

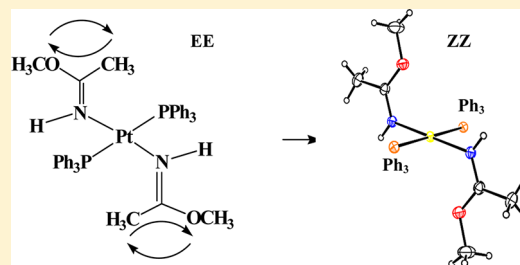
Isomerization of Platinum-Coordinated Iminoethers Induced by Spectator Ligands: Stabilization of the Z anti Configuration

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S Supporting Information

ABSTRACT: Iminoether derivatives of the formula $trans-[PtCl_2\{HN=C(R)OR'\}_2]$ proved to be endowed with remarkable antitumor activity in vivo. Moreover, these trans compounds were more cytotoxic than their cis congeners, a trend opposite to that generally observed for corresponding platinum complexes with amines. The imino ligands can have either *E* or *Z* configuration about the C=N double bond, and in the case of $R = R' = Me$, the *E* configuration is by far thermodynamically preferred. However, substitution of chloride anions with neutral ligands (*L*) alters the relative stability of the *E* and *Z* isomers. Upon investigation of the derivatives with $L = PPh_3$, $AsPh_3$, $Me_2S=O$, and $(H_2N)_2C=S$, it has been concluded that an electrostatic interaction between the oxygen lone pair of the iminoether and the platinum center, fostered by the net positive charge of the complex and the low dielectric constant around the metal core provided by the hydrophobic *L* ligands, stabilizes the *Z* configuration. The same factors can favor iminoether isomerization. These conclusions are fully supported by X-ray crystal data. In the case of a reaction with thiourea, an aminic group of thiourea can substitute the methoxy group of a *cis*-iminoether, leading to the formation of a cyclic compound in a process reminiscent of the McLafferty rearrangement. Such a rearrangement could play a role in the interaction of the platinum–iminoether compounds with target DNA and proteins.



■ INTRODUCTION

The antitumor activity of *cis*-diamminedichloridoplatinum(II) (*cis*-DDP), a drug used worldwide, is limited by side effects and acquired or intrinsic resistance of several types of tumors.^{1,2}

Because the trans isomer of *cis*-DDP is clinically ineffective, initially it was assumed that only compounds with *cis* geometry could have a therapeutic effect. However, over the years, several platinum compounds with trans geometry have been tested and found to exhibit remarkable antitumor activities, sometimes comparable to or even greater than that of *cis*-DDP.^{3,4}

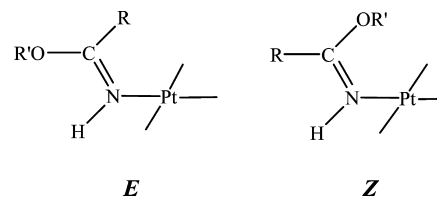
Of particular interest are the iminoether derivatives, analogous to *trans*-DDP, having the formula $trans-[PtCl_2\{HN=C(R)OR'\}_2]$, which have been shown to be endowed with remarkable antitumor activity in vivo.^{4–6} Moreover, these trans compounds were more cytotoxic than their cis congeners.^{4,7,8}

Iminoether complexes are generally prepared from related platinum nitrile complexes by reaction with an alcohol under basic condition, the configuration of the azomethine double bond can be *E* or *Z*, depending upon the relative position of the alkoxy group and the N-bonded Pt residue with respect to the C=N double bond (trans and cis for *E* and *Z* isomers, respectively, Scheme 1).⁹

The configuration of the iminoether ligand(s) can modulate the antitumor potential of the platinum complex and sometime species with the *Z* configuration resulted to be more active than those with the *E* configuration.^{8,10}

The *Z* isomer is always kinetically favored (trans addition of the alcohol to the nitrile triple bond), whereas the

Scheme 1. Sketches of the *E* and *Z* Configurations of Iminoether Ligand



thermodynamic stability of the planar iminoether ligand depends upon the steric interaction between cis substituents at the C=N double bond, the more sterically demanding substituent at the carbon atom (OR' or R) being better accommodated in position trans to the N-bound platinum moiety. Therefore, with constant OR' ($O-Me$), when $R = Me$, the *E* configuration is thermodynamically preferred, whereas when $R = t-Bu$, the *Z* configuration is preferred.¹¹

