Indian Journal of Chemistry
Vol. 36B, April 1997, pp. 312-317

Oxidation of geraniol and related volatile terpenoids with iodosylbenzene catalysed by 5,10,15,20-tetrakis(2′,6′-dichlorophenyl)porphyrinatoiron(III) chloride in dichloromethane, aqueous SDS and CTAB micelles

S M S Chauhan*, Som Parkash & P P Mohapatra
Department of Chemistry, University of Delhi, Delhi 110 007

Received 4 June 1996; revised and accepted 24 October 1996

Oxidation of geraniol with iodosylbenzene catalysed by 5,10,15,20-tetrakis(2′,6′-dichlorophenyl)porphyrinatoiron(III) chloride [Cl_8TPPFe(III)Cl] in dichloromethane gives geranial, geranic acid and 6,7-epoxygeraniol in moderate yields. In aqueous SDS micelles, the oxidation of geraniol with iodosylbenzene in the presence of Cl_8TPPFe(III)Cl gives geranial and geranic acid in high yields, whereas in CTAB micelles it gives the corresponding aldehyde and acid as well as both 6,7-epoxygeraniol and 2,3-epoxygeraniol in moderate yields. The changes in oxidation products and their yields in the presence of sodium chloride and sodium bromide have been reported in SDS micelles.

Cytochrome P450 heme monooxygenases catalyse the monooxygenation of a wide range of xenobiotics and endogenous substrates by utilizing molecular oxygen and NADPH[1]. They are among the most important monooxyenases utilized by herbivores in the detoxification of plant secondary metabolities[2]. Polyphagous insects feed on a narrow range of plants sharing common plant secondary metabolities which govern the diversification of insect cytochrome P450[3,4].

Characterization of the high valent oxo-iron intermediates and their reactions have contributed towards the mechanism of the active site of natural cytochrome P450[5,6] and their diversifications. The reactions of monooxygen donors with 5,10,15,20-tetraarylporphyrinatoiron(III) chlorides form the high valent oxo-iron(IV) porphyrins which are responsible for mimicking the different reactions of cytochrome P450[7,8]. Citral, linalool and other monoterpenoids are olfactory attractants for *Bombyx mori*[9] and these volatile products are also present in the primary food plants of tropical tasar silkworm *Antherea mylitta*[10]. We report here the reaction of geraniol **1** and citral with iodosylbenzene catalysed by 5,10,15,20-tetrakis-(2′,6′-dichlorophenyl)porphyrinatoiron(III) chloride (Cl_8TPPFe(III)Ci) **2** to elucidate themolecular mechanism of the oxidation of monoterpenoids by insect cytochrome P450 as well as preparation of oxidative intermediates to examine their effects on tasar silkworm *A. myllita* and related herbivores.

Results

5,10,15,20-Tetrakis(2′,6′-dichlorophenyl)porphyrinatoiron(III) chloride **2** was prepared by the published methods[11,12].

Iodosylbenzene is an efficient monoxygen donor, but it does not react with geraniol in dichloromethane at room temperature. The oxidation of **1** with iodosylbenzene catalysed by electron withdrawing iron(III)porphyrin (Cl_8TPPFe(III)Cl) **2** gave geranial **3**, geranic acid **4** and 6,7-epoxygeraniol **5** in 2, 22 and 6% yields, respectively. The reaction of **1** with iodosylbenzene catalysed by **2** in the presence of co-catalyst N-methylimidzole (NMeIm) gave **3, 4** and **5** in 3.3, 24.8 and 11% yields, respectively (Scheme I, Table I).

m-Chloroperbenzoic acid (*m*-CPBA) is another efficient monoxygen donor in acidic conditions. The oxidation of **1** with *m*-CPBA in organic solvents did not give any epoxide, whereas the reaction of **1** with *m*-CPBA catalysed by **2** gave **4** in 7.2% yield in 1 hr. The reaction of **1** with iodosylbenzene catalysed by **2** in the presence of benzoic acid gave **3, 4, 5** and 2,3-epoxygeraniol **6** in 2, 75, 10.54 and 2%, respectively (Table I).

The reaction of **3** with either *m*-CPBA or iodosylbenzene does not give any product. The reaction of **3** with *m*-CPBA catalysed by **2** gave **4** in 6.8% yield whereas the reaction of **3** with iodosylbenzene catalysed **2** gave **4** in 12.3% yield in 1 hr.

