(3),

N(1)-C(2)-S(2)-I(21)= -95.9(3),

C(2)-S(2)-I(21)-I(22)= -177.0(3).



$D + I_2 \longrightarrow DI_2$

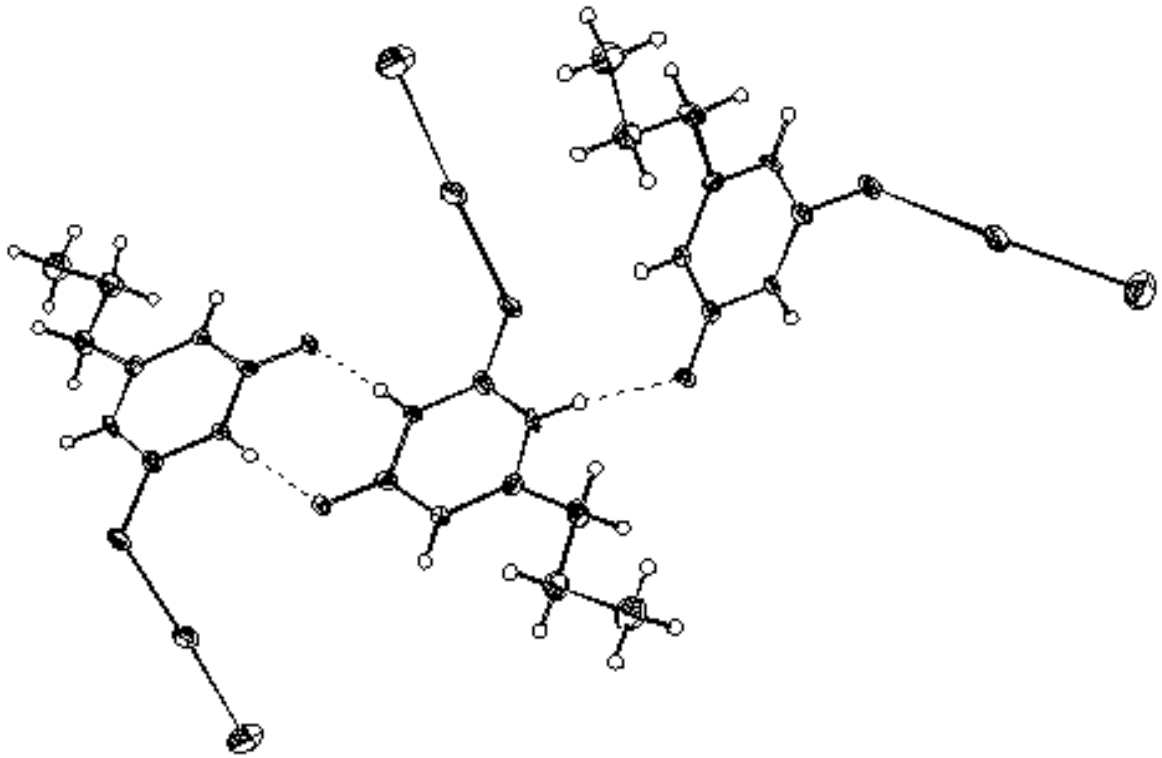
Perpendicular arrangement of I2 towards S=C<

N(1)-C(2)-S(2)-I(21)= 95.9(3)

S(2)-I(21)-I(22)= 175.85(2)

S.K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2003, 1635-1640

UNIT CELL OF [(PTU)I_2]



CRYSTAL STRUCTURE OF [(CMBZT)I_2]
CMBZT= 5-CHLORO-2-MERCAPTO-BENZOTHIAZOLE

(1)-I(2)= 2.9205(7),

I(1)-S(2) = 2.6337(15),

S(2)-C(2)= 1.680(6),

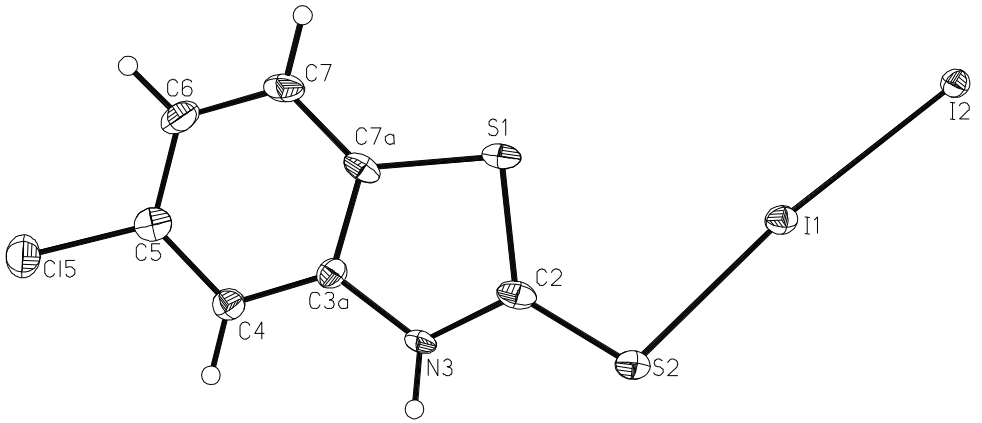
S(2)-I(1)-I(2)= 173.78(4),

C(2)-S(2)-I(1)= 105.07(19),

I(2)-I(1)-S(2)-C(2)= -157.1(4),

I(1)-S(2)-C(2)-N(3)= 167.9(4),

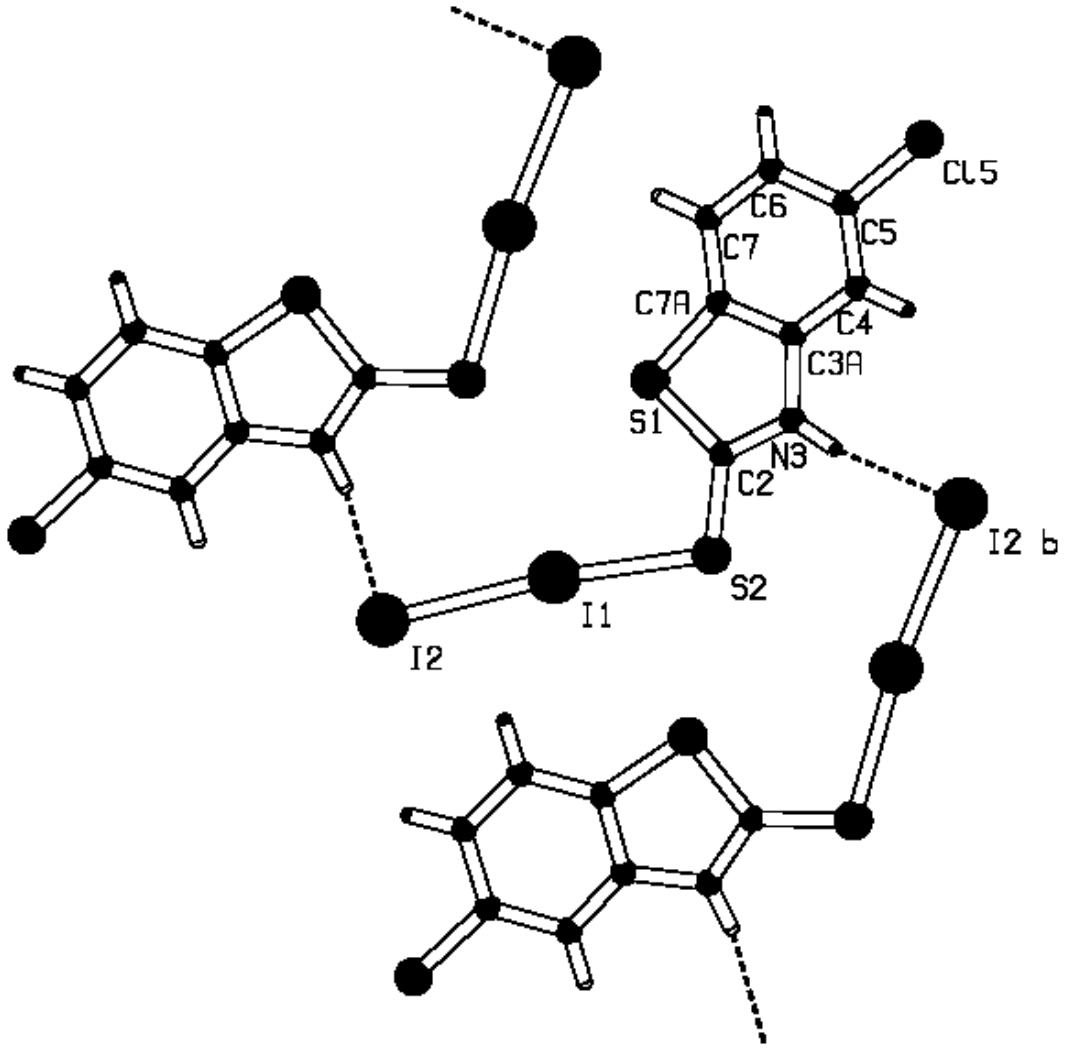
I(1)-S(2)-C(2)-S(1)= -13.7(4).



$$D + I_2 \longrightarrow DI_2$$

S.K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2003, 1635-1640

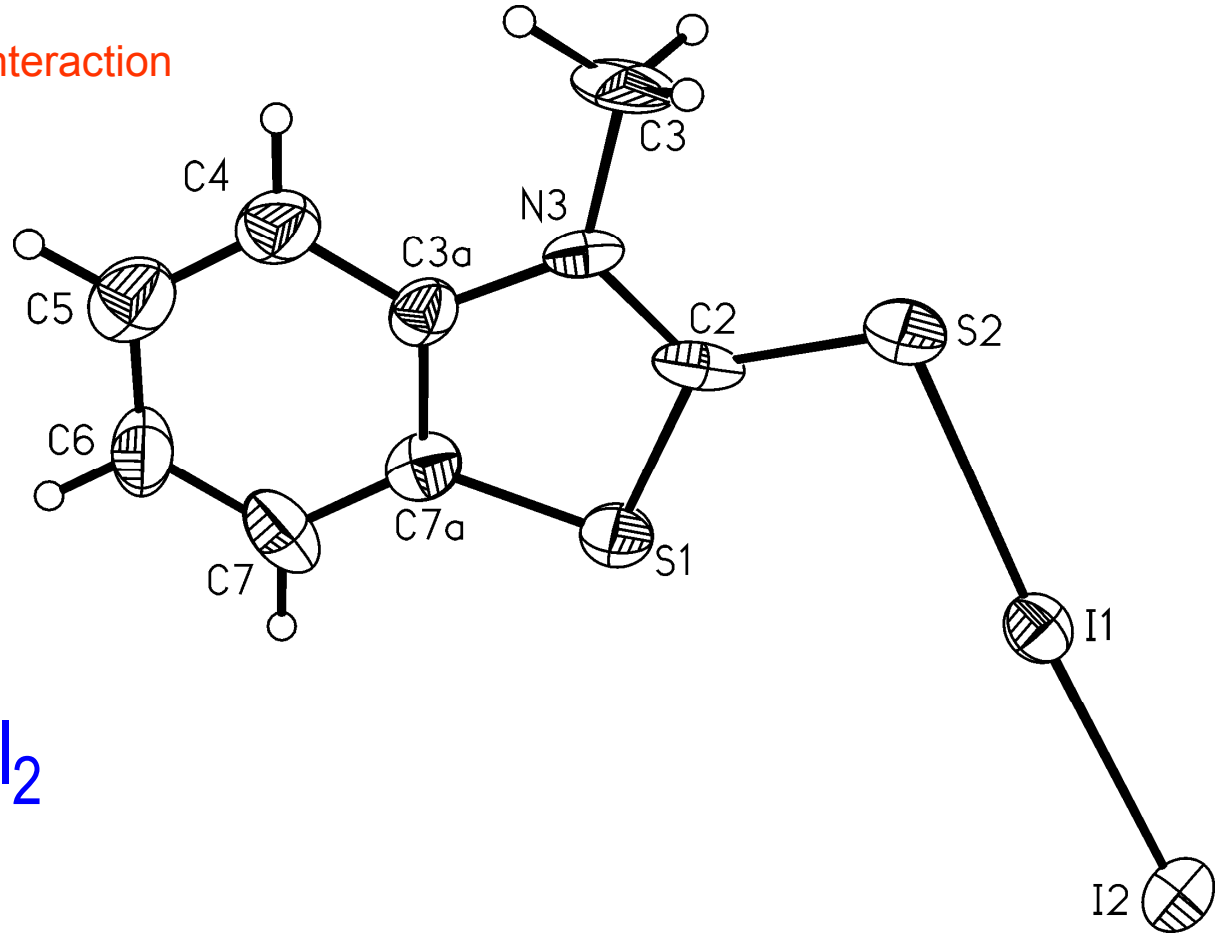
UNIT CELL OF [(CMBZT)I_2]



CRYSTAL STRUCTURE OF [(NMBZT)·I_2] NMBZT= N-METHYL-2-MERCAPTO-BENZOTHIAZOLE

I(1)-I(2) = 2.7912(9)
I(1)-S(2) = 2.808(3), weak interaction
S(1)-C(2) = 1.716(8)

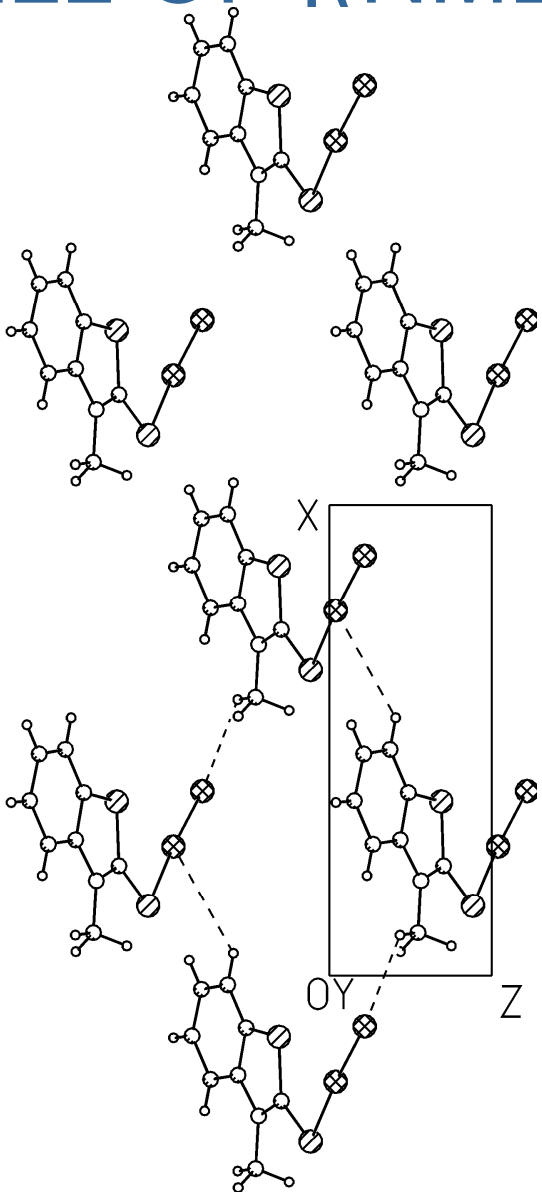
I(2)-I(1)-S(2)= 176.94(7)
C(2)-S(1)-C(7A)= 92.2(5)
N(3)-C(2)-S(2)= 123.6(7)
N(3)-C(2)-S(1)= 112.2(7)

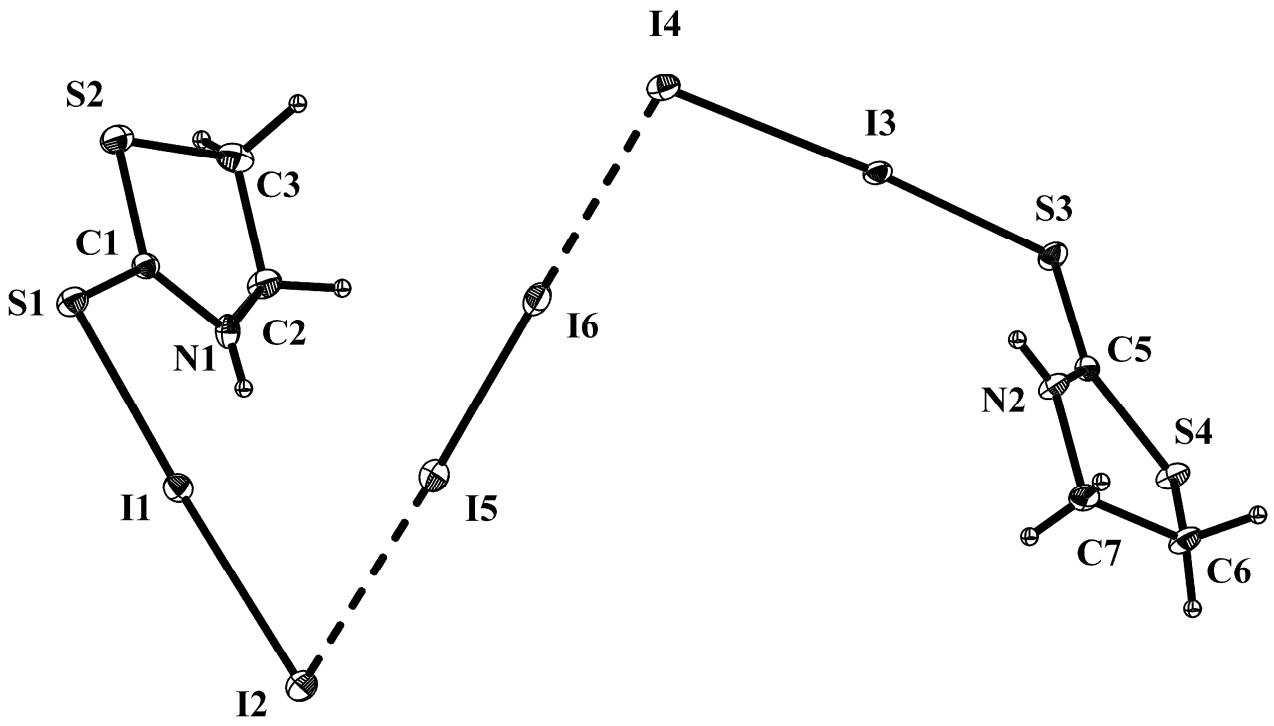


$D + I_2 \longrightarrow DI_2$

S..K. Hadjikakou, et.al, *Inorg. Chem.*, 2005, *44*, 8617-8627

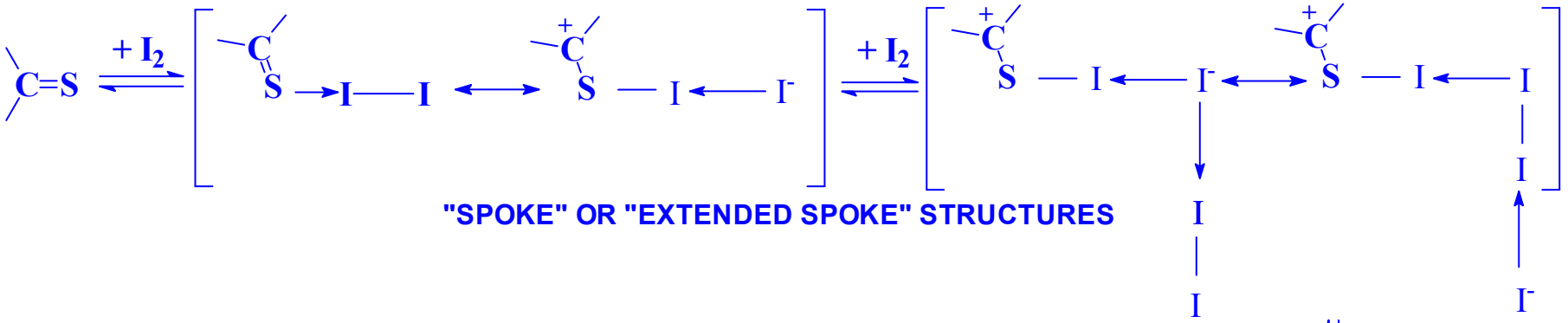
UNIT CELL OF [(NMBZT)·I_2]