In this paper, we report an investigation showing how, in complexes of the type $trans-[PtCl_{2-x}\{(E)-HN=C(Me)-OMe\}_2(L)_x]Y_x$ ($L = PPh_3$, $AsPh_3$, $DMSO$, thiourea; $Y = Cl^-$, ClO_4^- , BF_4^- ; $x = 1, 2$), the stability of the iminoether configuration (*E* or *Z*) can be modulated by the cis ligands and the rate of isomerization is influenced by the nature of the counteranion. Moreover, in the case of reaction with thiourea, an aminic group of thiourea substitutes the methoxy group of a

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cis-iminoether, leading to formation of a cyclic compound in a process reminiscent of the McLafferty rearrangement.¹² The latter reaction could play a role also in the interaction of the drug with target DNA.

EXPERIMENTAL SECTION

Starting Materials. The complex *trans*-[PtCl₂((*E*)-HN=C(Me)-OMe)₂] was prepared by a published procedure.¹³ Commercial reagent grade chemicals were used without further purification.

Physical Measurements. C, H, and N analyses were carried out on a Carlo Erba Model 1106 CHN Elemental Analyzer. IR spectra were recorded on a Perkin-Elmer 283 spectrophotometer. NMR spectra were recorded with a Bruker Avance 300 UltraShield spectrometer, frequencies being referenced to external Me₄Si (¹H and ¹³C), 85% H₃PO₄ (³¹P), and H₂PtCl₆ (¹⁹⁵Pt).

Because all compounds investigated have *trans* configurations, in the abbreviation used to identify a complex we will omit the prefix *trans* and indicate the configuration of the iminoether ligands (*E* or *Z*) followed by the letter code *ime*. For example, *trans*-[PtCl₂((*E*)-HN=C(Me)OMe)₂] will be abbreviated [PtCl₂((*E*)-*ime*)₂].

Synthesis of *trans*-[PtCl((*E*)-HN=C(Me)OMe)₂(PPh₃)₂]Cl, [PtCl((*E*)-*ime*)₂(PPh₃)₂]Cl. [PtCl₂((*E*)-*ime*)₂] (100 mg, 0.24 mmol) was suspended in Et₂O (5 mL) and treated with PPh₃ (73.4 mg, 0.29 mmol). The yellow suspension was stirred overnight at room temperature, and meanwhile it turned white. The white solid ([PtCl((*E*)-*ime*)₂(PPh₃)₂]Cl) was filtered off, washed with Et₂O (3 × 5 mL), and dried under vacuum. Yield: 159.9 mg (98%). Anal. Calcd for C₂₄H₂₉Cl₂N₂O₂PtP₂H₂O: C, 40.57; H, 4.68; N, 3.94%. Found: C, 40.42; H, 4.48; N, 3.89%. ESI-MS, exact mass for C₂₄H₂₉Cl₂N₂O₂PtP₂: 638.1. Measured *m/z*: 638.1 Da [M]⁺. ¹H NMR (D₂O, δ, 295 K, 300 MHz): 2.25 (s, 6H, C—CH₃), 3.44 (s, 6H, O—CH₃), 7.57 (ddd, 6H, PPh₃ *meta* H, ³J_{H,H(ortho)} = 7.8 Hz, ³J_{H,H(para)} = 7.6 Hz, ⁴J_{H,P} = 2.7 Hz), 7.66 (ddd, 3H, PPh₃ *para* H, ³J_{H,H(meta)} = 7.6 Hz, ⁴J_{H,H(ortho)} = 1.3 Hz, ⁵J_{H,P} = 6.4 Hz), 7.79 (ddd, 6H, PPh₃ *ortho* H, ³J_{H,H(meta)} = 7.8 Hz, ⁴J_{H,H(para)} = 1.3 Hz, ⁵J_{H,P} = 12.2 Hz). ¹³C NMR (D₂O, δ, 295 K, 75 MHz) (associated via 2D-¹H, ¹³C HMQC, and HMBC NMR): 21.5 (C—CH₃), 55.5 (O—CH₃), 128.8 (PPh₃ *meta* C), 132.1 (PPh₃ *para* C), 134.0 (PPh₃ *ortho* C), 174.0 (C=N). ³¹P{¹H} NMR (D₂O, δ, 295 K, 121.5 MHz): 2.47 (s with ¹⁹⁵Pt satellites, ¹J_{P-Pt} = 3960 Hz). ¹⁹⁵Pt{¹H} NMR (D₂O, δ, 295 K, 64 MHz): −3455 (d, ¹J_{P-Pt} = 3960 Hz).