The oxidation of **1** with iodosylbenzene catalysed by lipid soluble **2** in SDS micelles at *p*H 4.0

Table I—Oxidation of geraniol **1** and geranial **3** with iodosylbenzene catalysed by 5,10,15,20-tetrakis(2′6′-dichlorophenyl)porphyrinatoiron(III) chloride ($Cl_8TPPFe(III)Cl$) **2** in dichloromethane

Sl. No.	System[a,b,c]	% Yield (Products)			
		Geranial (**3**) (8.2)[d]	Geranic acid (**4**) (5.6)[d]	6,7-Epoxide (**5**) (4.7)[d]	2,3-Epoxide (**6**) (6.7)[d]
1	$1/2/C_6H_5IO$	2.0	22.0	6.0	—
2	$1/2/C_6H_5IP$/NMeIm	3.3	24.8	11.0	—
3	1/*m*-CPBA	—	—	—	—
4	1/2/*m*-CPBA	—	7.2	—	—
5	$1/2/C_6H_5IO$/Benzoic acid	2.0	75.0	10.5	2.0
6	$3/C_6H_5IO$	—	—	—	—
7	3/*m*-CPBA	—	—	—	—
8	3/2/*m*-CPBA	—	6.8	—	—
9	$3/2/C_6H_5IO$	—	12.3	—	—

[a]Substrate-oxidant-catalyst = 100:10:1.

[b]Reactions were carried out in nitrogen atmosphere.

[c]Reaction period = 1 hr.

[d]HPLC retention time in min.

Table II—Oxidation of geraniol **1** with iodosylbenzene catalysed by $Cl_8TPPFe(III)Cl$ **2** in aqueous SDS and CTAB micelles

Sl. No.	System* 1/PhIO/2	% Yield of products			
		Citral (**3**)	Geranic acid (**4**)	6,7-Epoxide (**5**)	2,3-Epoxide (**6**)
1	SDS micelles (*p*H 4.0)	4.0	56.0		
2	SDS micelles (*p*H 7.0)	2.0	48.0		
3	SDS micelles (*p*H 9.0)	2.0	43.0		
4	SDS micelles (*p*H 4.0)/NaCl		10.1	28.1	1.2
5	SDS micelles (*p*H 7.0)/NaCl		11.3	22.7	2.1
6	SDS micelles (*p*H 9.0)/NaCl		22.2	18.2	2.3
7	SDS micelles (*p*H 4.0)/NaBr			31.8	19.3
8	SDS micelles (*p*H 7.0)/NaBr			35.3	17.1
9	SDS micelles (*p*H 9.0)/NaBr			40.9	14.6
10	CTAB micelles (*p*H 4.0)	2.1	46.0	20.5	2.6
11	CTAB micelles (*p*H 7.0)	2.0	36.7	7.1	7.6
12	CTAB micelles (*p*H 9.0)	1.6	36.0	4.0	6.8

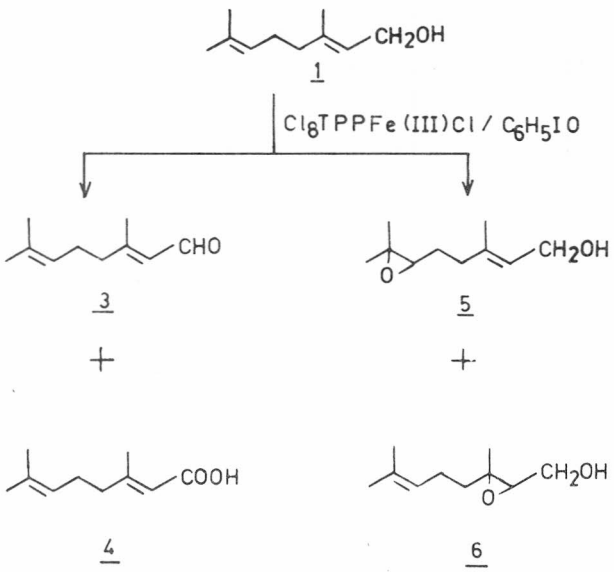
*Substrate-oxidant-catalyst = 100:10:1.

acetate buffer formed **3** and **4** i 4.0 and 56%, respectively. The yield of **4** decreased with the increase in *p*H of the aqueous bulk phase of SDS micelles (Table II).