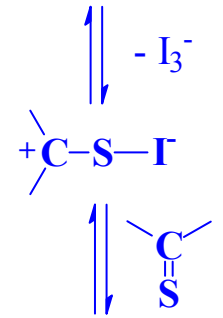


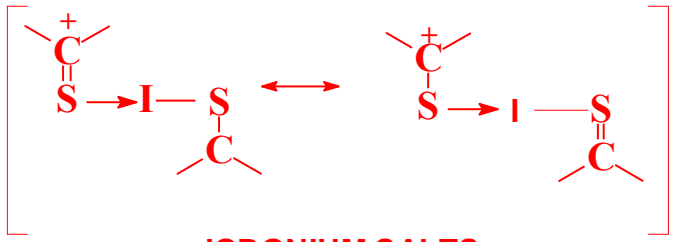
S.K. Hadjikakou et.al., Dalton, 2008

SYNTHESIS OF THIOAMIDE-DIIODINE COMPLEXES



"SPOKE" OR "EXTENDED SPOKE" STRUCTURES





IODONIUM SALTS

CRYSTAL STRUCTURE OF $[\{(TZD)_2I^+\}\cdot I_3^- \cdot 2I_2]$

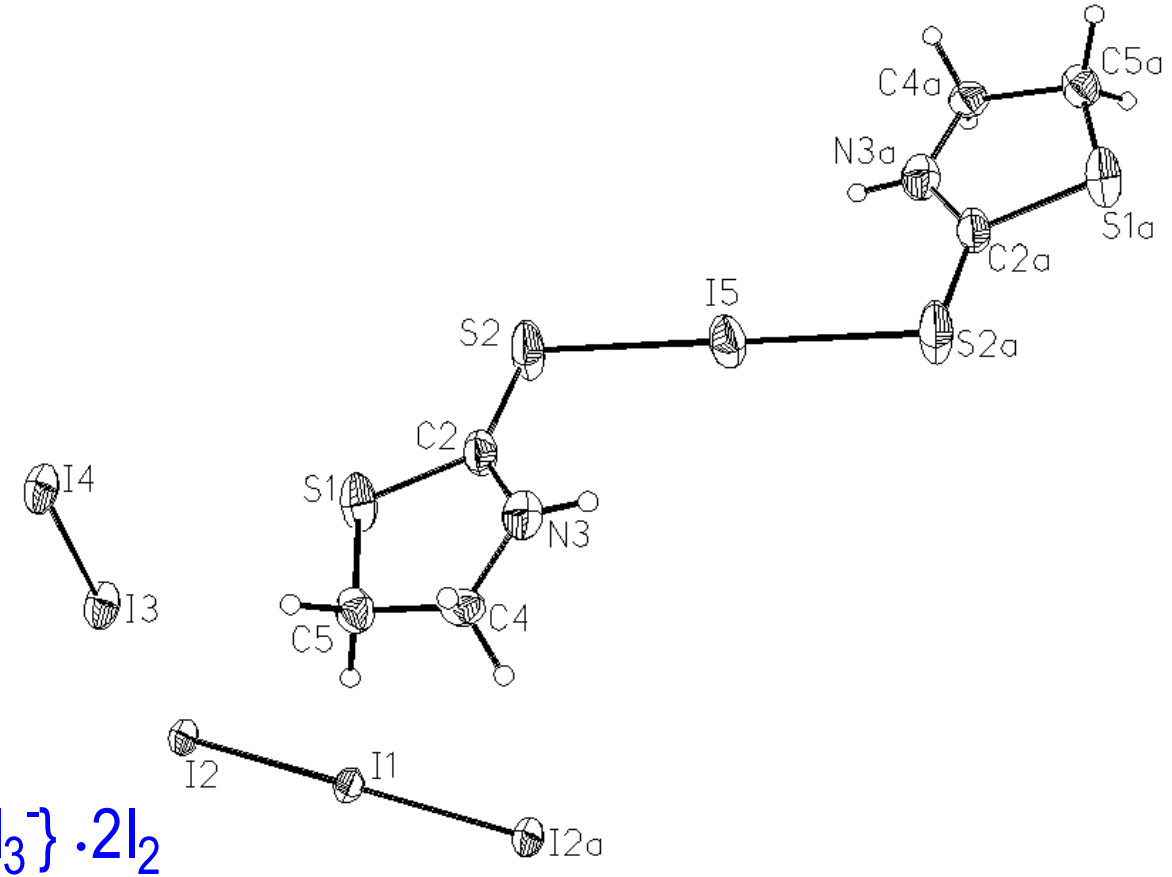
TZD= 2 MERCAPTO THIAZOLINE

(a) bond lengths (A)

I(1)-I(2)= 2.9195(14)
I(3)-I(4)= 2.741(2)
I(5)-S(2)= 2.654(6)
N(3)···I(4)^{I}= 3.82(2)
N(3)-H(3)= 0.860(19)
H(3)[N(3)]···I(5)= 2.9336(6)
N(3)···I(5) = 3.495(19)

(b) angles (deg)

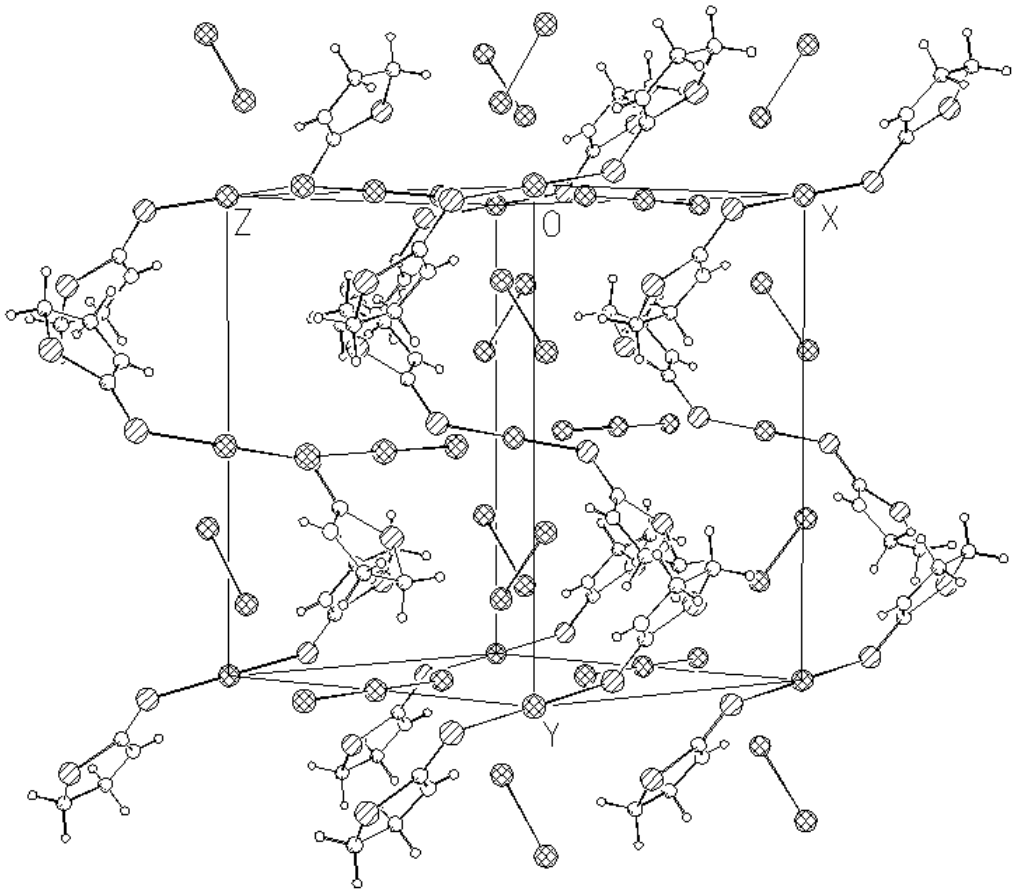
I(2)-I(1)-I(2)^{ii}= 180.0
S(2)-I(5)-S(2)^{iii}= 180.0
N(3)-H(3)···I(4)^{I}= 140



$2D + 4I_2 \longrightarrow \{[D_2I]^+ I_3^-\} \cdot 2I_2$

S..K. Hadjikakou, et.al, *Eur. J. Inorg. Chem*, 2002, 1718-1728

UNIT CELL OF $[\{(TZD)_2I^+\}\cdot I_3^-\cdot 2I_2]$

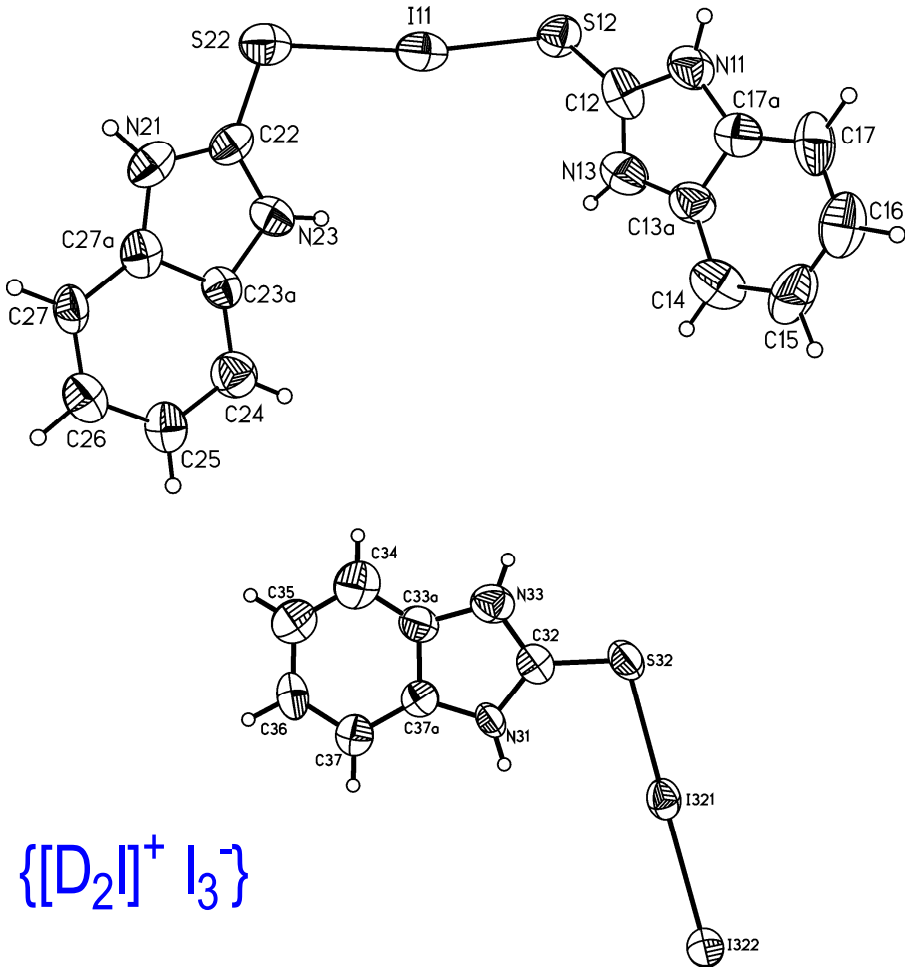


CRYSTAL STRUCTURE OF

$\{[(BZIM)_2I^+]\cdot I_3^-\}\cdot[(BZIM)I_2]\cdot$

BZIM= 2-MERCAPTO-BENZIMIDAZOLE

I(1)-I(2)= 2.9300(12)
I(2)-I(1)#1= 2.9300(12)
I(11)-S(12) = 2.597(4)
I(11)-S(22) = 2.702(4)
S(12)-C(12) = 1.666(15)
C(22)-S(22) = 1.692(13)
I(321)-S(32) = 2.670(4)
I(321)-I(322)= 2.8869(13)
C(32)-S(32) = 1.681(14)

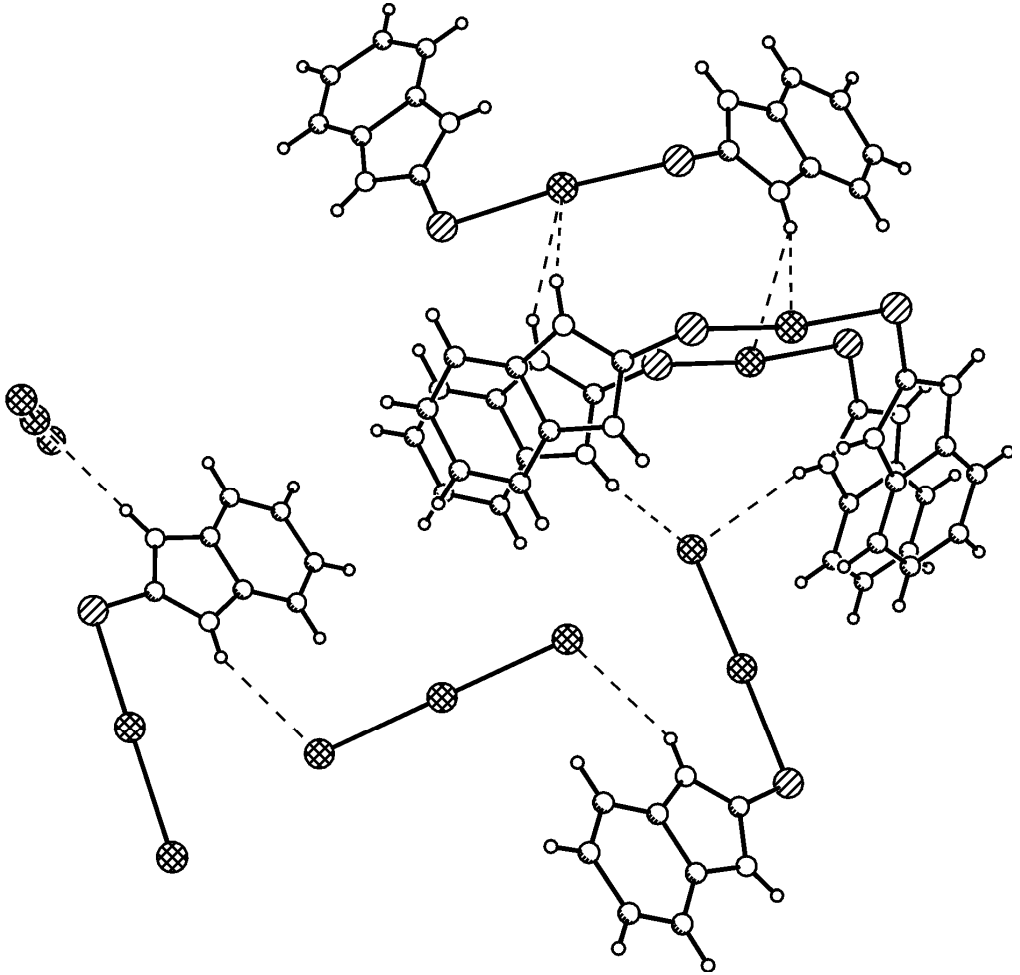


$$3D + 3I_2 \rightleftharpoons DI_2 + \{[D_2I]^+ I_3^-\}$$

S.K. Hadjikakou, et.al, *Inorg. Chem.*, 2005, *44*, 8617-8627

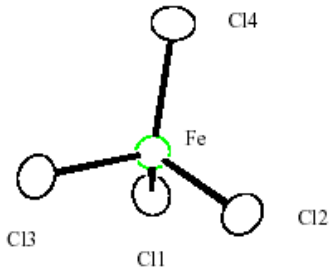
UNIT CELL OF

$\{[(BZIM)_2I^+\}\cdot I_3^-\}\cdot[(BZIM)I_2]\cdot$

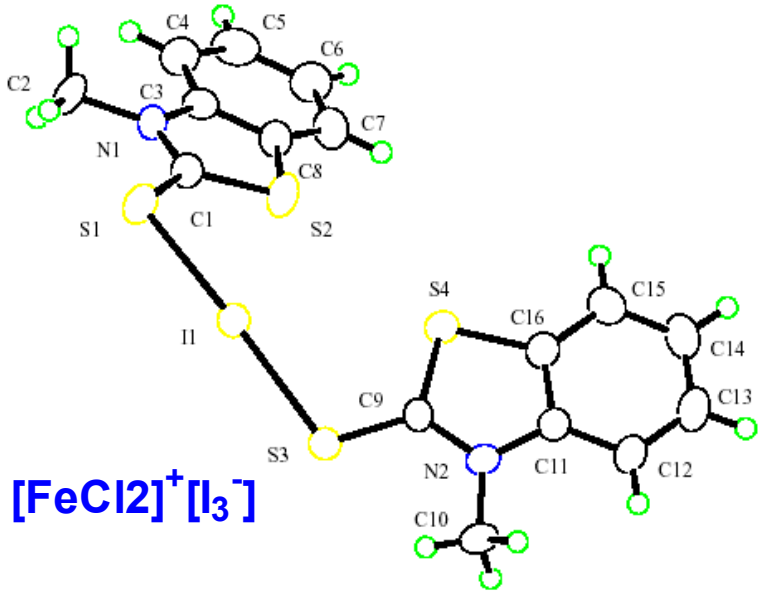


CRYSTAL STRUCTURE OF $\{[(NMBZT)_2I^+]\cdot[FeCl_4]^-\}$

NMBZT= N-METHYL-2-MERCAPTO-BENZOTHIAZOLE



I(1)-S(1)	**2.5961(15)**
I(1)-S(3)	**2.6596(14)**
S(1)-C(1)	**1.704(6)**
S(2)-C(1)	**1.719(6)**
Fe-Cl(1)	**2.2049(17)**
Fe-Cl(2)	**2.1887(17)**
Fe-Cl(3)	**2.1877(18)**
Fe-Cl(4)	**2.1973(17)**
S(1)-I(1)-S(3)	**177.77(5)**
I(1)-S(1)-C(1)	**100.4(2)**
I(1)-S(3)-C(9)	**104.14(19)**

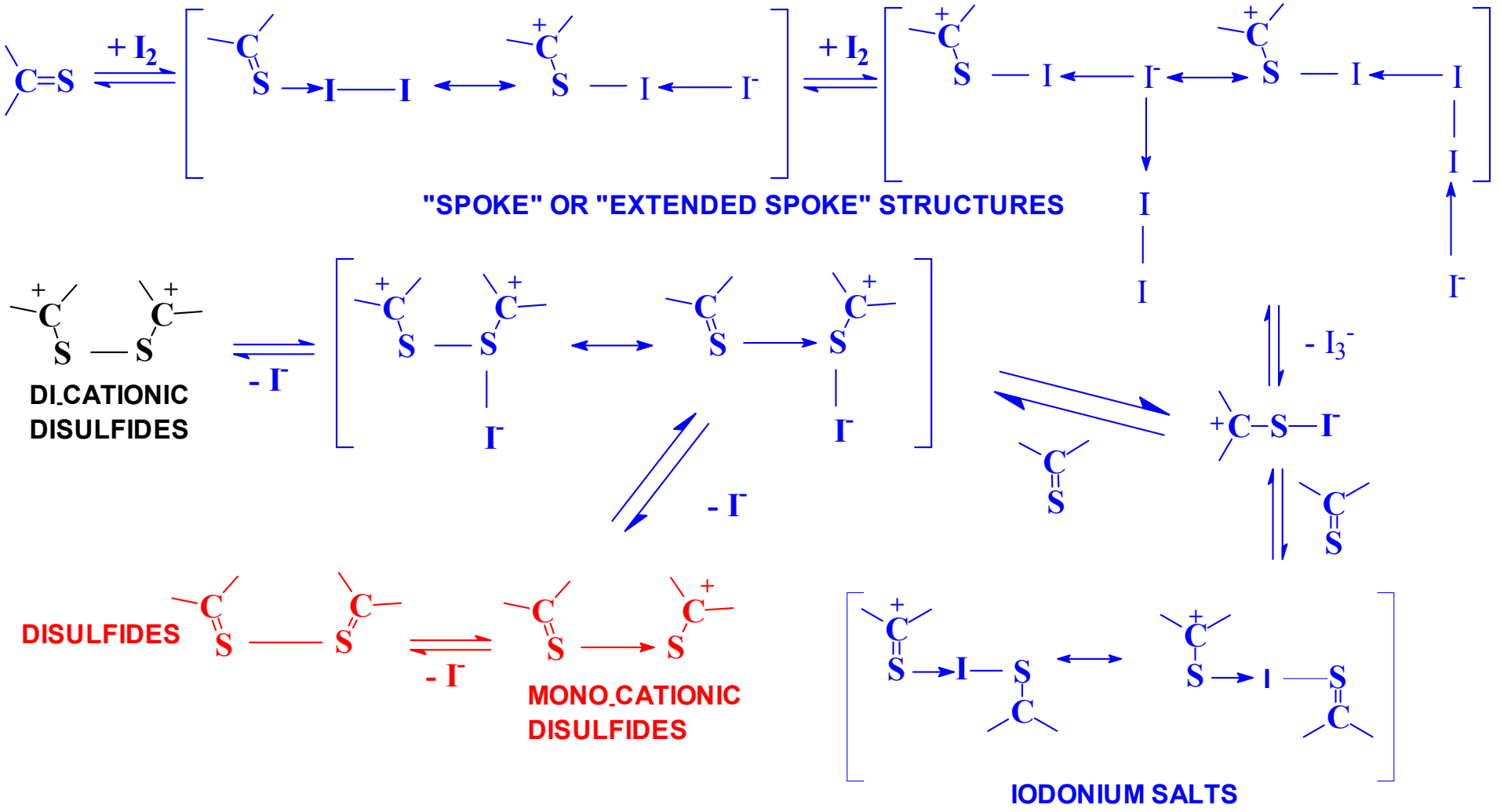


$FeCl_3$ + 3 NMBZT + 6 I_2 ⟶

(1/2) $[(NMBZT)_2I^+]$ $[FeCl_4]$} + $[(NMBZT)_2I^+]$ $[I_7^-]$} + (1/2) $[FeCl2]^+[I_3^-]$

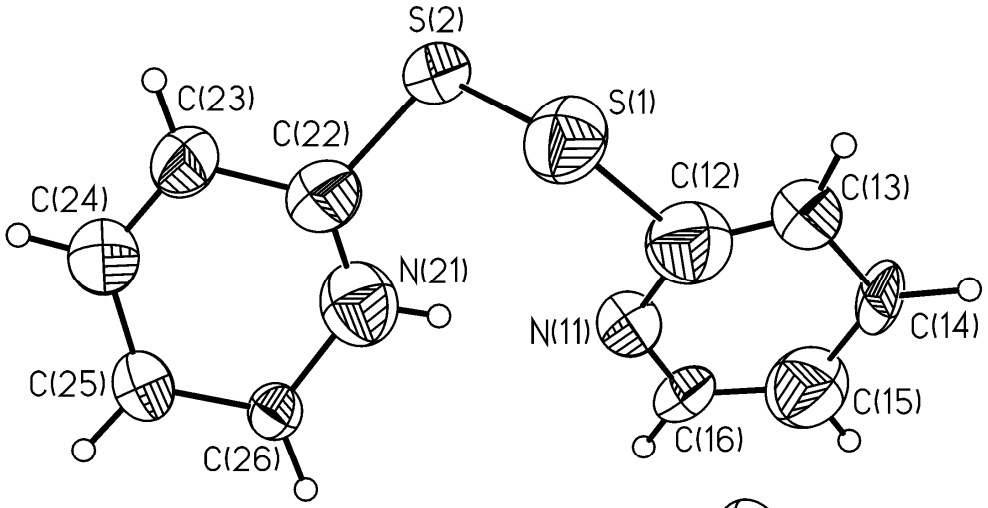
S.K. Hadjikakou, et.al, *Inorg. Chem.*, 2005, *44*, 8617-8627