***trans*-[PtCl((*E*)-HN=C(Me)OMe)₂(PPh₃)₂](ClO₄), [PtCl((*E*)-*ime*)₂(PPh₃)₂](ClO₄).** Addition of [PtCl((*E*)-*ime*)₂(PPh₃)₂]Cl (50 mg, 0.074 mmol) to a water solution of HClO₄ (pH = 3) caused the immediate precipitation of a white solid, which was collected by filtration of the mother liquor, washed with H₂O until pH = 7, and dried under vacuum. Yield: 54.5 mg (98%). Anal. Calcd for C₂₄H₂₉Cl₂N₂O₆PtP₂: C, 39.04; H, 3.96; N, 3.79%. Found: C, 39.50; H, 3.91; N, 3.32%. The complex, insoluble in water, dissolved in CH₂Cl₂ and CHCl₃ and was slightly soluble also in acetone. ¹H NMR (CDCl₃, δ, 295 K, 300 MHz): 2.27 (s, 6H, C—CH₃), 3.38 (s, 6H, O—CH₃), 6.55 (s, br, 2H, NH), 7.57 (m, 9H, PPh₃ *meta* + *para* H), 7.77 (m, 6H, PPh₃ *ortho* H). ¹³C NMR (CDCl₃, δ, 295 K, 75 MHz) (from 2D-¹H, ¹³C HMQC, and HMBC NMR): 22.1 (C—CH₃), 55.2 (O—CH₃), 130.9 (PPh₃ *meta* + *para* C), 134.4 (PPh₃ *ortho* C), 173.4 (C=N). ³¹P{¹H} NMR (CDCl₃, δ, 295 K, 121.5 MHz): 3.9 (s with ¹⁹⁵Pt satellites, ¹J_{P-Pt} = 3795 Hz).

***trans*-[PtCl((*E*)-HN=C(Me)OMe)₂(AsPh₃)₂]Cl, [PtCl((*E*)-*ime*)₂(AsPh₃)₂]Cl.** A chloroform solution (5 mL) of [PtCl₂((*E*)-*ime*)₂] (120 mg, 0.29 mmol) was treated with an excess of AsPh₃ (150 mg, 0.49 mmol) and stirred at room temperature for 20 min. The solution was evaporated to dryness, and the obtained white solid was washed with Et₂O (3 × 5 mL) and dried under vacuum. Yield: 184.5 mg (89%). Anal. Calcd for C₂₄H₂₉AsCl₂N₂O₂Pt: C, 40.12; H, 4.07; N, 3.90%. Found: C, 39.88; H, 4.06; N, 3.92%. ESI-MS, exact mass for C₂₄H₂₉AsCl₂N₂O₂Pt: 682.9. Measured *m/z*: 682.9 Da [M]⁺. The NMR characterization was carried out in D₂O because in CDCl₃ this complex is stable only in the presence of excess AsPh₃, whereas in the absence of free AsPh₃ partial displacement of AsPh₃ by Cl[−] takes place.

¹H NMR (D₂O, δ, 295 K, pH = 3): 2.23 (s, 6H, C—CH₃), 3.39 (s, 6H, O—CH₃), 7.58–7.77 (m, 15H, AsPh₃ *ortho* + *meta* + *para* H). ¹⁹⁵Pt{¹H} NMR (D₂O, δ, 295 K, 64 MHz): −3230 (s).