The oxidation of **1** with iodosylbenzene catalysed by **2** in aqueous cationic CTAB micelles at *p*H 4.0 acetate buffer gave **4, 5** and **6** in 46.0, 20.5 and 2.6%, respectively. The yield of all the oxidation products decreased with the increase in *p*H of the aqueous bulk phase of CTAB micelles (Table II).

Discussion

The reaction of $Cl_8TPPFe(III)Cl$ **2** with iodosylbenzene and *m*-CPBA formed the high valent oxo-iron(IV) radical cations **7a-b**. The physicochemical studies of the high valent oxo-iron radical cations have contributed towards understanding the active site mechanism of heme isoenzymes and proteins[13,14]. The high valent oxo-iron (IV) radical cations **7a-b** abstract hydrogen atom from **1** to form the carbon radical **8** and form hydroxyiron(IV)porphyrin **9** (Scheme II). The recombination of carbon with hydroxyiron(IV)porphyrin **9** and subsequent dehydration form the corresponding citral **3**. The above hydrogen abstraction and recombination mechanism may be responsible for the formation of geranic acid **4** through the corre-



Scheme I

sponding aldehyde **3** from geraniol **1**. This type of oxidation of primary alcohol to aldehyde[12] and oxidation of aldehyde to acid[12] with monooxygen donors catalysed by TAPFe(III)Cl have been proposed by hydrogen abstraction and recombination mechanism. The formation of initial charge transfer complexes leading to radical cations **10** and **11** of 6,7- and 2,3-double bonds of geraniol and subsequent transfer of oxygen from **9** form the epoxides **5** and **6**, respectively[8,15]. It is interesting to note that regioselectivity of the epoxidation of 6,7- and 2,3-double bonds is opposite to Sharpless epoxidation[16]. This type of regioselective epoxidation of 6,7-double bond as compared to 2,3-double bond of nerol by high valent oxomanganese(IV) radical cations formed by the reaction of molecular oxygen and water soluble manganese(III)porphyrin reduced by reducing agent has been reported[17].

The micellar media affect the spin and oxidation states of metalloporphyrins[18-22] which are responsible for the change in reaction products in homogeneous and micellar media. The axial ligand of **2** changes from Cl to OH_2 and subsequently to OH depending on the *p*H of the SDS micelles (Scheme III). The formation of geranic acid in the oxidation of **1** with iodosylbenzene catalysed by **2** at different *p*H values may be explained by the change in the axial ligand of **2** in SDS micelles. This has been further confirmed by the addition of sodium chloride and sodium bromide to SDS micelles leading to change in the oxidation products of geraniol **1** (Table II). The formation of geranic acid **4** as well as epoxides **5** and **6** in CTAB micelles indicates the partial change of axial Cl of **2** by OH_2 or OH axial ligands leading to different oxidation products of geraniol. This kind of change in reactivity by the change of axial ligands in metalloporphyrins in micelles[23] and reverse micelles has been reported[24].