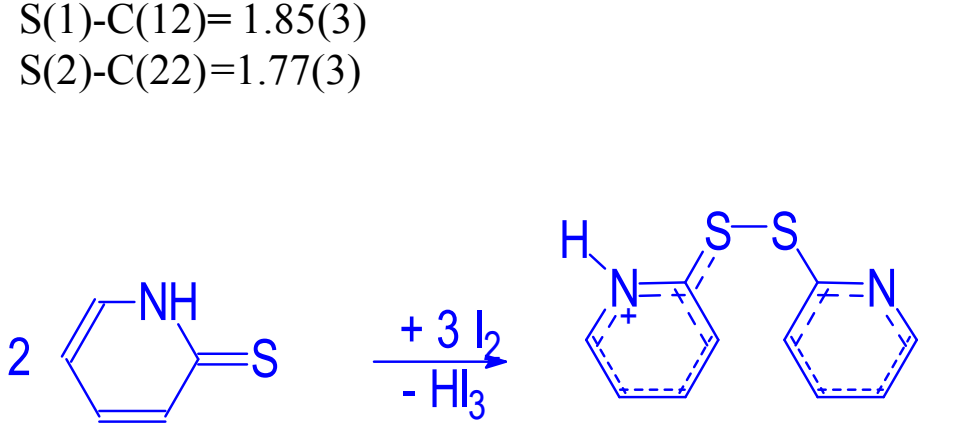
SYNTHESIS OF THIOAMIDE-DIIODINE COMPLEXES

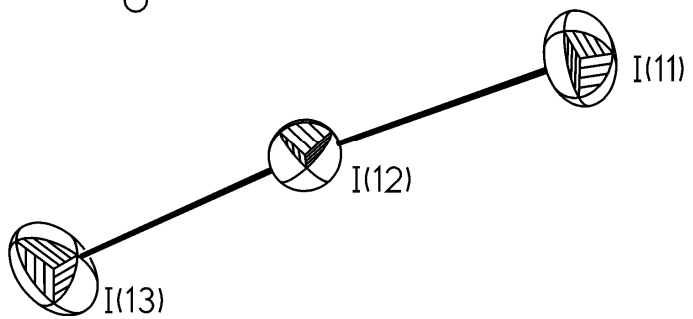


CRYSTAL STRUCTURE OF $\{(PYS\text{-}PYSH)^{+}\cdot I_3^{-}\}$ PYSH= 2-MERCAPTO-PYRIDINE

I(11)-I(12) = 2.892(4)	S(3)-S(4)= 2.010(15)
I(12)-I(13) = 2.943(3)	S(3)-C(32)= 1.78(3)
I(21)-I(22) = 2.880(4)	S(4)-C(42)= 1.75(3)
I(22)-I(23) = 2.960(3)	S(5)-S(6)= 2.052(14)
I(31)-I(32) = 2.860(4)	S(5)-C(52)= 1.65(2)
I(32)-I(33) = 2.963(3)	S(6)-C(62)= 1.77(3)
I(41)-I(42) = 2.855(4)	S(7)-S(8)= 2.062(14)
I(42)-I(43) = 2.928(3)	S(7)-C(72)= 1.71(2)
S(1)-S(2)= 2.003(15)	S(8)-C(82)= 1.69(3)
S(1)-C(12)= 1.85(3)	
S(2)-C(22)=1.77(3)	

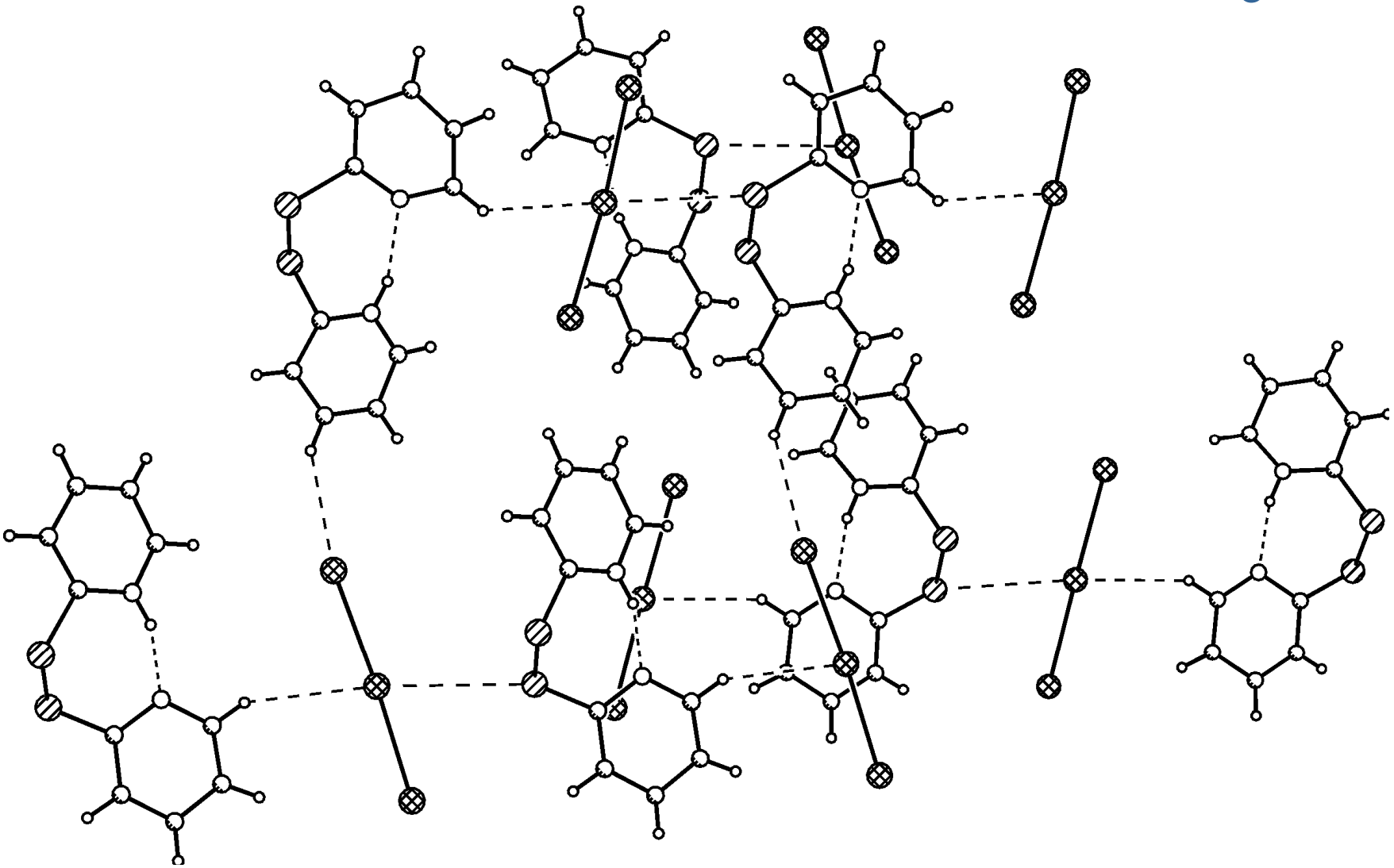






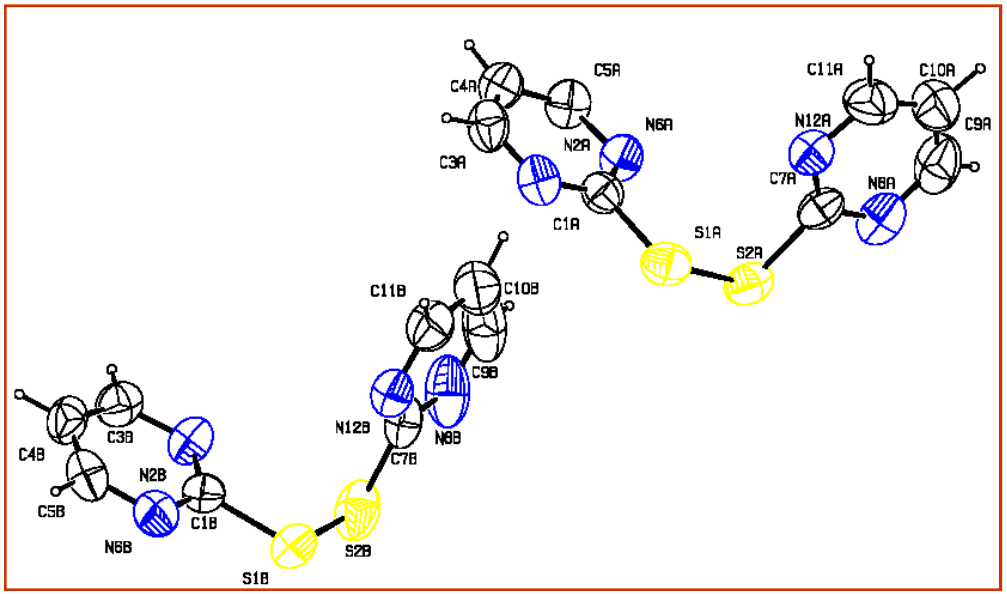
S.K. Hadjikakou, et.al, *Eur. J. Inorg Chem.*, 2004, 4324-4329

UNIT CELL OF {(PYS-PYSH)$^{+}$·I_3^{-}}



CRYSTAL STRUCTURE OF (PMT-PMT)
PMT=2-MERCAPTO-PYRIMIDINE

$2D + I_2 \rightleftharpoons D_2 + 2HJ^-$ DISULFIDE

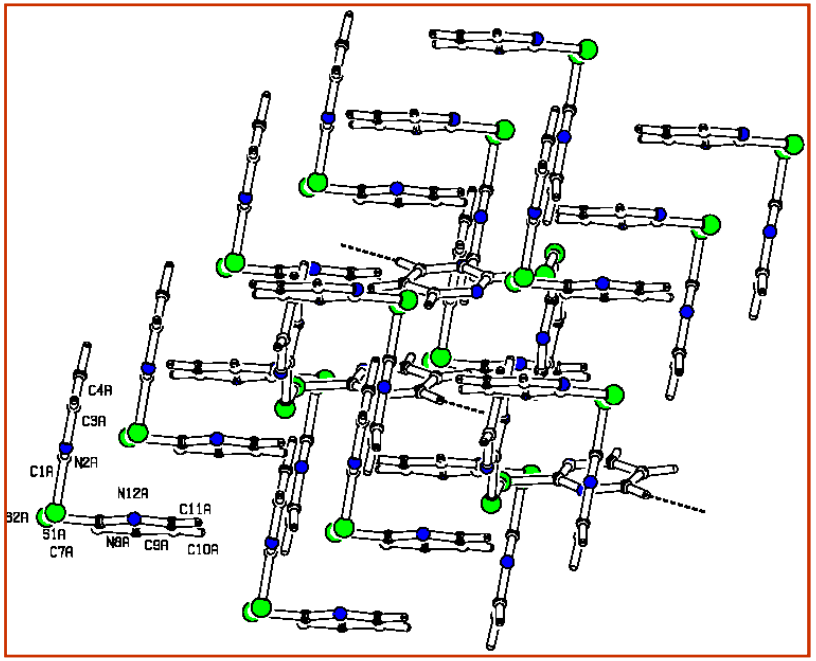


C11B-- H9= 0.9837

(C11B)H9 .. N2B=2.5926

H9(C11B) .. N2B=3.5683

<(C11B)H9 .. N2B=171.46°



S1A-S2A = 2.0204

S1A-C1A = 1.7682

S2A-C7A = 1.7827

S1B-S2B = 2.0156

S1B-C1B = 1.7721

S2B-C7B = 1.7756

S2A-S1A-C1A = 104.29

S1A-S2A-C7A = 104.96

S2B-S1B-C1B = 105.23

S1B-S2B-C7B = 104.72

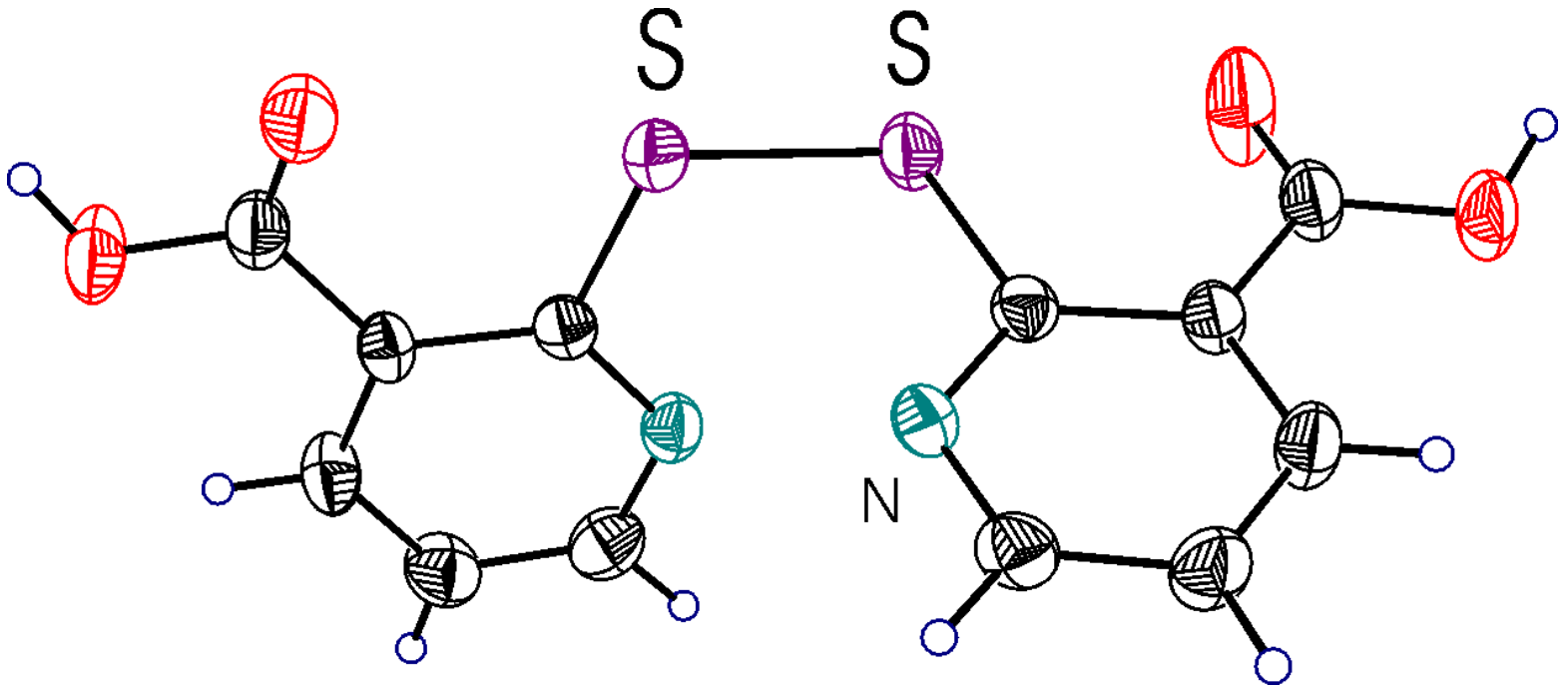
C1A-S1A-S2A-C7A = 85.48°

C1B-S1B-S2B-C7B = 83.80°

Hadjikakou S.K., et.al., *unpublished results*;

CRYSTAL STRUCTURE OF $(MNA)_2$ MNA= 2-MERCAPTO-NICOTINIC ACID

$$2D + I_2 \rightleftharpoons D_2 + 2HJ^-$$



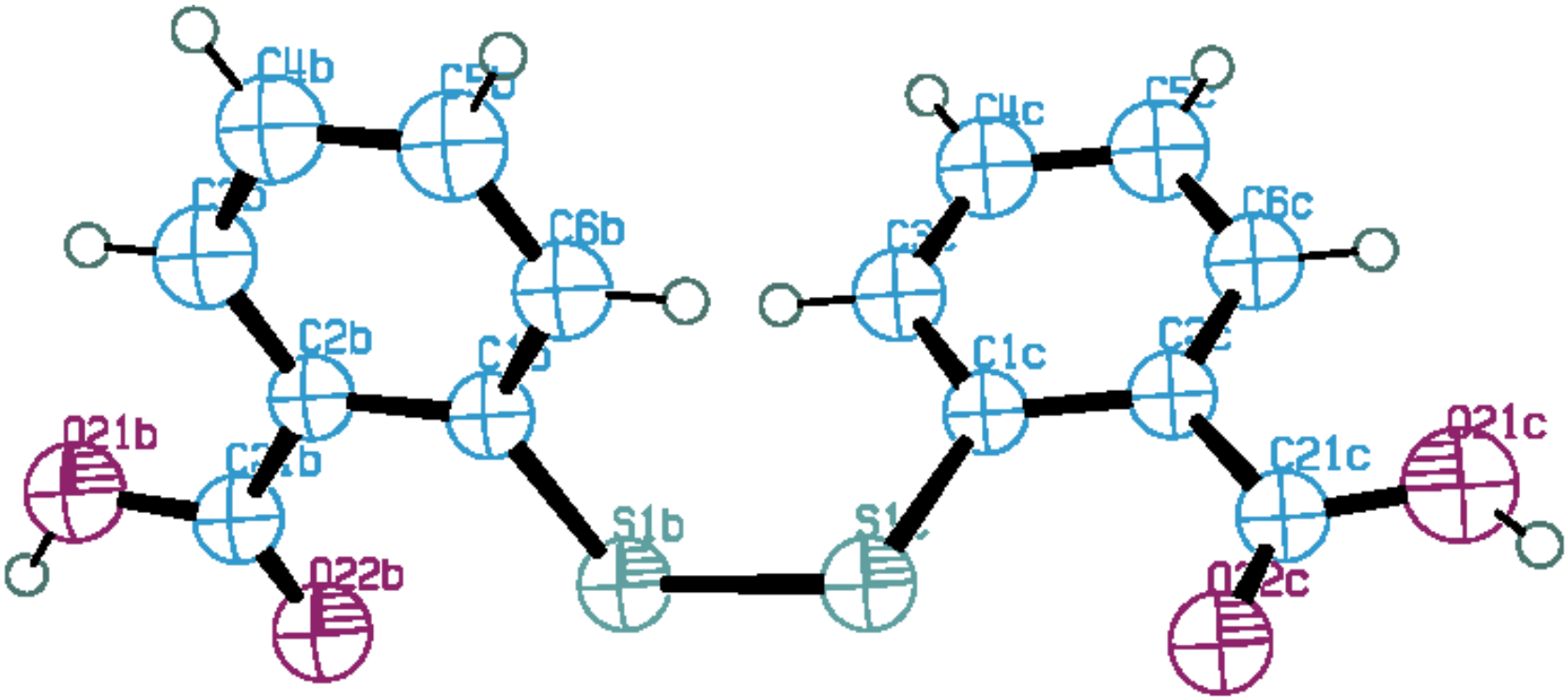
DISULFIDE

S11	-S21	2.0317(9)
S11	-C12	1.7856(18)
S21	-C22	1.7944(18)

Hadjikakou S.K., et.al., *unpublished results*;