***trans*-[PtCl((*E*)-HN=C(Me)OMe)₂(DMSO)](NO₃), [PtCl((*E*)-*ime*)₂(DMSO)](NO₃).** A solution of *trans*-[PtCl(NO₃)((*E*)-HN=C(Me)OMe)₂] (50 mg, 0.11 mmol) in water (5 mL) was treated with an excess of DMSO (86 mg, 1.1 mmol) and stirred at room temperature for 30 min. The colorless solution was evaporated to dryness, and the obtained white solid was washed with Et₂O (3 × 5 mL) and dried under vacuum. Yield: 57.1 mg (97%). Anal. Calcd for C₈H₂₀Cl₂N₂O₃PtS: C, 19.60; H, 4.11; N, 5.71%. Found: C, 19.66; H, 4.05; N, 5.58%. ESI-MS, exact mass for C₈H₂₀Cl₂N₂O₃PtS: 454.9. Measured *m/z*: 455.0 Da [M]⁺. ¹H NMR (D₂O, δ, 295 K, 300 MHz): 2.54 (s, 6H, C—CH₃), 3.46 (s, 6H, S—CH₃), 3.91 (s, 6H, O—CH₃). ¹³C NMR (D₂O, δ, 295 K, 75 MHz, 2D-¹H, ¹³C HMQC, and HMBC): 28.0 (C—CH₃), 43.3 (S—CH₃), 55.9 (O—CH₃), 175.5 (C=N). ¹⁹⁵Pt{¹H} NMR (D₂O, δ, 295 K, 64 MHz): −3000 (s).

***trans*-[Pt((*E*)-HN=C(Me)OMe)₂(thiourea)₂]Cl₂, [Pt((*E*)-*ime*)₂(thiourea)₂]Cl₂.** A chloroform solution (5 mL) of [PtCl₂((*E*)-*ime*)₂] (100 mg, 0.24 mmol) was treated with a small excess of thiourea (38.0 mg, 0.50 mmol), and the mixture was stirred at room temperature for 4 h; meanwhile, the yellow solution turned into a white suspension. The white solid ([Pt((*E*)-*ime*)₂(thiourea)₂]Cl₂) was filtered off, washed with Et₂O (3 × 5 mL) and with a small amount of cold chloroform (1 mL), and dried under vacuum. Yield: 130.0 mg (99%). Anal. Calcd for C₈H₂₂Cl₂N₆O₂PtS₂·H₂O: C, 16.50; H, 4.15; N, 14.43%. Found: C, 15.93; H, 3.92; N, 14.69%. ESI-MS, exact mass for C₈H₂₂N₆O₂PtS₂: 493.1. Measured *m/z*: 460.0 Da corresponding to [M − CH₃OH]⁺ formed via McLafferty's type rearrangement. The NMR characterization of this compound was carried out in CD₂Cl₂. ¹H NMR (CD₂Cl₂, δ, 295 K, 300 MHz): 2.61 (s, 6H, C—CH₃), 3.99 (s, 6H, O—CH₃), 7.08 (s, br, 2H, NH), 7.34 (s, br, 8H, S(NH₂)₂). ¹³C NMR (CD₂Cl₂, δ, 295 K, 75 MHz, 2D-¹H, ¹³C-HMQC, and HMBC): 21.5 (C—CH₃), 54.7 (O—CH₃), 173.4 (C=N). ¹⁹⁵Pt{¹H} NMR (D₂O, δ, 295 K, 64 MHz): −3111 (s).