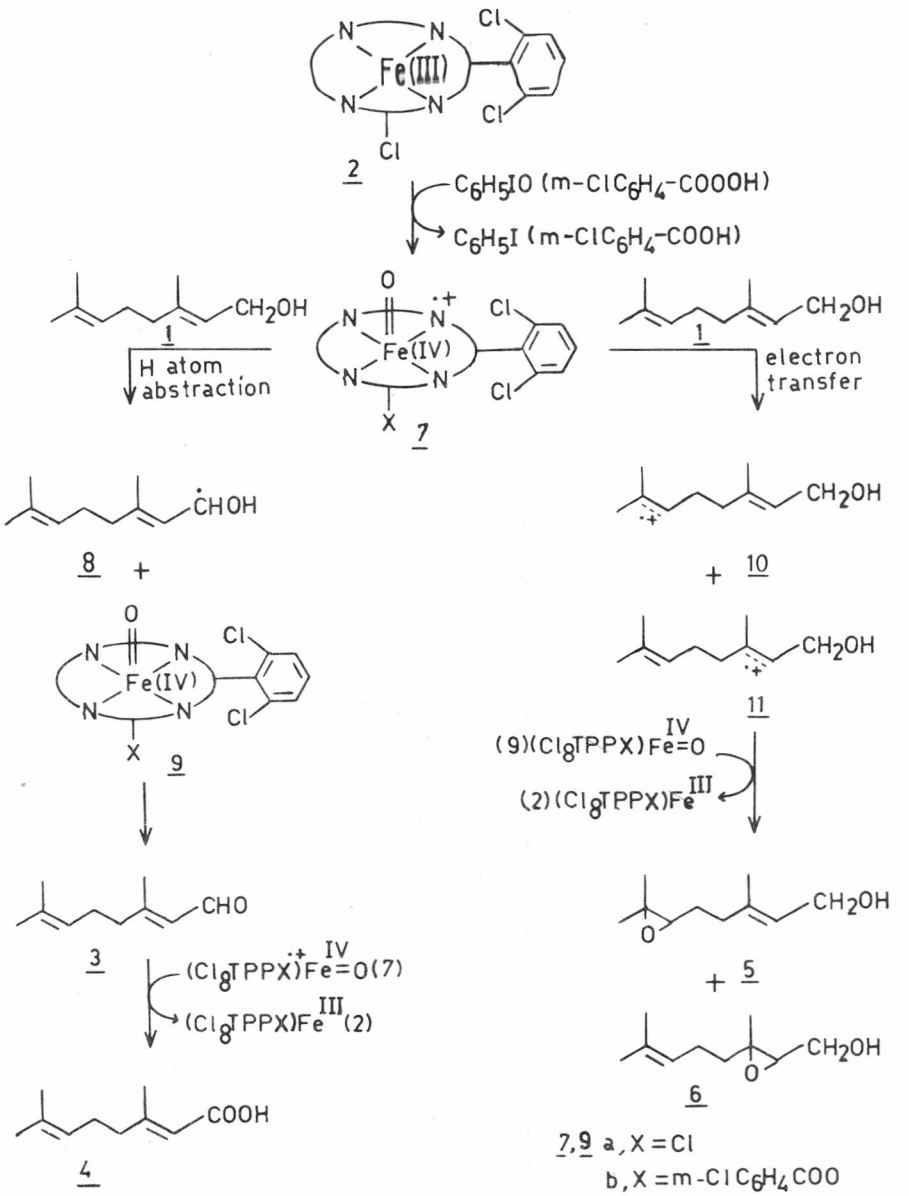
Thus, the oxidations of geraniol **1** with iodosylbenzene catalysed by $Cl_8TPPFe(III)Cl$ **2** in dichloromethane gives geranial **3** and geranic acid **4** as well as 6,7-epoxygeraniol **5** and 2,3-epoxygeraniol **6**. The reaction of **1** with iodosylbenzene catalysed by **2** in SDS micelles gives geranial **3** and geranic acid **4**, whereas the above reaction in CTAB micelles gives both the epoxides **5** and **6** with geranial **3** and geranic acid **4**. The use of a saturated solution of sodium chloride or sodium bromide in SDS micelles has changed the course of the reaction mechanism. The above selectivity in the oxidation of geraniol with iodosylbenzene catalysed by **2** in different reaction conditions may be extended in the biomimetic oxidation of other substrates by chemical models for cytochrome P450 in different reaction media.

Experimental Section

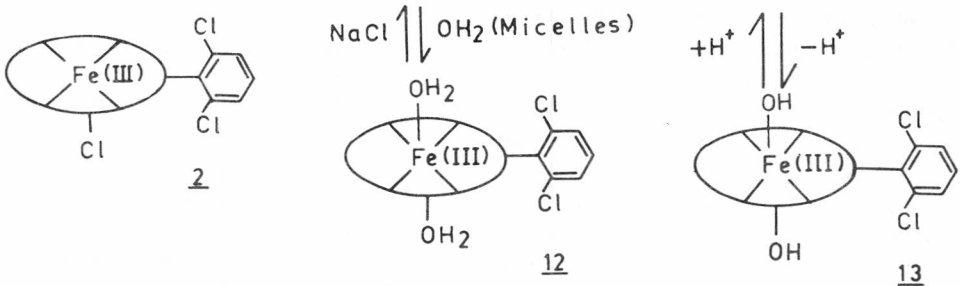
General. UV-Visible spectra were recorded on a Shimadzu UV-260 spectrophotometer (absorption maxima are expressed in nanometers). GC-MS recordings were made on a Jeol JMS DX 303 GC-MS spectrometer. CPSILS (50 m × 0.32 mm) column was used. Column temperature was 150-250°C and injection temperature was 250°C. HPLC was performed on a Waters Photo Diode Array Detector based binary gradient HPLC system with μ-Bondapak C18 (3.9 × 300 mm) column using acetonitrile-water (70:30) as eluent at a flow rate of 0.6 mL/min monitored at 235 nm.