CRYSTAL STRUCTURE OF $(MBA)_2$ MBA= 2-MERCAPTO-BENZOIC ACID

$2D + I_2 \rightleftharpoons D_2 + 2HJ^-$



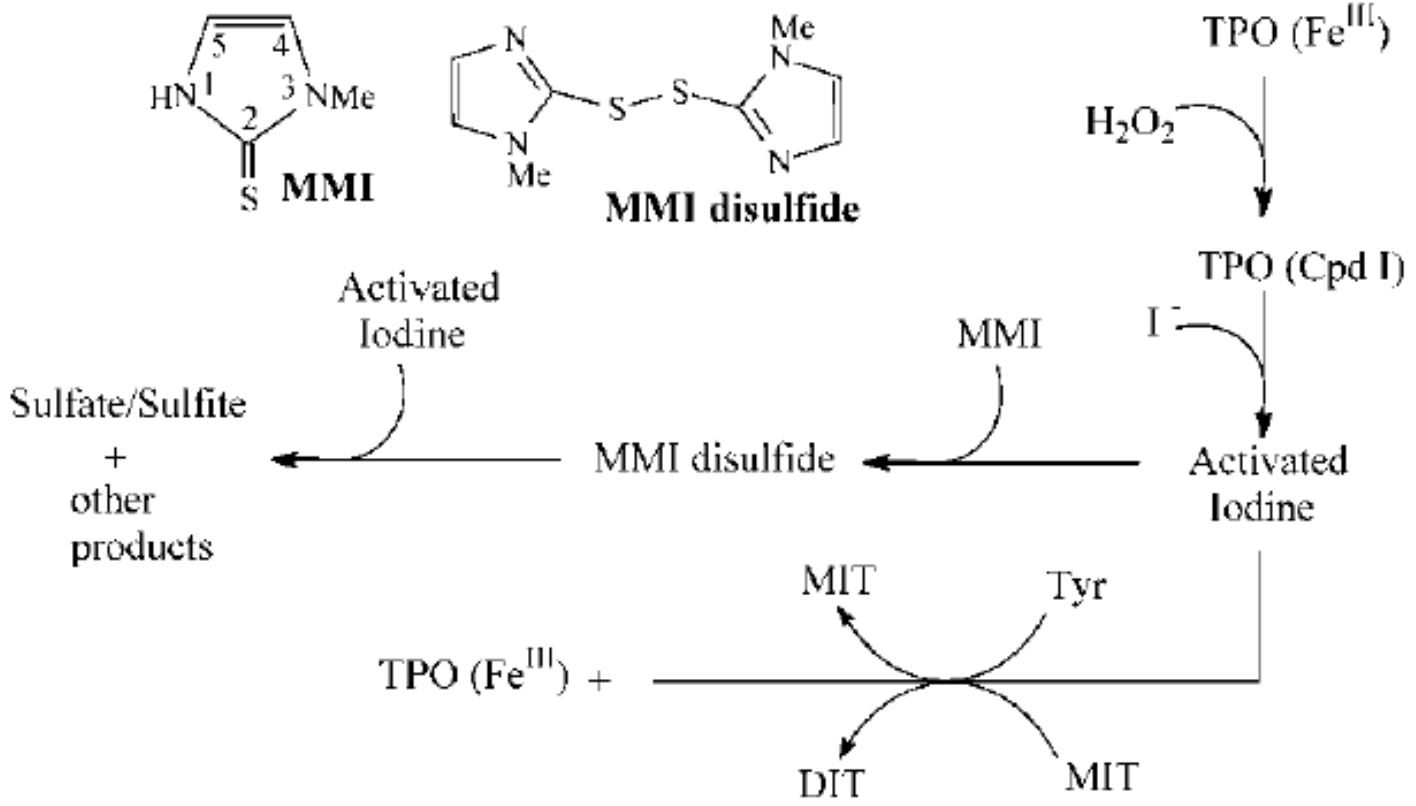
DISULFIDE

S1B	-C1B	1.779(4)
S1B	-S1C	2.0465(16)
S1C	-C1C	1.778(4)

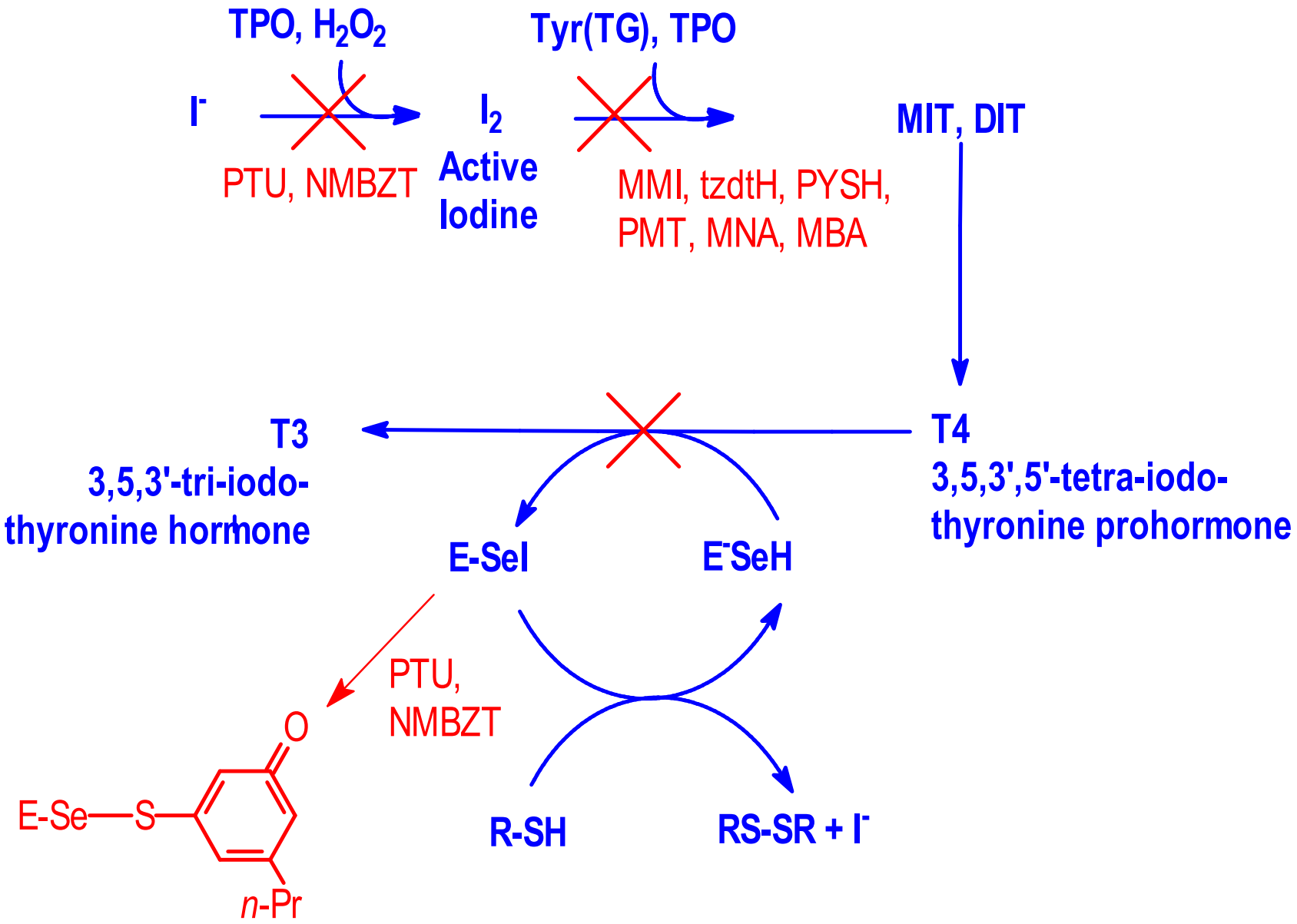
Hadjikakou S.K., et.al., *unpublished results*;

CONCLUSIONS

•Recently, a mechanism for the transformation of MMI to MMI disulfide has been proposed based on crystallographic and electrochemical data by Lippois et al (J. Am. Chem. Soc.. 2002, 124, 4538-4539). The proposed redox process involved the formation of a di- and a mono-cationic disulfide species of MMI prior to the full transformation of MMI to MMI-disulfide.

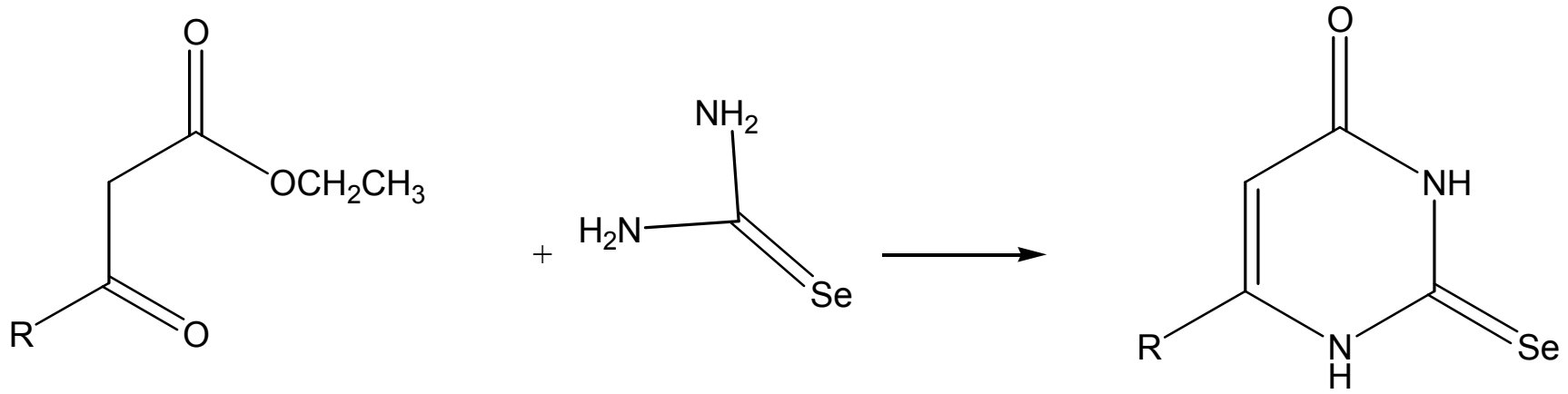


•Thus, thioamides like MMI or tzdtH, exhibiting anti-thyroidal activity against the hyper-thyroidism (Graves' disease) are either oxidized by the TPO-I system to form disulfides or act as strong donors against di-iodine, forming iodonium salts, while activated iodine is reduced to iodide anion simultaneously.
•PYSH reacts with iodine to form a disulfide while iodine is reduced to iodide anion simultaneously
•Thioamides able to form weak charge transfer molecules with di-iodine like PTU on the other hand, interfere in other steps of the mechanism, either in the formation of thyroid peroxides (TPO) - iodonium complex or inhibit the activity of the iodothyronine deiodinase type I (ID-1), an enzyme responsible for the monodeiodination of the T4 prohormone to the T3 hormone .



(1) S. Hadjikakou, et.al., *Eur. J. Inorg Chem.,* 2003, 1635-1640
(2) M.C. Aragoni, et.al., *J Am. Chem. Soc.,* 2002, 124, 4538-4539
(3) W.W. du Mont, et.al., *Angew. Chem. Int. Ed*. 2001, *40*, 2486-2489

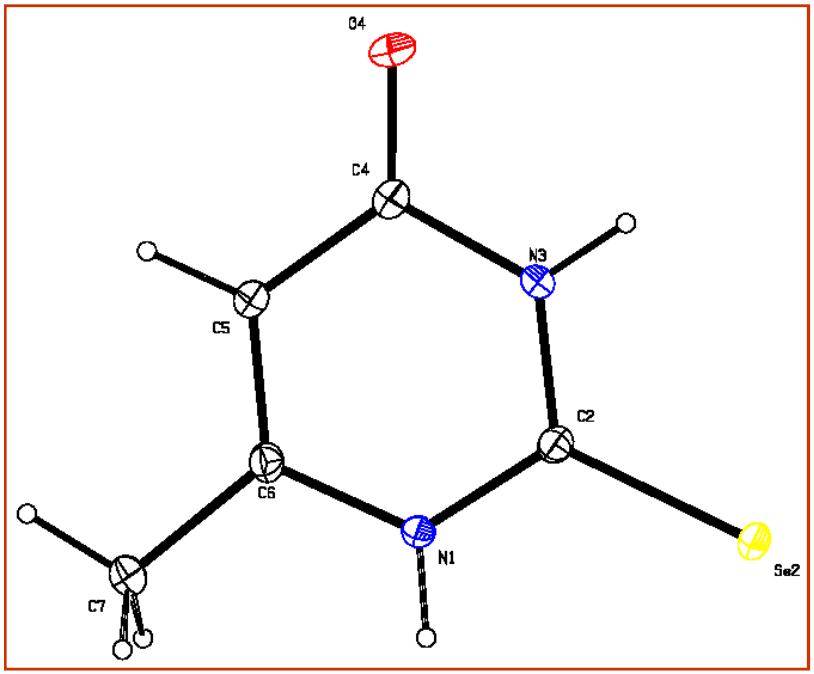
Since thyroid de-iodinase contains selenocysteine (M. J. Berry, L. Banu, P. R. Larsen, *Nature* 1991, *349*, 438-440), the seleno-analog of PTU (PSeU) is expected to exhibit a higher antithyroid activity than PTU, because of the easier formaiton of Enzyme-Se-Se-PSeU species, than the Enzyme-Se-S-PTU due to the higher nucleophilicity of Se.