***trans*-[Pt((*E*)-HN=C(Me)OMe)₂(PPh₃)₂]Cl₂, [Pt((*E*)-*ime*)₂(PPh₃)₂]Cl₂.** A chloroform solution (5 mL) of [PtCl₂((*E*)-*ime*)₂] (100 mg, 0.24 mmol) was treated with PPh₃ (125.9 mg, 0.48 mmol) and stirred at room temperature for 10 min. The solution was evaporated to dryness and the obtained white solid was washed with Et₂O (3 × 5 mL) and dried under vacuum. Yield: 213.6 mg (95%). Anal. Calcd for C₄₂H₄₄Cl₂N₂O₂Pt₂H₂O: C, 52.84; H, 4.86; N, 2.93%. Found: C, 52.97; H, 4.71; N, 2.71%. ESI-MS, exact mass for C₄₂H₄₄N₂O₂Pt₂: 865.8. Measured *m/z*: 864.9 Da [M − H]⁺. ¹H NMR (CDCl₃, δ, 295 K, 300 MHz): 1.34 (s, 6H, C—CH₃), 3.31 (s, 6H, O—CH₃), 7.50 (m, 9H, PPh₃ *meta* + *para* H), 8.08 (ddd, 6H, PPh₃ *ortho* H, ³J_{H,H(meta)} = 5.9 Hz, ⁴J_{H,H(para)} = 1.5 Hz, ⁵J_{H,P} = 11.6 Hz), 9.18 (s, br, 2H, NH). ¹³C NMR (CDCl₃, δ, 295 K, 75 MHz, 2D-¹H, ¹³C-HMQC, and HMBC): 22.5 (C—CH₃), 57.8 (O—CH₃), 129.0 (PPh₃ *meta* C), 131.4 (PPh₃ *para* C), 135.2 (PPh₃ *ortho* C), 172.0 (C=N). ³¹P{¹H} NMR (CDCl₃, δ, 295 K, 121.5 MHz): 12.8 (s with ¹⁹⁵Pt satellites, ¹J_{P-Pt} = 2598 Hz).

***trans*-[Pt((*Z*)-HN=C(Me)OMe)₂(PPh₃)₂]Cl₂, [Pt((*Z*)-*ime*)₂(PPh₃)₂]Cl₂.** Under the conditions of the previous preparation, if the reaction is not stopped 10 min after mixing of the reactants by evaporation of the solvent but left standing at room temperature, the initially formed [Pt((*E*)-*ime*)₂(PPh₃)₂]Cl₂ isomerizes to the *EZ* and *ZZ* forms. The latter form, [Pt((*Z*)-*ime*)₂(PPh₃)₂]Cl₂, is sparingly soluble in chloroform and precipitates in a crystalline form.

***trans*-[Pt((*E*)-HN=C(Me)OMe)₂(PPh₃)₂](BF₄)₂, [Pt((*E*)-*ime*)₂(PPh₃)₂](BF₄)₂.** Addition of [Pt((*E*)-*ime*)₂(PPh₃)₂]Cl₂ (50 mg, 0.053 mmol) to a water solution of HBF₄ (pH = 3) caused the immediate precipitation of a white solid. This was collected by filtration of the mother liquor, washed with H₂O until pH = 7, and dried under vacuum. Yield: 54.9 mg (98%). Anal. Calcd for C₄₂H₄₄B₂F₈N₂O₂Pt₂: C, 48.53; H, 4.27; N, 2.70%. Found: C, 48.07; H, 4.24; N, 2.66%. The complex, insoluble in chloroform and water, dissolves in CH₂Cl₂. ¹H NMR (CD₂Cl₂, δ, 295 K, 300 MHz): 1.27 (s, 6H, C—CH₃), 2.88 (s, 6H, O—CH₃), 6.95 (s, br, 2H, NH), 7.58–7.98 (m, 30H, PPh₃ *ortho* + *meta* + *para* H). ¹³C NMR (CD₂Cl₂,

δ , 295 K, 75 MHz, $2D\text{-}^1\text{H}$, ^{13}C HMQC, and HMBC): 21.7 (C—CH₃), 55.6 (O—CH₃), 129.7 (PPh₃ *meta* C), 132.1 (PPh₃ *para* C), 134.4 (PPh₃ *ortho* C), 174.0 (C=N). $^{31}\text{P}\{^1\text{H}\}$ NMR (CD_2Cl_2 , δ , 295 K, 121.5 MHz): 13.5 (s with ^{195}Pt satellites, $^1J_{\text{P-Pt}} = 2488$ Hz).