Epoxidation of geraniol 1. A benzene solution (6 mL) of geraniol (0.62 mL, 3.51×10^{-3} mole) and *m*-chloroperlbenzoic acid (0.673 g, 3.9×10^{-3} mole) was stirred for 48 hr at room temperature. The solution was washed with saturated aq. Na_2SO_3, saturated aq. $NaHCO_3$ and saturated aq. NaCl, then dried on anhyd. Na_2SO_4. The benzene solution was separated by preparative TLC (silica gel) using chloroform as eluent. The epoxides were characterized by different spectroscopic techniques.

6,7-Epoxygeraniol 5. IR (film): 3400, 2985, 2920, 2860, 1450, 1360, 1240, 1320, 1120, 1060 and 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, C_{10}-H), 1.4-1.7 (m, 2H, C_5-H_2), 1.5 (s, 3H, C_8-H), 1.6 (s, 3H, C_9-H), 2.0 (m, 2H, C_4-H_2), 2.9 (dd, 1H, C_6-H), 3.5-3.6 (m, 2H, CH_2-OH), 5.2 (m, 1H, C_2-H); GC-MS (relative intensity): m/z 169 (M − I,



Scheme II



Scheme III

15%), 153 (M−I−O, 20), 139 (M−O−CH_3, 100), 124 (M−O−2×CH_3, 5) and 109 (M−O−3×CH_3, 30).

2,3-Epoxygeraniol 6. IR (film): 3400, 2980, 2850,1450, 1360, 1250, 1220, 1120, 1060 and 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H, C_8-H), 1.4-1.7 (m, 2H, 4-CH_2), 1.48 (s, 3H, C_9-H_3), 1.62 (s, 3H, C_{10}-H_3), 2.05 (m, 2H, C_5-H_2), 2.98 (m, 2H, C_2-H), 3.4-3.6 (m, 2H, CH_2-OH) and 5.1 (m, 1H, C_6-H); GC-MS (relative intensity): m/s 169 (M−1,15%), 153 (M−1−O, 20), 139 (M−O−CH_3, 100), 124 (M−O−2×CH_3, 5) and 109 (M−O−3×CH_3, 20).

Oxidation of geraniol 1 with iodosylbenzene catalysed by 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrinatoiron(III) chloride 2 in dichloromethane. Iodosylbenzene (11 mg, 0.05 mmole) was added to a stirred solution of geraniol **1** (89 μL, 0.5 mmole) and Cl_8TPPFe)Cl **2** (0.005 mmole) in dichloromethane (10 mL). The stirring was continued for additional 1 hr and the solvent removed under pressure. The residue was subjected to HPLC analysis for the identification of products. The results are presented in Table I.

Oxidation of geranial 3 with iodosylbenzene catalysed by 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrinatoiron(III) chloride 2 in dichloromethane. Iodosylbenzene (11 mg, 0.05 mmole) was added to a stirred solution of geranial **3** (88 μL, 0.5 mmole) and Cl_8TPPFe(III)Cl **2** (0.005 mmole) in dichloromethane (10 mL). The stirring was continued for additional 1hr and the solvent removed under pressure. The residue was subjected to HPLC analysis for the identification of products. The results are presented in Table I. Geranic acid was isolated by preparative TLC on silica gel using benzene-ethyl acetate (90:10) as eluent; UV (CH_3OH): 269.5 nm; GC-MS (relative intensity): m/z 167 (M−1, 25%), 149 (M−1−H_2O, 100), 137 (M−2×CH_3, 10), 124 (M−CO_2, 20), 109 (M−CO_2−CH_3, 12), 94 (M−CO_2−2×CH_3, 20), 81 (M−CO_2−3×CH_3, 20).

Oxidation of geraniol 1 with iodosylbenzene catalysed by Cl_8TPPFe(III)Cl 2 in SDS and CTAB micelles. Micellar solutions were prepared[25] by warming at 50°C a 5% solution of the SDS containing 0.1 mole dm^{-3} tetramethylammonium bromide or 5% solution of CTAB in an aqueous solution of appropriate *p*H. Solid sample of Cl_8TPPFe(III)Cl (0.1 mg, 0.0001 mmole) was dissolved in a minimum amount of acetone and added to the aqueous micelles (3 mL) and finally acetone was evaporated by warming the solution. Geraniol (1.8 μL, 0.01 mmole) was added to the above porphyrin incorporated micellar solution followed by iodosylbenzene (0.22 mg, 0.001 mmole) and the reaction mixture kept at room temperature for 1 hr. The solvent was removed and residue dissolved in a known amount of HPLC grade acetonitrile. The results are given in Table II.