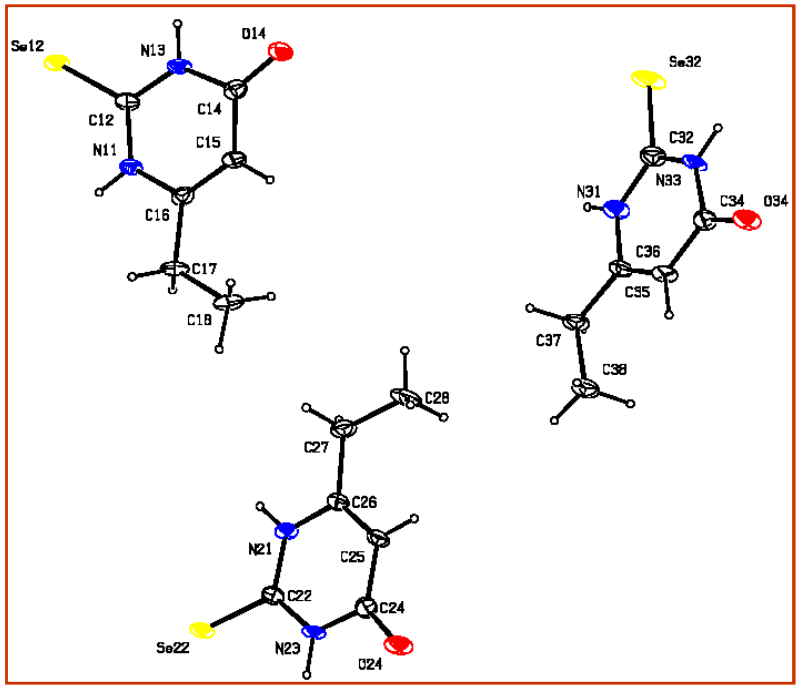


R=Me, Et, n-Pr, i-Pr

T.J. Visser, ετ.al, *Biochem. Biophys. Res. Commun.*, 1992, *189*, 1362-1367

Me-Seleno-Uracil (MSeU), Et-Seleno-Uracil (ESeU)
SOLVENT WATER





C2-Se2=1.831

C2-N1=1.352

C2-N3=1.354

C4-O4=1.233

C12-Se12=1.835

C12-N11=1.355

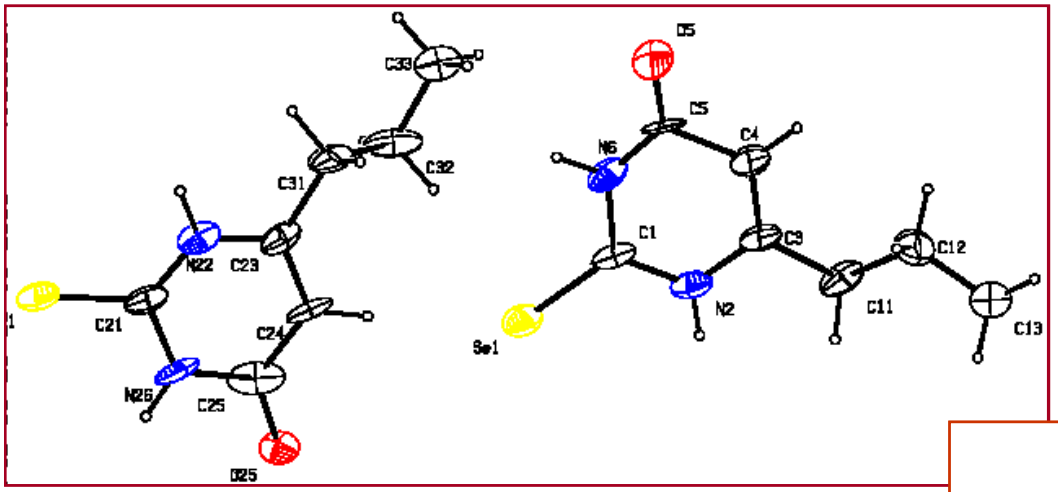
C12-N13=1.351

C14-O14=1.240

Hadjikakou S.K., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897

Hadjikakou S.K.,., et.al., *Acta Cryst, B.* 2006, B62, 580–591

n-Pr-Seleno-Uracil (*n*-PSeU), *i*-Pr-Seleno-Uracil (*iso*-PSeU) SOLVENT WATER



C2-Se1=1.835

C2-N1=1.339

C2-N3=1.354

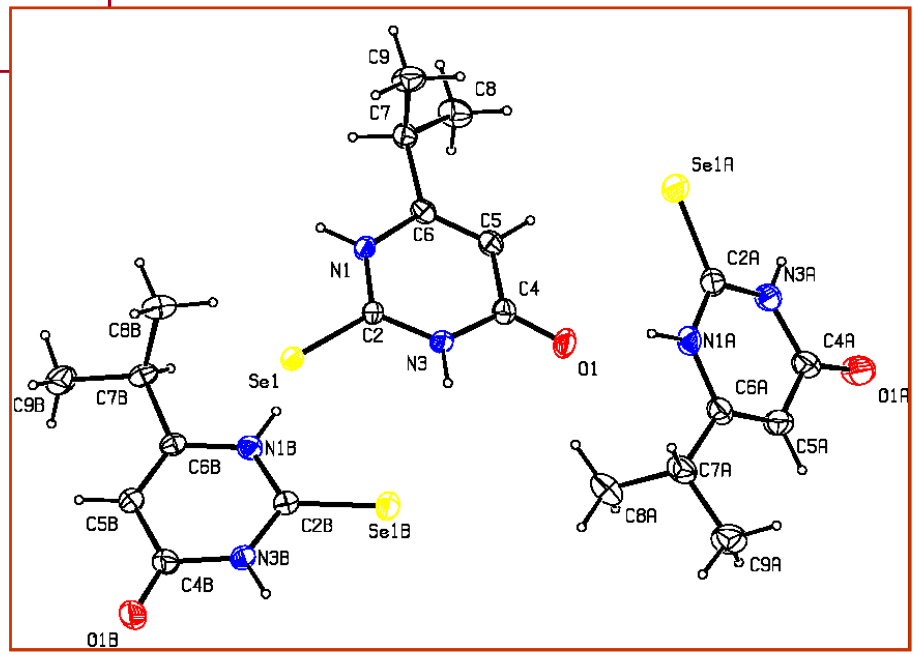
C4-O1=1.227

C1-Se1= 1.8486

C1-N2= 1.3346

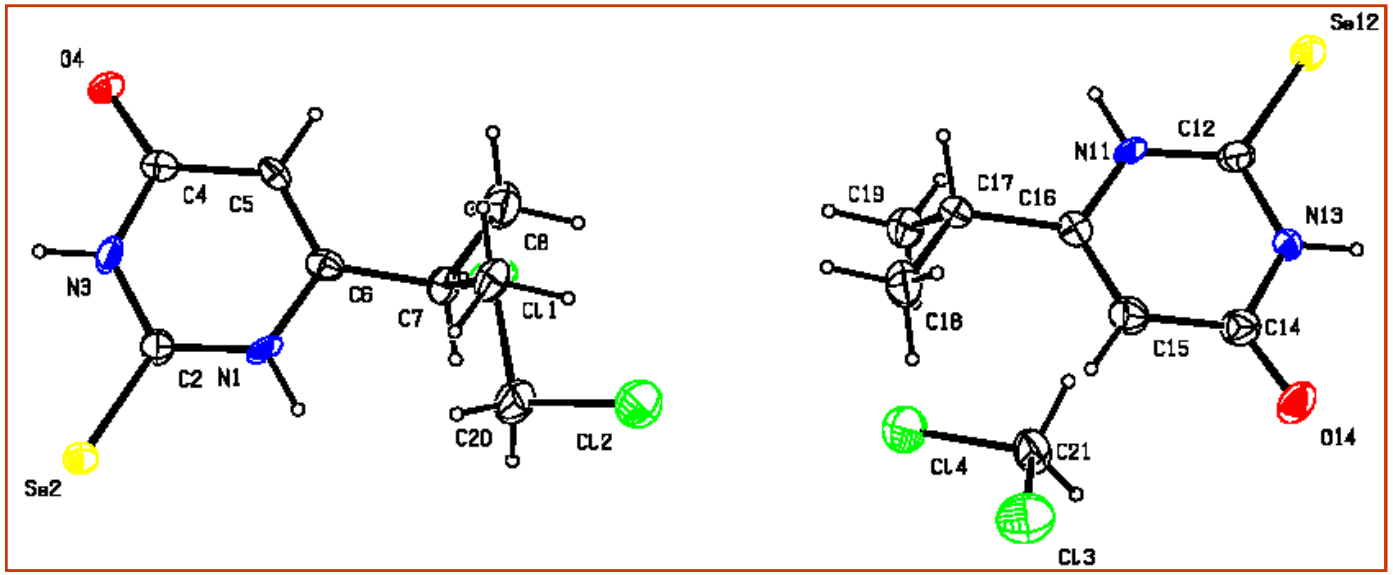
C1-N6= 1.4435

C5-O5= 1.2292



Hadjikakou S.K., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897

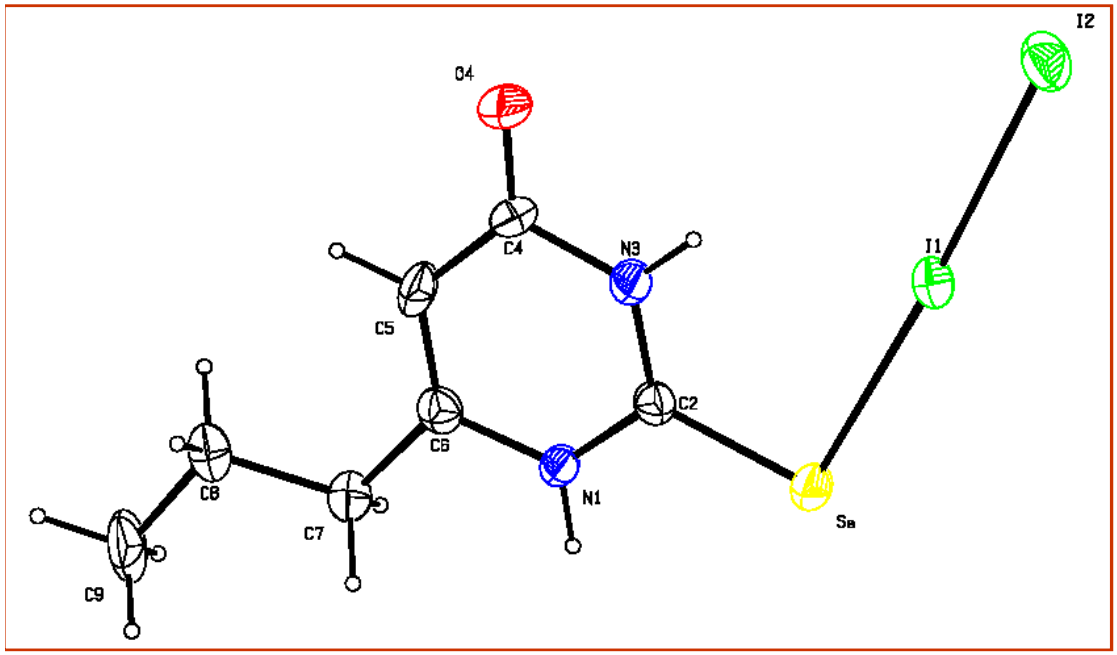
i-Pr-Seleno-Uracil (*iso*-PSeU)
SOLVENT CH_2Cl_2

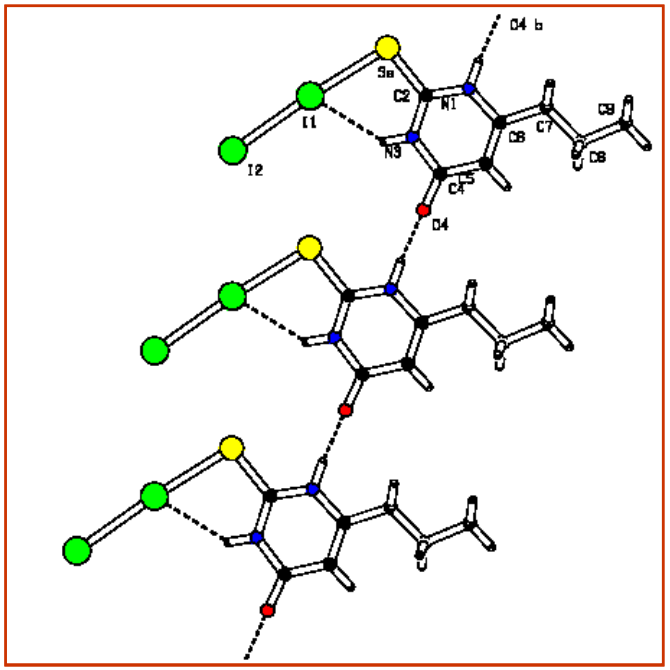


C2-Se2	1.829(5)
N1-C2	1.346(6)
C2-N3	1.351(6)
C4-O4	1.232(6)

Hadjikakou S.K.,., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897
Hadjikakou S.K., et.al., *Acta Cryst, B.* 2006, B62, 580–591

STRUCTURE OF *n*-PrSeU-I_2 SOLVENT $CHCl_3$





$D + I_2 \longrightarrow DI_2$

C2-Se=1.8758

Se-I1=2.7807

I1-I2=2.8927

C2-N1=1.3306

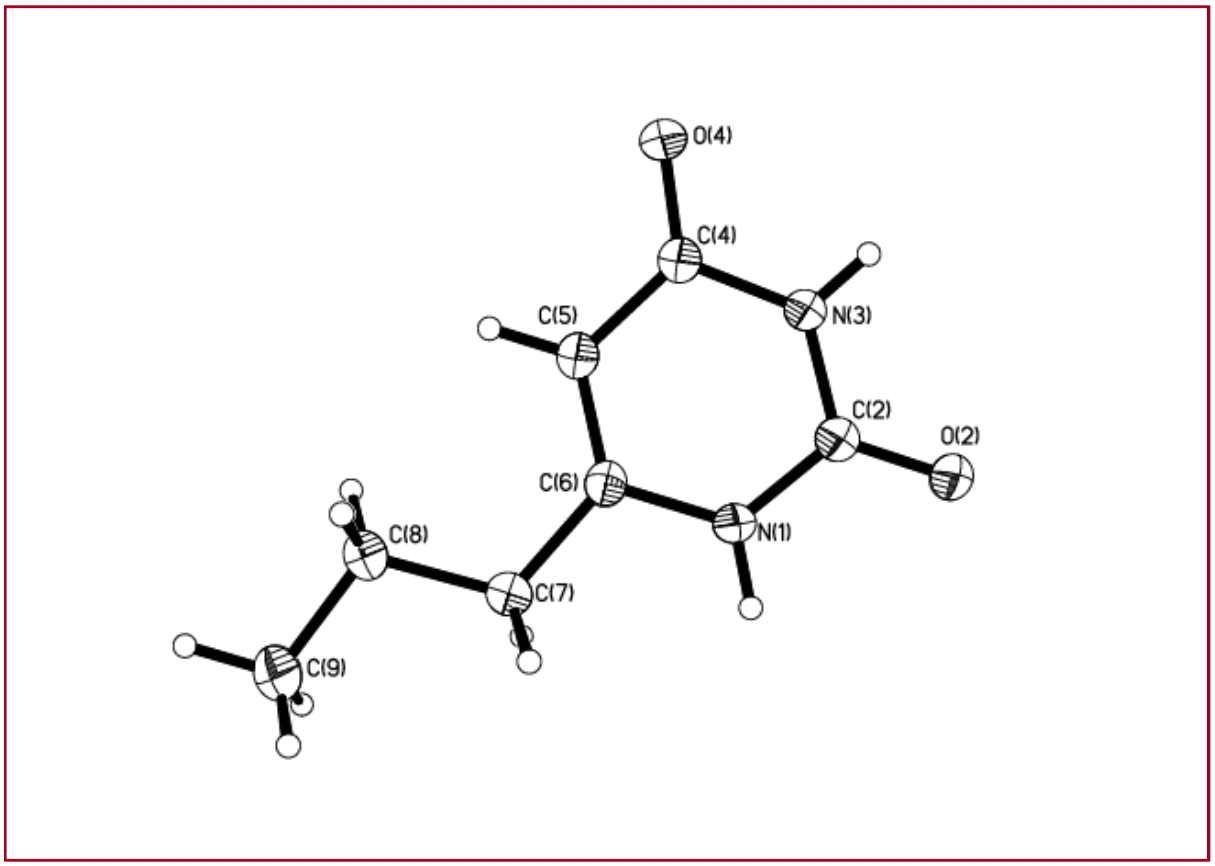
C2-N3=1.3337

C4-O4=1.2127

Hadjikakou S.K.,., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897

Hadjikakou S.K., et.al., *Acta Cryst, B.* 2006, B62, 580–591

CRYSTAL STRUCTURE OF *n*-PrU SOLVENT MeOH-MeCN 1:1



C2-O2=1.229

C4-O4=1.239

C2-N1=1.367

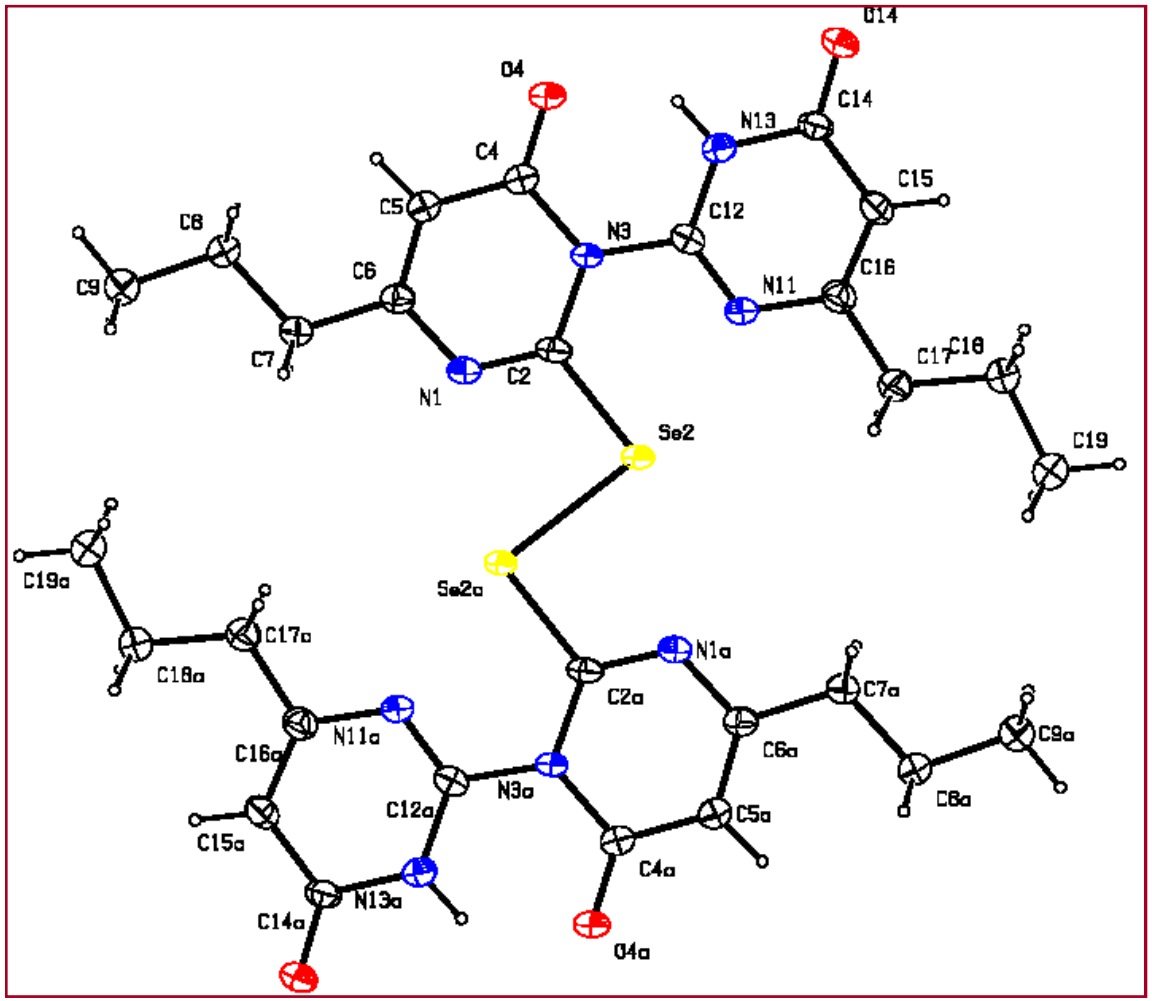
C2-N3=1.365

C4-N3=1.390

Hadjikakou S.K., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897

Hadjikakou S.K.,., et.al., *Acta Cryst, B.* 2006, B62, 580–591

CRYSTAL STRUCTURE OF $(n\text{-PrSeU})_2$ SOLVENT ACETONE



Se-Se=2.443

C2-Se2=1.921

C2-N1=1.296

C2-N3=1.407

C4-04=1.236

N3-C12=1.437

C12-N11=1.272

C12=N13=1.356

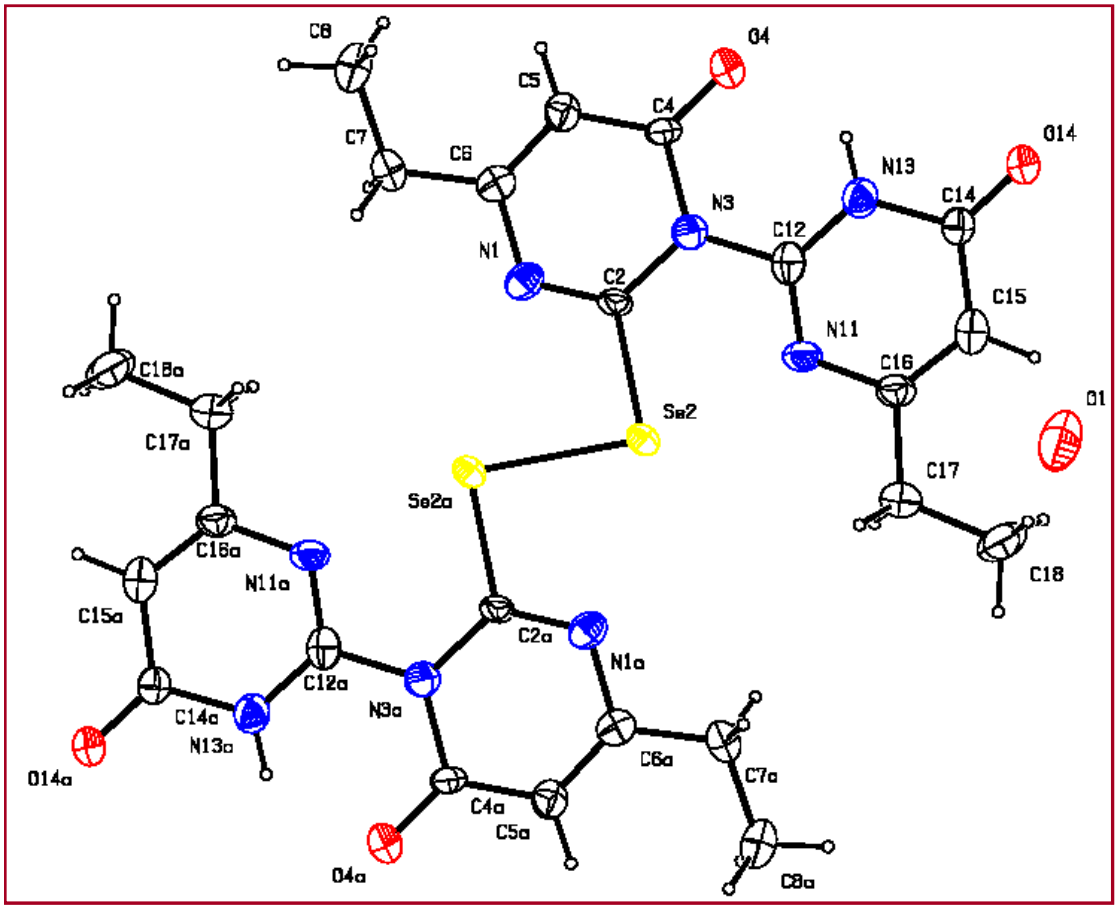
C14-O14=1.230

C2-Se-Se=89.43

Hadjikakou S.K., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897

Hadjikakou S.K.., et.al., *Acta Cryst, B.* 2006, B62, 580–591

CRYSTAL STRUCTURE OF $(Et\text{-}SeU)_2$ SOLVENT ACETONE



Se2-Se2 2.4283(19)

C2-Se2 1.925(4)

N1-C2 1.282(5)

N1-C6 1.395(6)

C2-N3 1.412(5)

N3-C12 1.420(4)

C4-O4 1.234(5)

O14 C14 1.232(3)

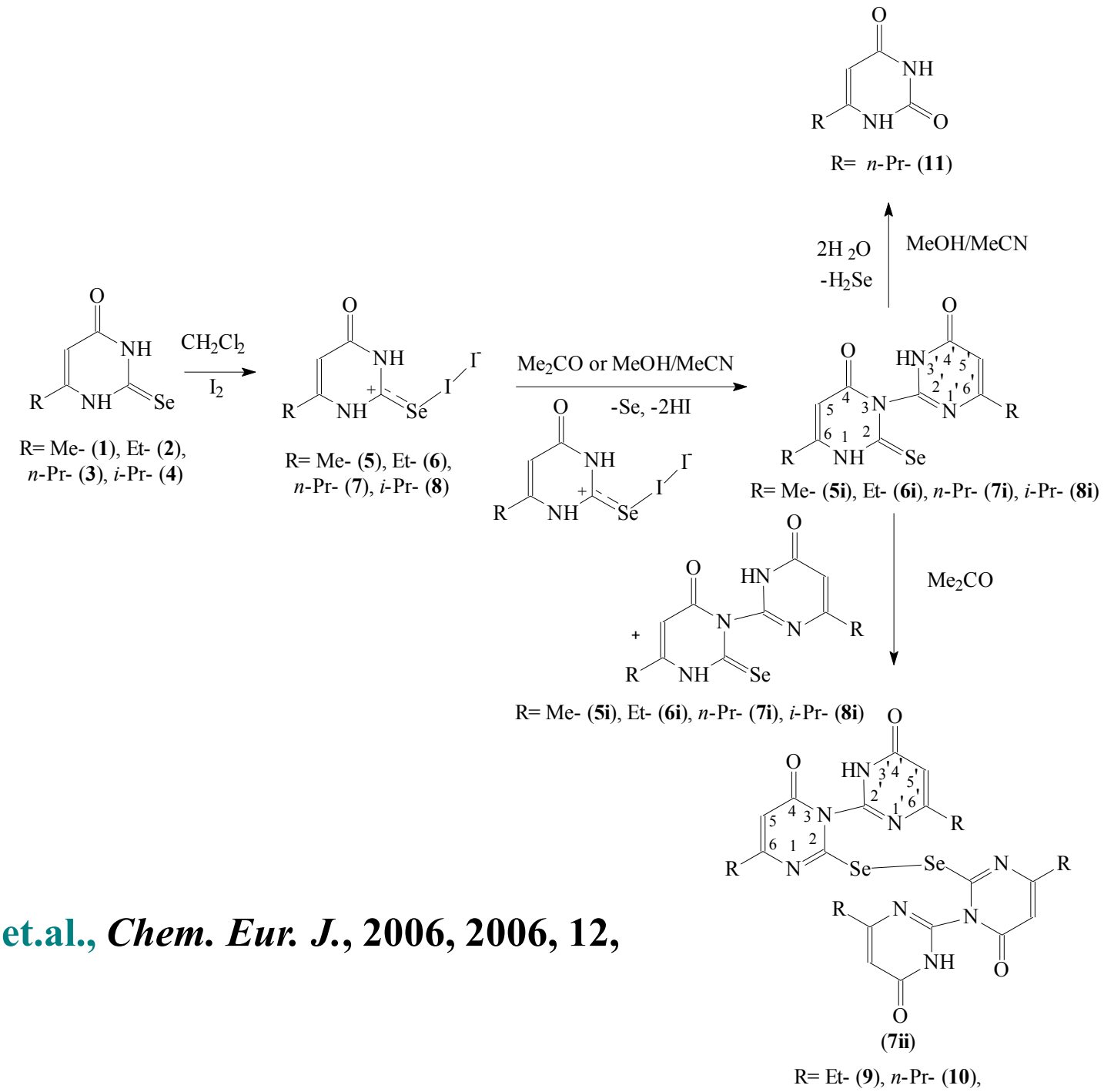
N11 C12 1.2958

N11 C16 1.369(3)