X-ray Crystallography. A selected crystal of *trans*-[Pt{(Z)-HN=C(Me)OMe}₂(PPh₃)₂]Cl₂, [Pt{(Z)-ime)₂(PPh₃)₂]Cl₂, was mounted on a Bruker AXS X8 APEX CCD system equipped with a four-circle Kappa goniometer and a 4K CCD detector (radiation Mo K α). For data reduction and unit cell refinement, the SAINT-IRIX package was employed.¹⁴ A total of 13 286 reflections ($\Theta_{\text{max}} = 36.35^\circ$) were collected, indexed, integrated, and corrected for Lorentz, polarization, and absorption effects using the program SADABS.¹⁵

The compound [Pt{(Z)-ime)₂(PPh₃)₂]Cl₂, which crystallizes from CHCl₃, incorporates three disordered molecules of solvent per molecule of compound ([Pt{(Z)-ime)₂(PPh₃)₂]Cl₂·3CHCl₃). The unit cell dimensions were calculated from all reflections, and the structure was solved using direct methods technique in the $P\bar{1}$ space group. The model was refined by full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. Two bond lengths in a phenyl ring were restrained to be equal (SADI in SHELXL). All hydrogen atoms were placed at calculated positions and refined given isotropic parameters equivalent to 1.5 (methyl groups) or 1.2 (other groups) times those of the atom to which they were attached.

All atoms, except platinum and the coordinating nitrogens and phosphorus, are arranged in two different sets of coordinates (the two sets labeled “a” and “b”) each one having an occupancy factor of 0.5. For the iminoether ligands, the disorder corresponds to 180° rotation around the Pt—N bond. Adjacent molecules cannot be both “a” or both “b” because this would lead to some very short intermolecular distances such as (C23b...C23b($x + 1$, $-y + 1$, $-z + 2$) = 2.46(1) Å, C16b...C17b($-x - 1$, $-y$, $-z + 2$) = 2.98(1) Å, and H16b...H17b($-x - 1$, $-y$, $-z + 2$) = 1.81 Å).

All calculations and molecular graphics were carried out using SIR2004,¹⁶ SHELXL97,¹⁷ PARST97,¹⁸ WinGX,¹⁹ and ORTEP-3 for Windows packages.²⁰ Details of the crystal data are listed in Table 1. Selected bond lengths and angles are listed in Table 2.

Because there are disordered solvent molecules of crystallization, the PLATON software²¹ was used to assess the solvent-accessible volume (25.2%), then the “SQUEEZE” method, as implemented in PLATON,²² was used to subtract from the observed data the contribution to the diffraction pattern of the solvent molecules (located in the voids of the lattice channels), and the modified F_o^2 was written to a new HKL file. The PLATON SQUEEZE procedure evaluated that the contribution of the solvent molecules to the unit cell was equivalent to 183 e[−], these were assigned to three molecules of chloroform. Therefore, three chloroform molecules are included in the formula, formula weight, calculated density, μ , and $F(000)$.

RESULTS

While investigating the reaction of *trans*-[PtCl₂{(E)-HN=C(Me)OMe}₂] with guanine bases, we observed that, although starting from the pure *E* isomer ([PtCl₂{(E)-ime)₂]), with time, partial *E* → *Z* isomerization of the iminoether ligands took place. Such an isomerization does not take place as long as the chlorides are retained in the platinum-coordination shell. To unravel the effect of ancillary ligands upon the thermodynamic stability of the iminoether configuration, we have undertaken a systematic investigation in which the chlorido ligands have been replaced by neutral ligands chosen among those most frequently used in coordination chemistry such as PPh₃, AsPh₃, DMSO, and thiourea.

Reaction of *trans*-[PtCl₂{(E)-HN=C(Me)OMe}₂] ([PtCl₂{(E)-ime)₂]) with PPh₃. Performing the reaction of [PtCl₂{(E)-ime)₂] with excess PPh₃ in Et₂O, only the monosubstituted complex *trans*-[PtCl{(E)-HN=C(Me)OMe}₂(PPh₃)]Cl, [PtCl{(E)-ime)₂(PPh₃)]Cl, which precipitates from solution, is formed in quantitative yield. The