Oxidation of geraniol 1 with iodosylbenzene catalysed by Cl_8TPPFe(III)Cl in the presence of sodium halides in SDS micelles. Solid sample of CL_8TPPFe(III)Cl (0.1 mg, 0.0001 mmole) was dissolved in a minimum amount of acetone and added to the aqueous micelles (3 μL), and finally acetone evaporated by warming the solution as above. A saturated solution (10 μL) of NaCl/NaBr was added to the above solution. Geraniol (1.8 μL, 0.01 mmole) was then added to the above micellar solution followed by iodosylbenzene (0.22 mg, 0.001 mmole). After 1 hr the reaction mixture was subjected to HPLC analysis. The results are given in Table II.

Acknowledgement

We are thankful to the Department of Science and Technology (DST), New Delhi, Department of Biotechnology (DBT) and University Grants Commission (UGC), New Delhi for financial assistance.

References

1 Nebert D W, Nelson D R, Coon M J, Estabrook R W, Feyeseisem R, Fujii-Kuriyama Y, Gonzalez F J, Guengerich F D, Gunsalus J C, Johnson E F, Loper J C, Sato R, Waterman M R & Waxman D J, *DNA Cell Biol*, 10, **1991**, 1.

2 Cohen M B, Schuler M A & Berenbaum M R, *Proc Natl Acad Sci USA*, 89, **1992**, 10920.

3 Nelson D R & Strobel H W, *Mol Biol Evol*, 4, **1987**, 572.

4 Gonzalez F J & Nebert D W, *Trends Genet*, 6, **1990**,182.

5 Mansuy D, *Pure Appl Chem*, 62, **1990**,741.

6 Anderson L A & Dawson J H, *Structure Bonding*, 74, **1990**, 1.

7 Meunier B, *Chem Rev*, 92, **1992**, 1411.

8 Chauhan S M S, *J Indian Chem Soc*, (in press).

9 Hamamura Y, Hayashiya K, Naito K, Matsuura K & Nishida J, *Nature*, 194, **1962**, 754.

10 Parkash Som, *Chemical and biomimetic studies of selected terpenoids and phenolics*, thesis submitted to the University of Delhi, April 1996.

11 Viyayarahavan V & Chauhan S M S, *Tetrahedron Letters*, 31, **1990**, 6223.

12 Chauhan S M S & Ray P C, *Bioorg Med Chem Letters*, 1, **1991**, 601.

13 Bill E,Ding X R, Trautwein A X, Winkler H, Mandon D,Weiss R, Gold A, Jayaraj K, Hatfield G E & Kirk M L, *Eur J Biochem*, 188, **1990**, 665.

14 Jayaraj K, Terner J, Gold A, Roberts D A, Austin R N, Mandon D, Weiss R, Bill E, Muther M & Trautwein A X, *Inorg Chem*, 35, **1996**, 1632.

15 Ostovic D & Bruice T C, *J Am Chem Soc*, 111, **1989**, 6511.

16 Sharpless K B & Michaelson R C, *J Am Chem Soc*, 95, **1973**, 6136.

17 Tabushi I & Kodera M, *J Am Chem Soc*, 108, **1987**, 1101.
18 Mazumdar S, Medhi O K & Mitra S,*Inorg Chem*, 27,**1988**, 2541.
19 Mazumdar S, Medhi O K & Mitra S, *J Chem Soc Dalton Trans*, 1990, 1057.
20 Medhi O K, Mazumdar S & Mitra S, *Inorg Chem*, 28,**1989**, 3243.
21 Mazumdar S & Medhi O K, *J Chem Soc Dalton Trans*, **1990**, 2663.
22 Mazumdar S, Medhi O K, Kannadaguli N & Mitra S, *J Chem Soc Dalton Trans*, **1989**, 1003.
23 Kojo S & Sano S, *J Chem Soc Perkin Trans-I*, **1981**, 2864.
24 Chauhan S M S, Mahopatra P P, Kalra B, Kohli T S & Satapathy S, *J Mol Cat A: Chemical* (in press).
25 Simplicio J, Schwenzer K & Maenpa F, *J Am Chem Soc*, 97, **1975**, 7319.