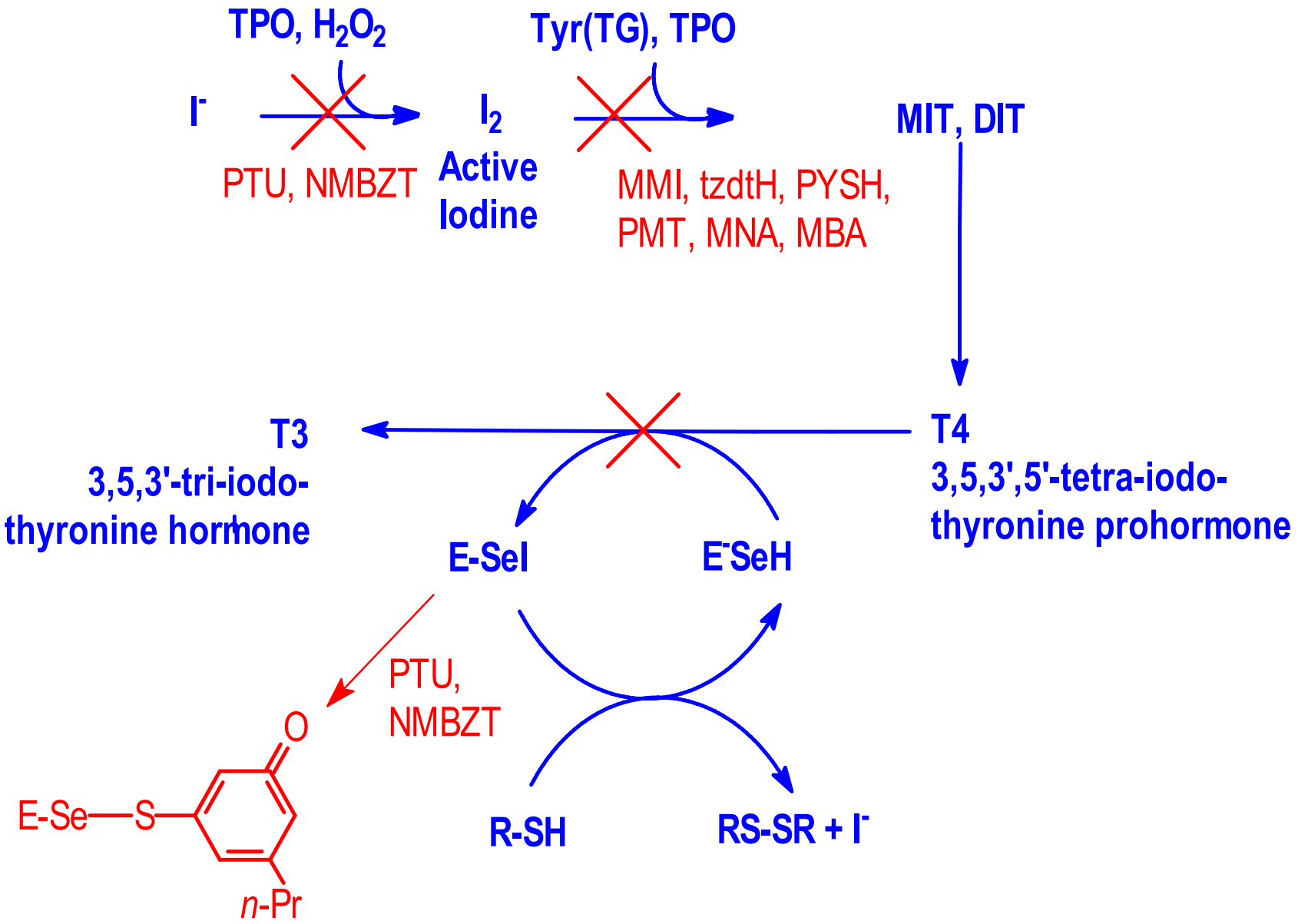
C12 N13 1.337(3)

C2-Se2-Se2 88.99(14)

Hadjikakou S.K.., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897



Hadjikakou S.K., et.al., *Chem. Eur. J.*, 2006, 2006, 12, 6888 – 6897



(1) S. Hadjikakou,, et.al., *Eur. J. Inorg Chem.,* 2003, 1635-1640
(2) M.C. Aragoni, et.al., *J Am. Chem. Soc.,* 2002, 124, 4538-4539
(3) W.W. du Mont, et.al., *Angew. Chem. Int. Ed*. 2001, *40*, 2486-2489

CONCLUSIONS

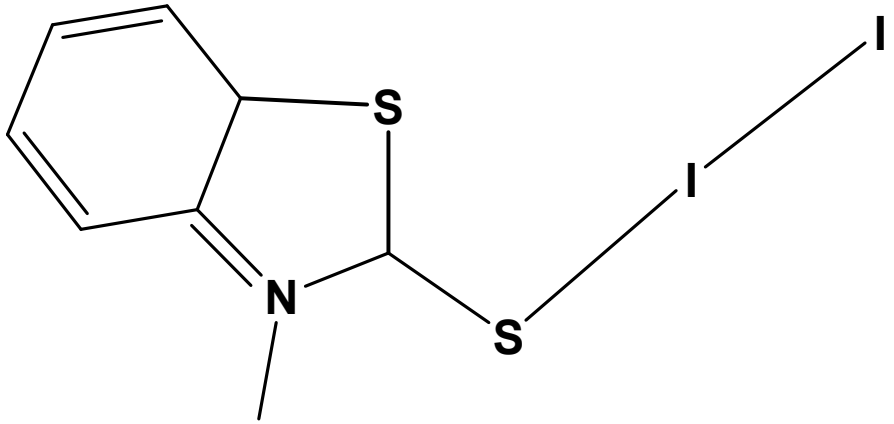
•6-*n*-propyl-2-selenouracil (PSeU) is tranformed in to {[*N*-(6-n-*Pr*-PM)(6-*R*-SeU)]$_2$} di-selenide or to 6-*n*-propyl-2-uracil (6-n-*Pr*U), in polar solvents, in the presence of di-iodine.

•The higher inhibition activity of 6-*n*-propyl-2-selenouracil (PSeU) as compared with the corresponding thioamide 6-*n*-propyl-2-thiouracil (PTU) (almost double), against thyroid de-iodinase, (ID-I) is most probably due to the easier formation of the Enzyme-Se-Se-PSeU species than the Enzyme-Se-S-PTU and possibly also to the formation of the very reactive deselenide intermediates (carbenes).

Since the active site of TPO contains porphyrine rink the interaction of thioamide with di-iodine were studied in the presence of iron compounds.

Thus:
Direct reaction of NMBZT with I_2 in a molar ratio of 1:1 caused the formation of [(NMBZT)·I_2] (1) charge-transfer (c.t.) complex

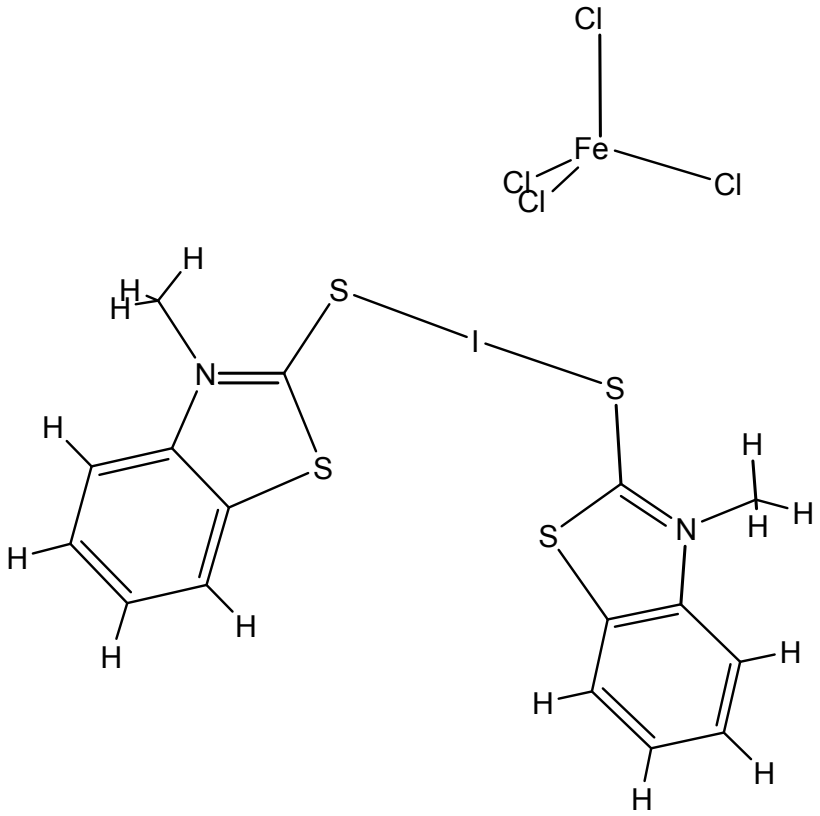
I_2 + NMBZT ⟶



[S.K. Hadjikakou, et.al, *Inorg. Chem.*, 2005, *44*, 8617-8627}.

When NMBZT reacts with I_2 in the presence of $FeCl_3.6H_2O$ in a molar ratio of 3:6:1 it forms the $\{[(NMBZT)_2I^+\}\cdot[FeCl_4]^-$ (2) ionic complex simultaneously with the $\{[(NMBZT)_2I^+\}\cdot[I_7]^-$ (1a) iodonium salt.

$$6I_2 + 3NMBZT + FeCl_3.6H_2O \longrightarrow$$

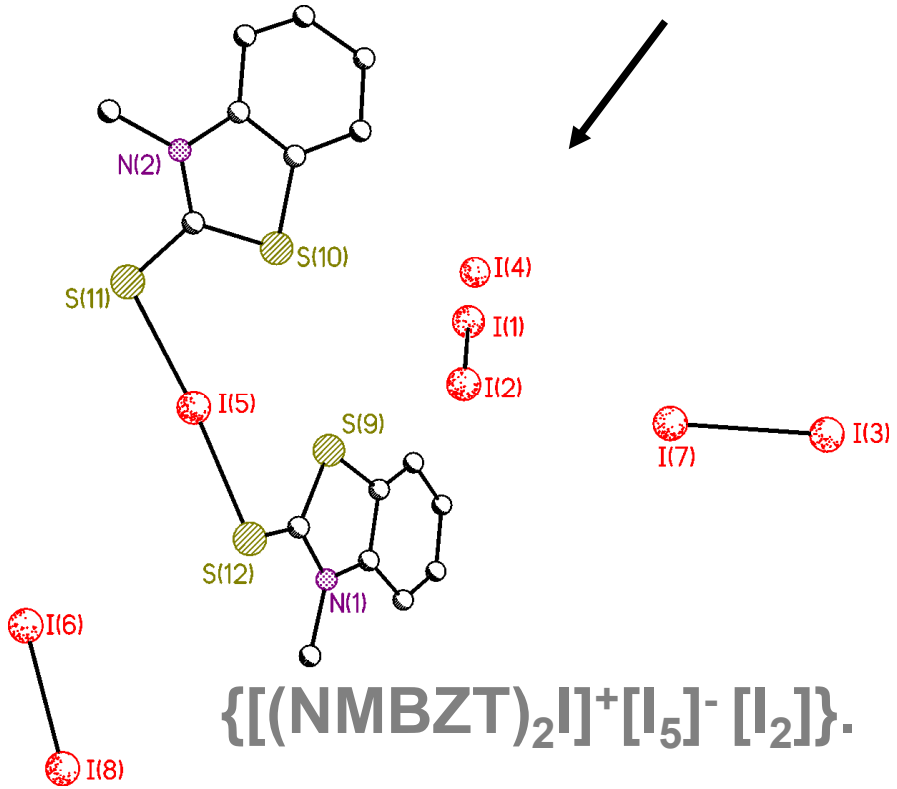


$$+ \{[(NMBZT)_2I]^+[I_7]^-\}.$$

[S.K. Hadjikakou, et.al, *Inorg. Chem.*, 2005, *44*, 8617-8627}.

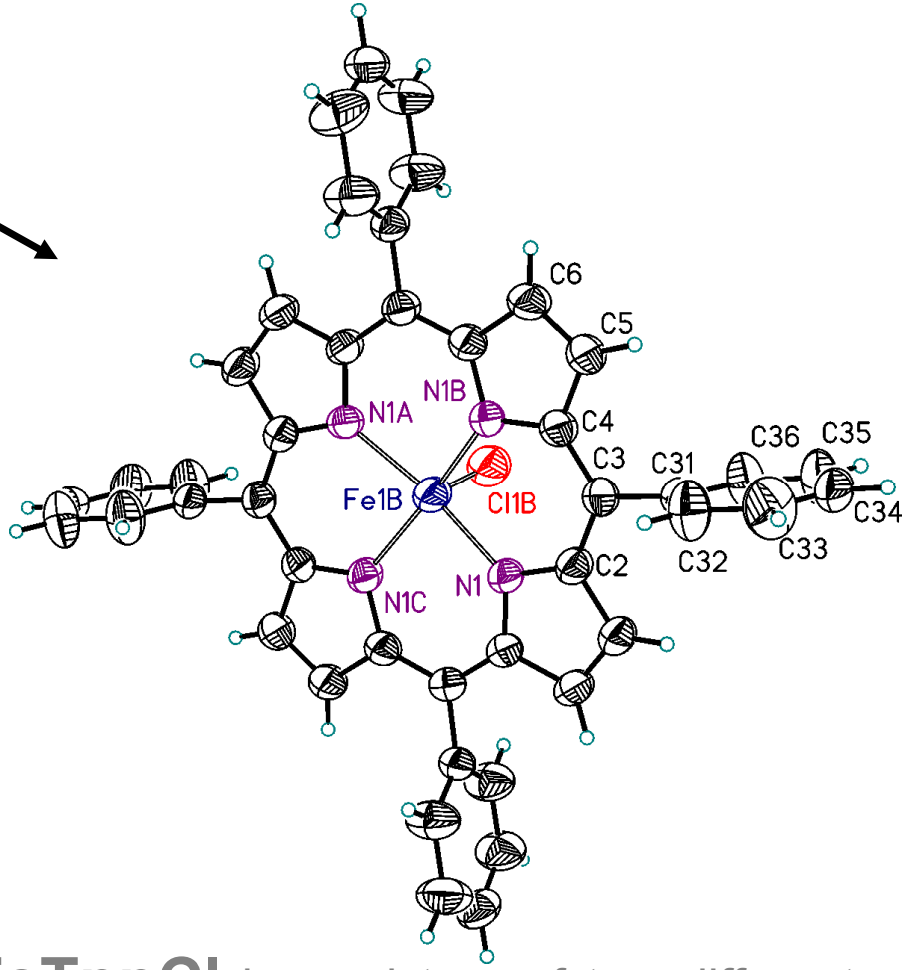
While its reaction with FeTppCl in the molar ratio 3:6:1 forms $\{[(NMBZT)_2I]^+ [I_7]^-\}$ (1a) co-crystallized with molecules of the ligand FeTppCl (II).

$$6I_2 + 3NMBZT + FeTppCl$$



$$\{[(NMBZT)_2I]^+[I_5]^- [I_2]\}.$$

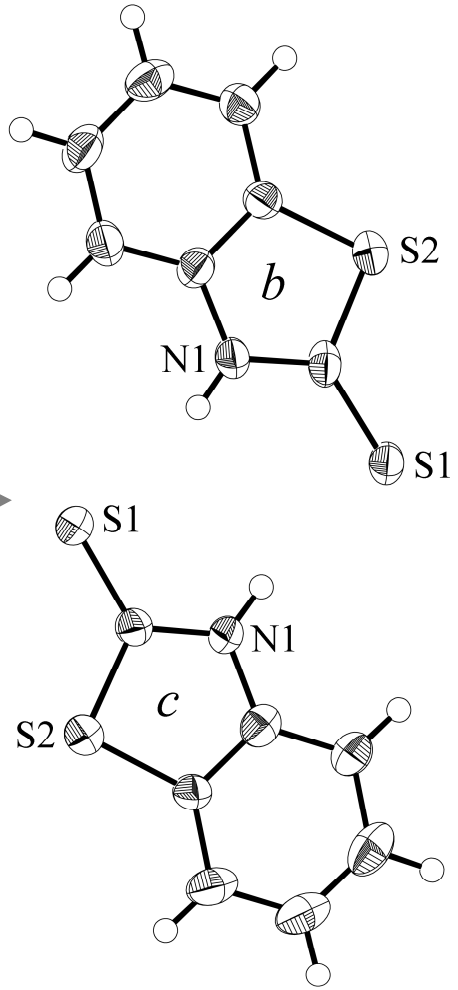
Hadjikakou S.K., et.al.,
unpublished results

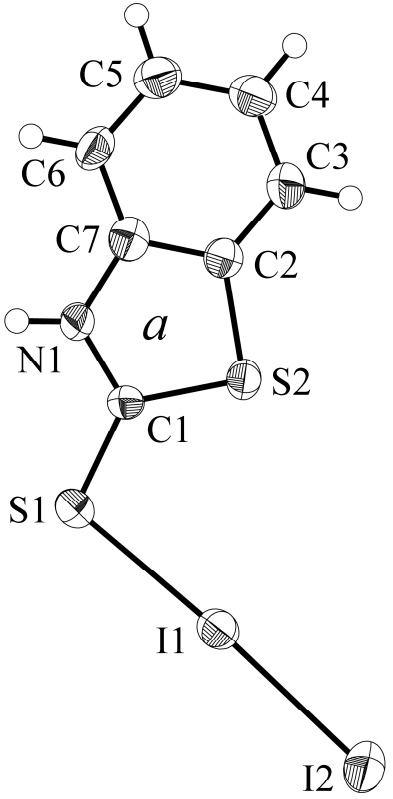


FeTppCl is a mixture of two different structures one of which is published by Hoard et.al. J.Am.Chem.Soc. 1989, 1992, (1967) while the second one has been reported for the first time here

MBZT reacts with I_2 and $FeCl_2.4H_2O$ in the molar ratio 2:2:1 forming the neutral complex {[(MBZT)I_2]·[(MBZT)$_2$]} (3).