Table 1. Crystal Data and Structure Refinement Parameters for [Pt{(Z)-ime)₂(PPh₃)₂]Cl₂·3CHCl₃

empirical formula	C ₄₅ H ₄₇ Cl ₁₁ N ₂ O ₂ P ₂ Pt
formula weight	1294.81
wavelength (Å)	0.71073
crystal system	triclinic
space group	$P\bar{1}$
<i>a</i> (Å)	9.5619(1)
<i>b</i> (Å)	11.8213(2)
<i>c</i> (Å)	13.9609(2)
α (deg)	102.679(1)
β (deg)	113.885(1)
γ (deg)	96.269(1)
volume (Å ³)	1372.59(3)
<i>Z</i>	1
density (calculated) (Mg/m ³)	1.566
absorption coefficient (mm ^{−1})	3.186
$F(000)$	642
crystal size (mm ³)	0.45 × 0.36 × 0.135
Θ range for data collection	1.67–36.35°
index ranges	−15 ≤ <i>h</i> ≤ 15, −19 ≤ <i>k</i> ≤ 19, −23 ≤ <i>l</i> ≤ 23
reflections collected	36675
independent reflections	13286 [$R(\text{int}) = 0.0441$]
data/restraints/parameters	13286/1/399
goodness-of-fit on F^2	1.073
final <i>R</i> indices [$I > 2\sigma(I)$]	$R_1 = 0.0399$, $wR_2 = 0.0950$
<i>R</i> indices (all data)	$R_1 = 0.0418$, $wR_2 = 0.0962$
largest diff peak and hole (e [−] Å ^{−3})	+2.574 and −0.961

Table 2. Selected Bond Lengths (Å) and Angles (deg) for [Pt{(Z)-ime)₂(PPh₃)₂]Cl₂

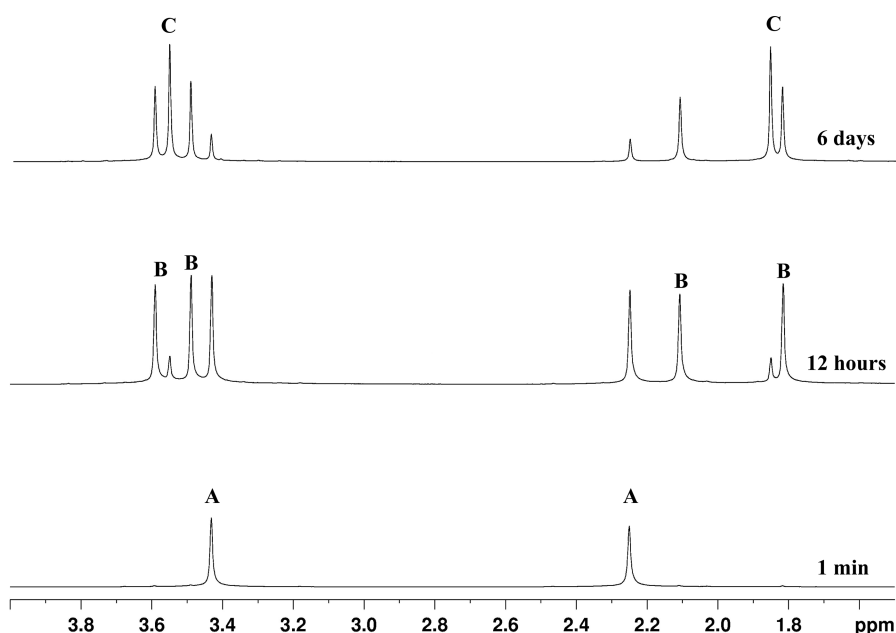
Pt1—P1	2.3265(6)	N1#—Pt1—N1 ^a	180.00(1)
Pt1—N1	2.021(2)	N1#—Pt1—P1 ^a	87.93(7)
P1—C13	1.802(3)	N1—Pt1—P1	92.07(7)
P1—C1	1.803(3)	P1—Pt1—P1 ^a	180.00(1)
P1—C7	1.811(3)	C21a—N1—Pt1	123.0(3)
N1—C21a	1.297(6)	C21b—N1—Pt1	121.9(3)
N1—C21b	1.288(6)	C21a—O1a—C23a	121.9(7)
O1a—C21a	1.316(8)	N1—C21a—O1a	117.4(5)
O1a—C23a	1.434(10)	N1—C21a—C22a	121.6(6)
C21a—C22a	1.497(9)	O1a—C21a—C22a	121.0(6)
O1b—C21b	1.333(7)	C21b—O1b—C23b	121.2(6)
O1b—C23b	1.433(8)	N1—C21b—O1b	117.9(5)
C21b—C22b	1.490(9)	N1—C21b—C22b	122.0(5)
		O1b—C21b—C22b	120.0(6)