$2I_2 + 2MBZT + FeCl_2\ 4H_2O \rightarrow$

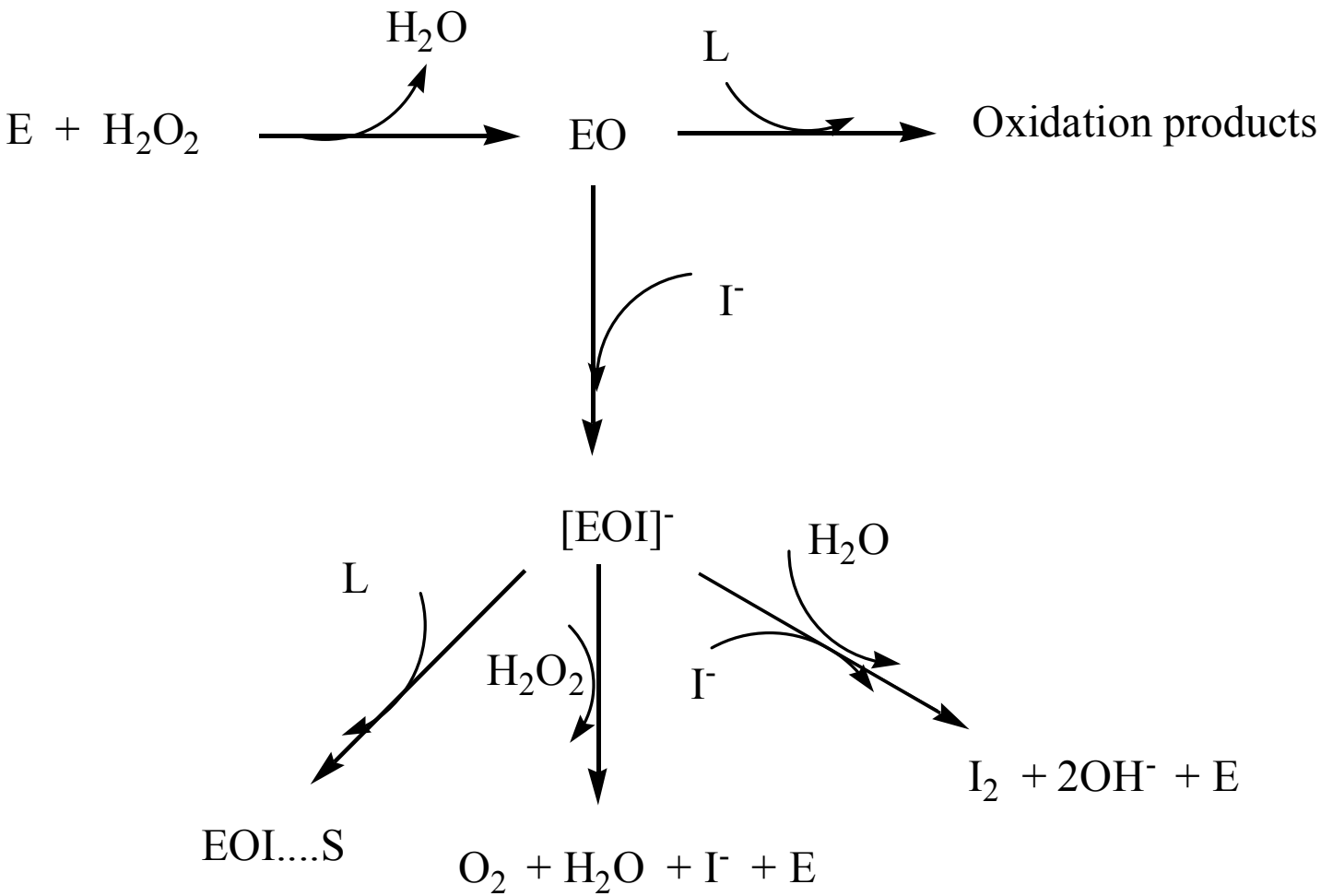




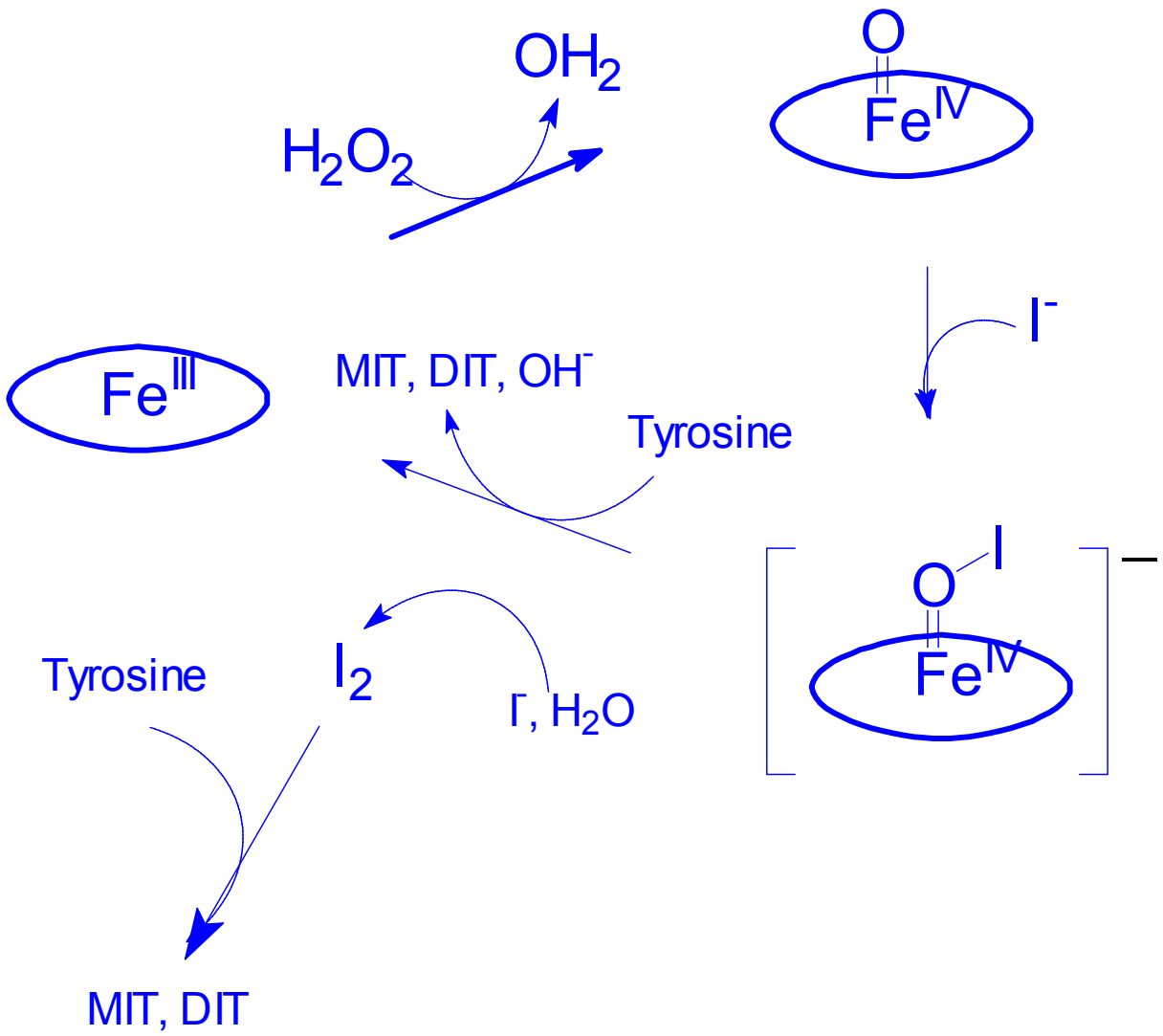
$(LH)I_2.2HL$

Hadjikakou S.K.,., *unpublished results*

The mechanism of inhibition of the thioamides for the catalytic activity of FeTppCl (E). EO=FeTppO. $[EOI]^-$= $[FeTppOI]^-$ and L=thioamide inhibitor



The mechanism of catalytic activity of FeTppCl in the TPO



R.P. Magnusson, A. Taurog, MI. Dorris *J. Biological Chemistry*, 13783-13790, (1984)

Inhibition of the catalytic activity of FeTppCl.

The inhibition activity of the thioamide ligands was measured in the presence of FeTppCl and H_2O_2 as a result of the yield of I_3^- resulting from the oxidation of I^- according to the following equation

$$2I^- + H_2O_2 \longrightarrow I_2 + {}_2OH^-$$

$$I_2 + 2I^- \rightleftharpoons I_3^-$$

Hadjikakou S.K., et.al., *unpublished results*

The inhibition percent of FeTppCl catalysed oxidation of iodide by the compounds of the study

Thioamide ligands	% Inhibition	Confidence Limit
MBZT	27.11	0.62
MMI	25.48	0.86
PySH	21.87	1.48
NMBZT	20.20	0.70
PmSH	19.54	1.33
MBZIM	19.05	0.72
NiBZIM	17.86	0.81
MTZT	16.80	0.61
PmOH	15.78	0.84
TU	10.98	1.14
MeBZIM	10.24	0.86
PyOH	9.51	0.55
PTU	7.81	0.77
PyTU	7.09	0.38
THP	5.61	0.55
CMBZT	3.95	1.15
MPmCl	1.31	0.78

Hadjikakou S.K., et.al., *unpublished results*

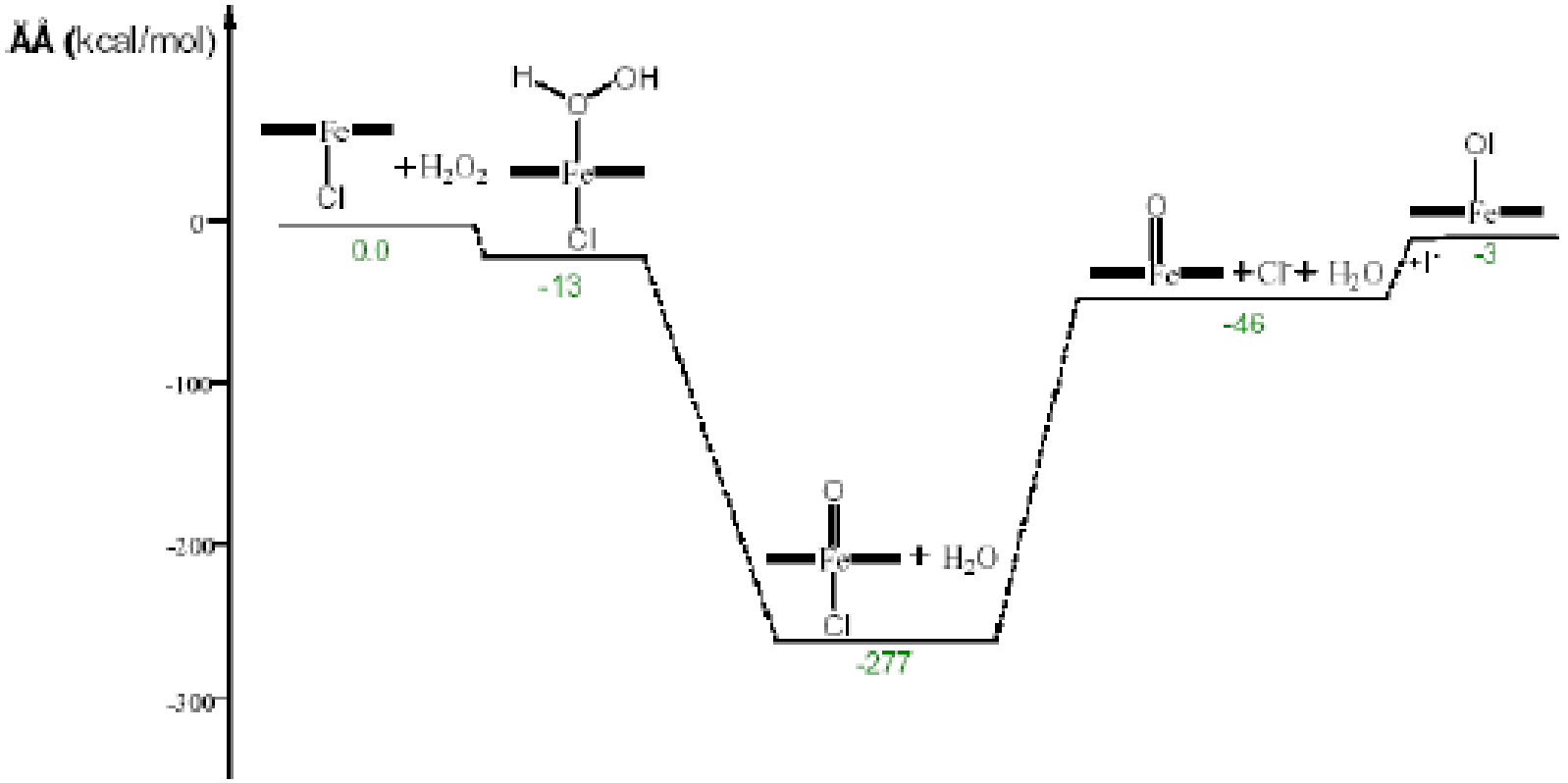
IC_{50} (μM) values of LPO inhibition by thioamides

L	*IC50*	*Confidence limit*
		R^2
DTUC	3.62	0.904
NiBZIM	5.04	0.8939
MBZT	6.74	0.8254
PySH	7.71	0.8946
CMBZT	11.02	0.9861
MBZIM	13.49	0.9749
MPmSH	14.65	0.9353
PmSH	15.51	0.9098
MeBZIM	21.00	0.9944
MMI	28.52	0.7905
PTU	34.30	0.8345
TUC	41.51	0.7299
MTU	47.80	0.8394
MNA	48	0.8376
PyOH	49.16	0.8053
TU	66.65	0.9843
MTZT	78.77	0.9052
BzimOH	406.50	0.9997
PmOH	630.14	0.7958
THP	1155.25	0.5863
NMBZT	651.24	0.2045
PyTU	866.43	0.7159
BztOH	364.82	0.3634

Hadjikakou S.K., et.al., *unpublished results*

Theoretical Calculations of FeTppCl Inhibition Mechanism.

According to the relative potential energies of the equilibrium intermediates of FeTppCl, it is found that the more feasible bath is that shown below



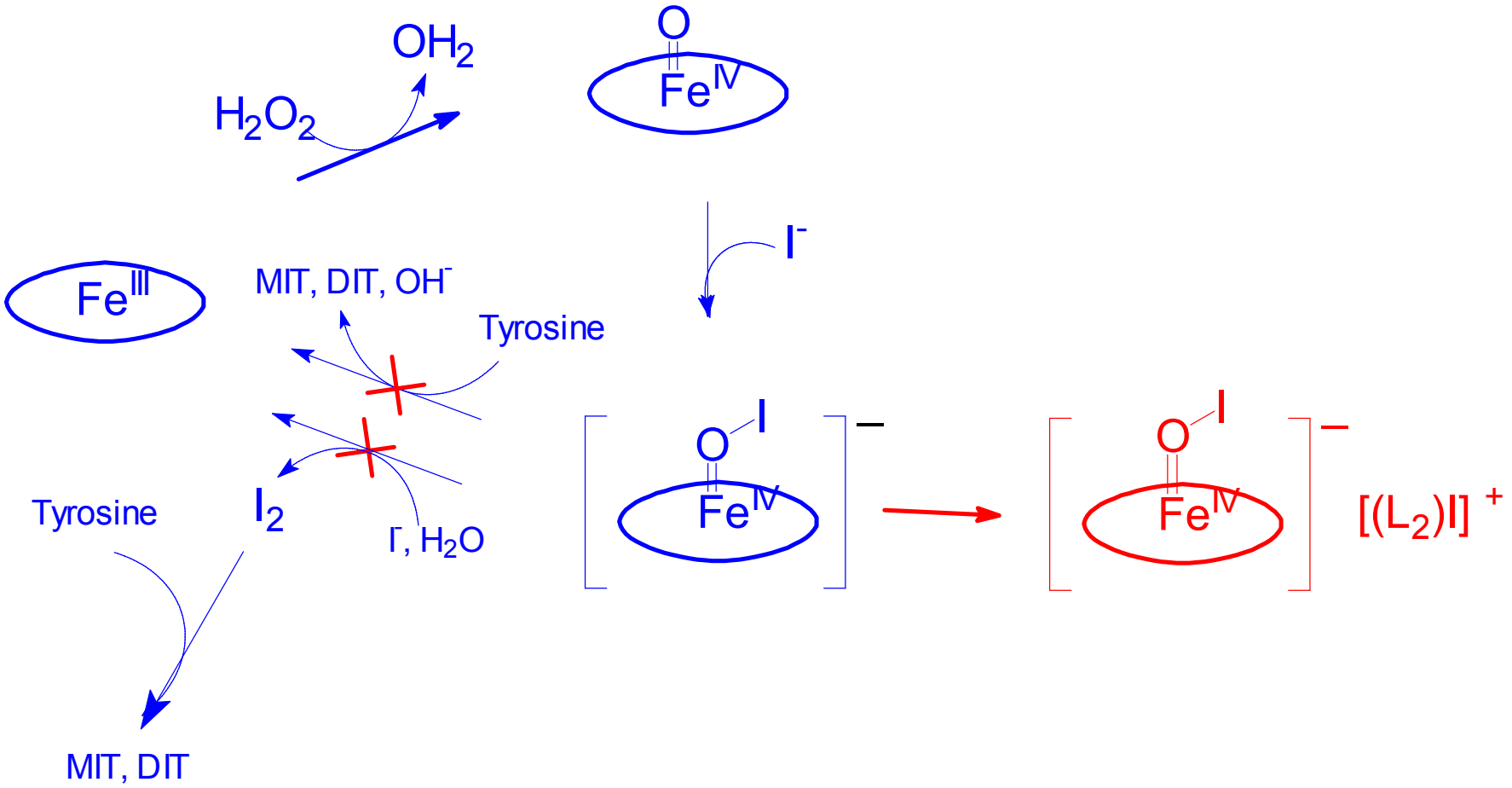
Hadjikakou S.K., et.al., *unpublished results*

CONCLUSIONS

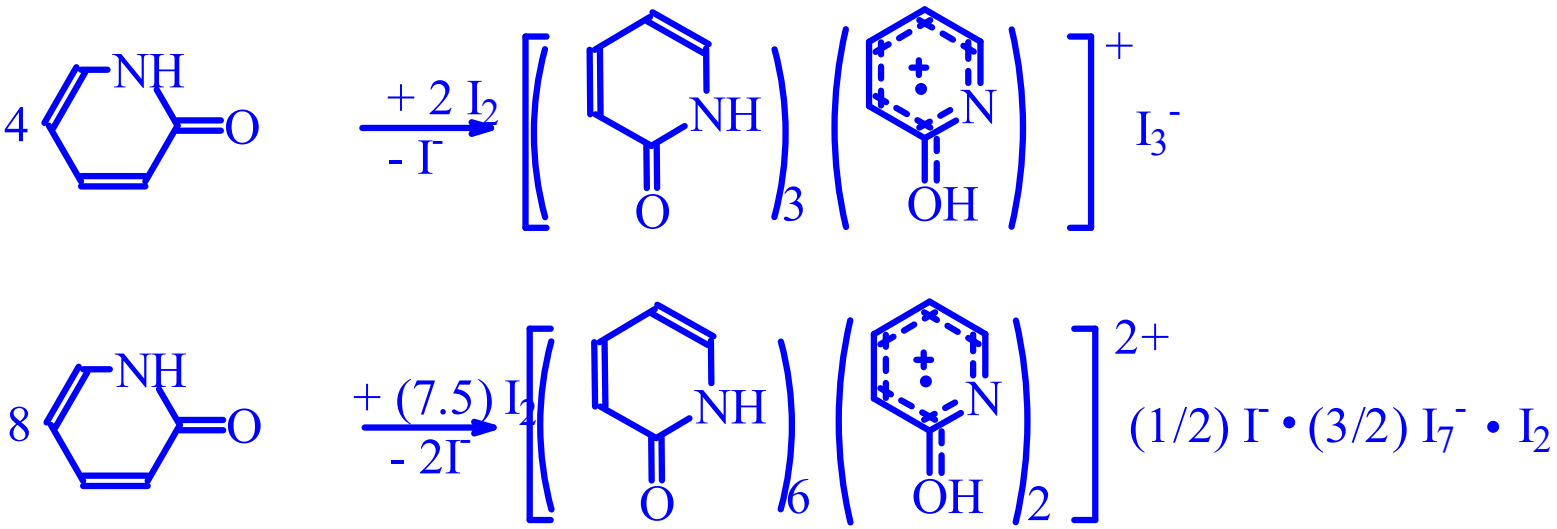
- We have examined experimentally the process of the complexation between di-iodine and thioamides with possible anti-thyroidal activity at different molar ratios in the presence of iron compounds. The products obtained varied from the same product in the absence of iron (for CMBZT, MTZT, PTU and MBZIM), to ionic complexes with iodine and iron $\{(L)_2I^+\}$, counter ion is (I_7^-) or metallic anion $[MX_n]^-$.

- the inhibition of the catalytic activity of FeTppCl in the presence of hydrogen peroxide was found to be strong, medium and very weak depending on the thioamide ligands. The strong and medium inhibition occurred with the ligands that are able to form disulfides and ionic compounds with diiodine and/or iron. The weak or no inhibition is observed by the ligands that can only form the spoke structure like PTU and CMBZT.

- **The mechanism of action and inhibition of the catalytic activity of FeTppCl could be due to the interaction of the ligands with the $[EOI]^-$ compounds of FeTppCl leading to dead end products where the catalyst could not be regenerated. The thioamide that inhibit the FeTppCl catalytic activity interact with the ionic intermediate formed $[FeTppOI]^-$**

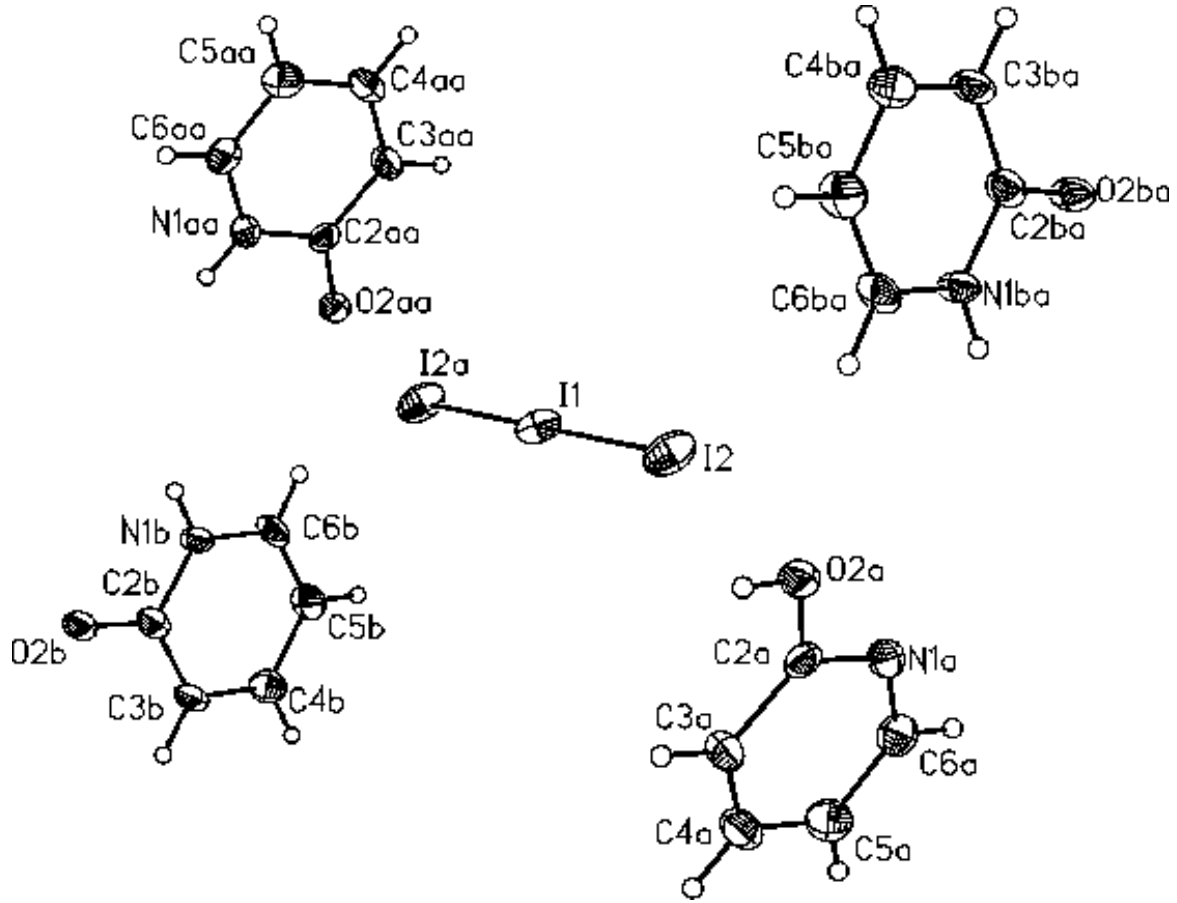


EXTENSION OF THIS WORK. SYNTHESIS OF COMPLEXES WITH PYOH



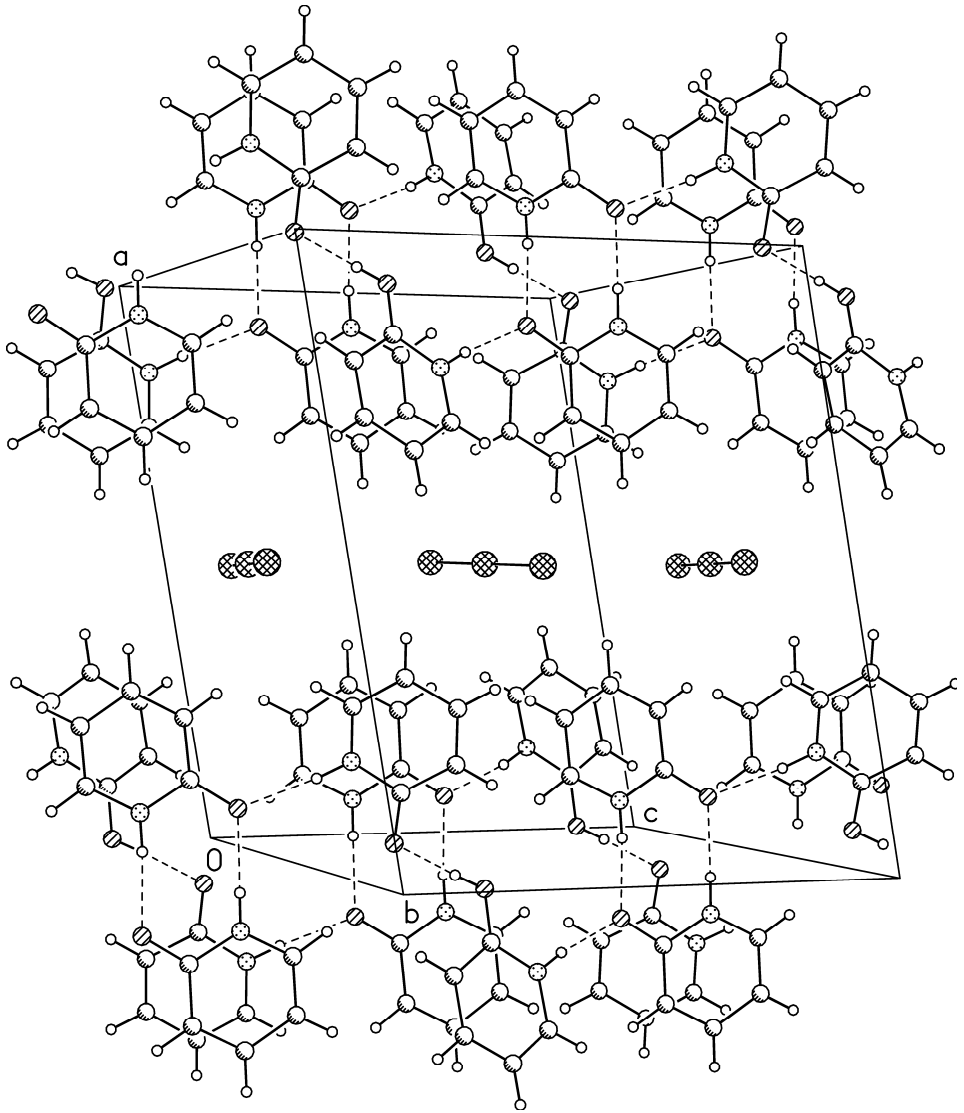
S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

CRYSTAL STRUCTURE OF $\{[(PYOH)_3[(PYOH)]^+ \cdot I_3^-\}$



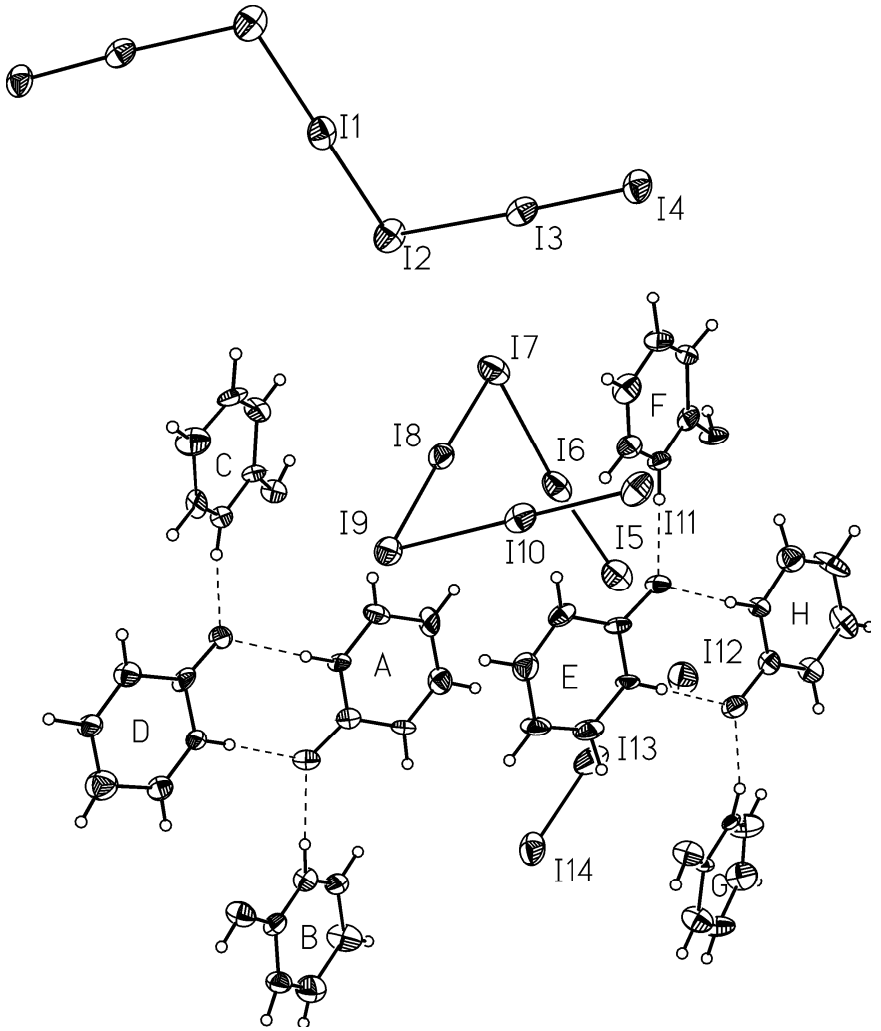
S.K. Hadjikakou,, et.al, *New J. Chem.*, 2005, 29, 714–720

UNIT CELL OF $\{[(PYOH)_3[(PYOH)]^+ \cdot I_3^-\}$



S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

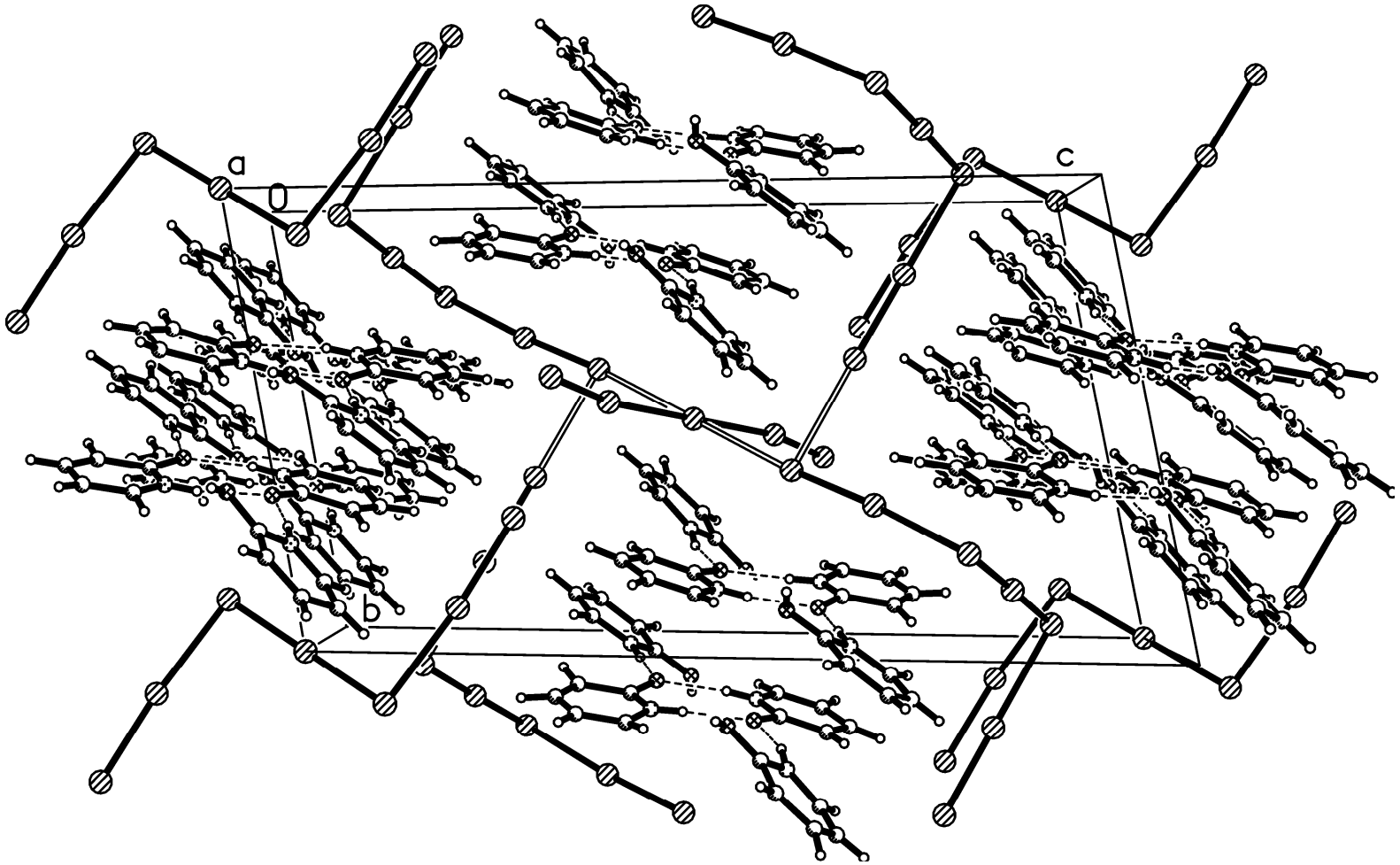
CRYSTAL STRUCTURE OF
$\{(PYOH)_6 \cdot [(PYOH)_2]^{2+} \cdot ((1/2)I^-) \cdot ((3/2)I_7^-) \cdot (I_2)\}$



S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

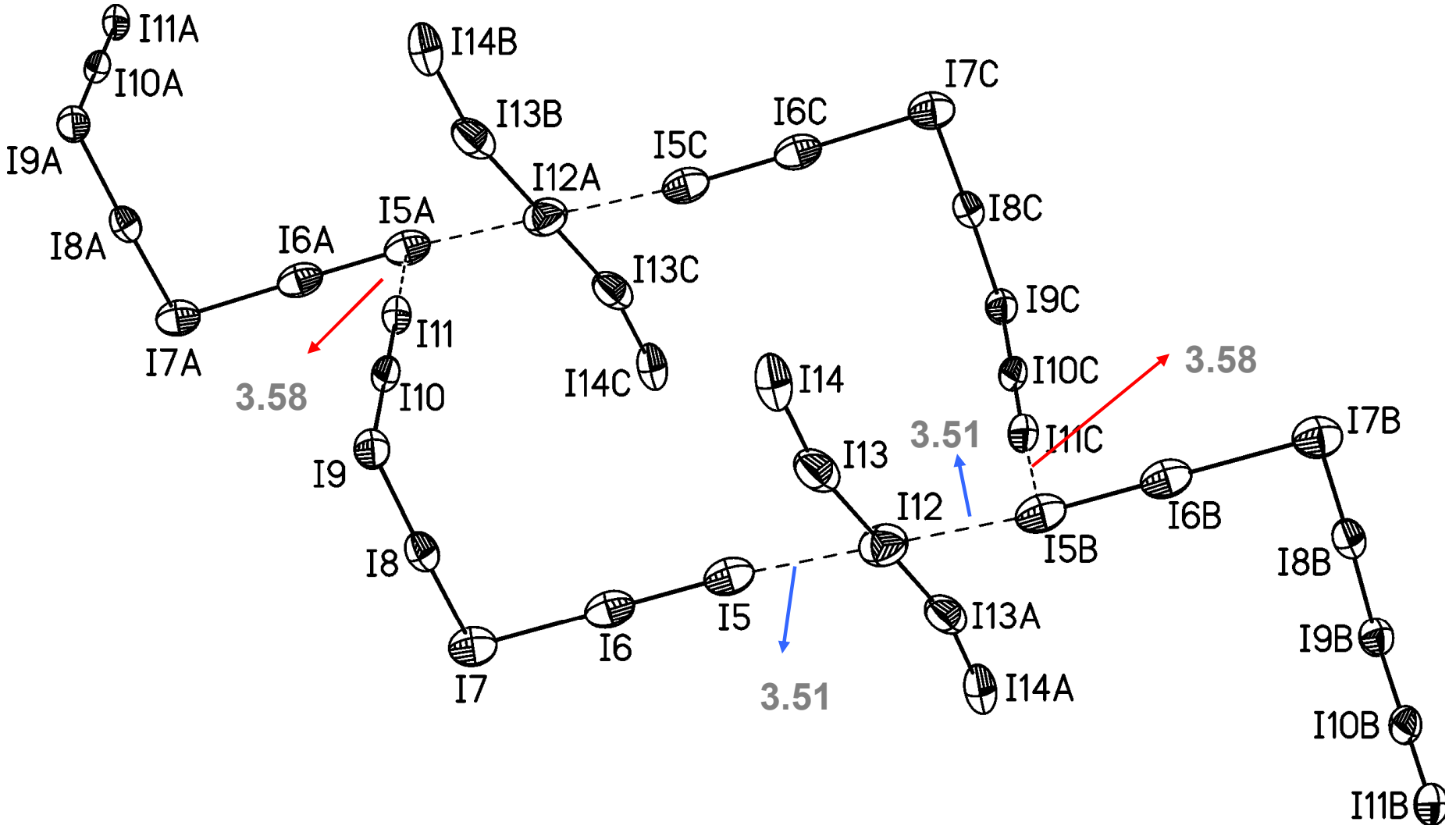
UNIT CELL OF

$\{(PYOH)_6 \cdot [(PYOH)_2]^{2+} \cdot ((1/2)I^-) \cdot ((3/2)I_7^-) \cdot (I_2)\}$



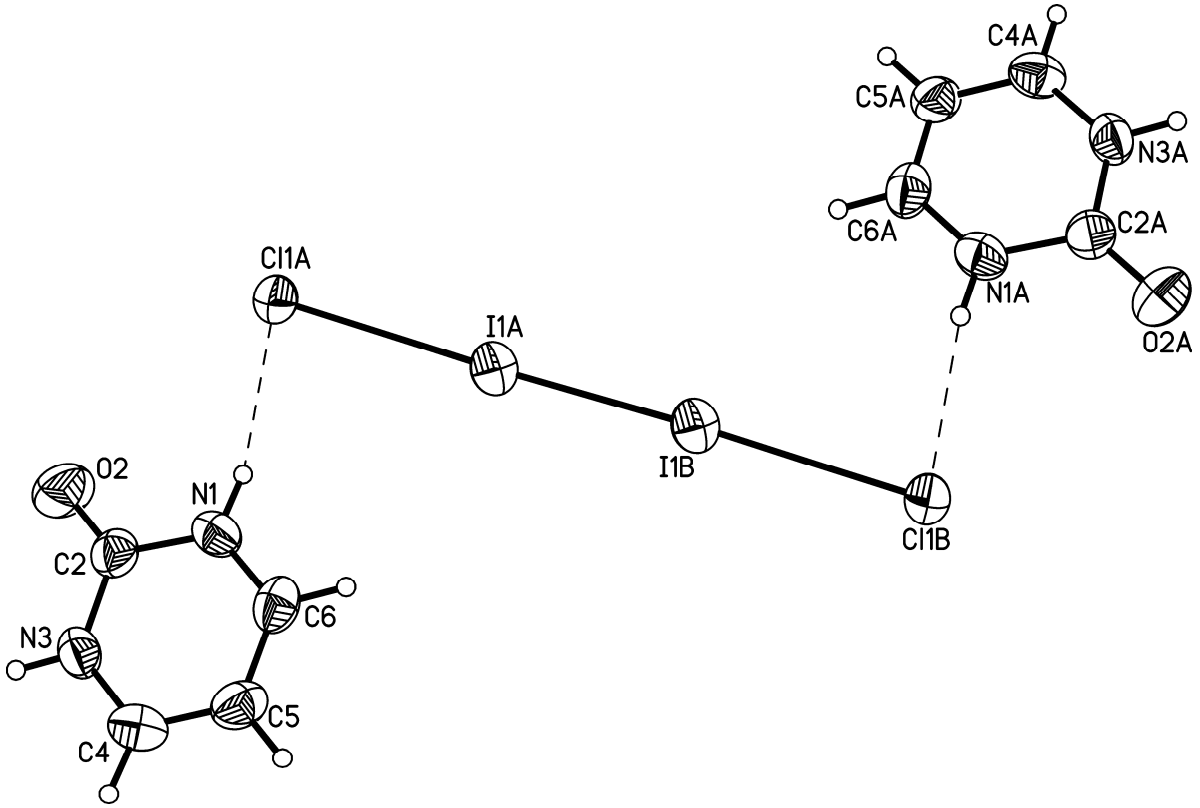
S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

Polyiodine network established by weak halogen-halogen interactions, in the distance range 3.51-3.58, between I_7^- and $I_2\cdots I^-\cdots I_2$ ions in the $\{(PYOH)_6\cdot[(PYOH)_2]^{2+}\cdot((1/2)I^-)\cdot((3/2)I_7^-)\cdot(I_2)\}$



S.K. Hadjikakou, et.al, *New J. Chem.*, 2005, 29, 714–720

CRYSTAL STRUCTURE OF $\{[(PMOH_2)]^+Cl^-\cdot I_2\}$



Hadjikakou S.K., et.al., *Dalton, 2008*;

CONCLUSIONS

•**Structures containing polyiodide anions, with cationic aromatic ligands as counter parts of formula {[(L)(HL$^+$)]·(I_n^-)} can be synthesized by the treatment of the appropriate amide with HI [(a) F.H. Herbstein, et.al., *Helv. Chim. Acta*, 1983, *66*, 35-43. (b) F.H. Herbstein, et.al., *Philos.Trans. R. Soc. London, Ser.A*, 1979, *291*, 199- 201 (c) J.M. Reddy, et.al., *J. Chem. Phys.*, 1964, *40*, 1082-1089].**

•**In contrast, the complexes with PYOH, in the present case, were formed by the direct reaction of 2-hydroxypyridine with di-iodine in a molar ratio of 2:1 and 1:2 This is a redox reaction, where 2-hydroxy-pyridine firstly is oxidized to pyridinone-2 radical cation.**

•**In the case of 2-hydroxy-pyridine however, peroxide structures are not formed like disulphides in the case of PYSH. Polyiodide anions are simultaneously produced in this case This should be a consequence of redox differences between –SH and OH groups and may be proven a useful pathway for the synthesis of polyiodide materials.**