^aSymmetry transformations used to generate equivalent atoms: # $-x$, $-y + 1$, $-z + 2$.

displacement of a chlorido ligand is in accord with the greater lability of *trans*-chlorides, as compared to *trans*-N-donor iminoethers.¹¹ The ^1H NMR signals (Table 3) indicate a downfield shift of the N—H and an upfield shift of the C—Me and O—Me protons, with respect to the corresponding signals in the starting [PtCl₂{(E)-ime)₂] substrate. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum (D_2O solution) shows a singlet flanked by ^{195}Pt satellites (2.47 ppm, $^1J_{\text{P-Pt}} = 3960$ Hz), whereas the $^{195}\text{Pt}\{^1\text{H}\}$ NMR spectrum (D_2O solution), shows a doublet (−3455 ppm, $^1J_{\text{P-Pt}} = 3960$ Hz).

Table 3. Proton Chemical Shifts (δ , Downfield from Me₄Si) of the Complexes in CDCl₃^a

compound		NH	O–CH ₃	C–CH ₃
<i>trans</i> -[PtCl ₂ {(<i>E</i>)-HN=C(Me)OMe} ₂]	[PtCl ₂ ((<i>E</i>)-ime) ₂]	7.72	3.76	2.64
<i>trans</i> -[PtCl{(E)-HN=C(Me)OMe} ₂ (PPh ₃)]Cl	[PtCl((<i>E</i>)-ime) ₂ (PPh ₃)]Cl	7.94	3.46	2.20
<i>trans</i> -[PtCl{(E)-HN=C(Me)OMe} ₂ (PPh ₃)](ClO ₄)	[PtCl((<i>E</i>)-ime) ₂ (PPh ₃)](ClO ₄)	6.55	3.36	2.30
<i>trans</i> -[Pt{(E)-HN=C(Me)OMe} ₂ (PPh ₃) ₂]Cl ₂	[Pt((<i>E</i>)-ime) ₂ (PPh ₃) ₂]Cl ₂	9.18	3.31	1.34
<i>trans</i> -[Pt{(E)-HN=C(Me)OMe} ₂ (PPh ₃) ₂](BF ₄) ₂ *	[Pt((<i>E</i>)-ime) ₂ (PPh ₃) ₂](BF ₄) ₂ *	6.95	3.13	1.27
<i>trans</i> -[PtCl ₂ {(<i>Z</i>)-HN=C(Me)OMe} ₂]	[PtCl ₂ ((<i>Z</i>)-ime) ₂]			
<i>trans</i> -[PtCl{(Z)-HN=C(Me)OMe} ₂ (PPh ₃)]Cl	[PtCl((<i>Z</i>)-ime) ₂ (PPh ₃)]Cl	8.98	3.54	2.10
<i>trans</i> -[PtCl{(Z)-HN=C(Me)OMe} ₂ (PPh ₃)](ClO ₄)	[PtCl((<i>Z</i>)-ime) ₂ (PPh ₃)](ClO ₄)	7.70	3.62	2.15
<i>trans</i> -[Pt{(Z)-HN=C(Me)OMe} ₂ (PPh ₃) ₂]Cl ₂	[Pt((<i>Z</i>)-ime) ₂ (PPh ₃) ₂]Cl ₂	10.90	2.88	1.51
<i>trans</i> -[Pt{(Z)-HN=C(Me)OMe} ₂ (PPh ₃) ₂](BF ₄) ₂ **	[Pt((<i>Z</i>)-ime) ₂ (PPh ₃) ₂](BF ₄) ₂ **	8.53	3.44	1.45

^a(* solvent CD₂Cl₂, ** solvent acetone-*d*₆).**Figure 1.** ¹H NMR spectra taken at various times for [PtCl((*E*)-ime)₂(PPh₃)]Cl dissolved in D₂O at 295 K and pH 6.5. Isomers: [PtCl((*E*)-ime)₂(PPh₃)]Cl (A), [PtCl((*E*)-ime)((*Z*)-ime)(PPh₃)]Cl (B), [PtCl((*Z*)-ime)₂(PPh₃)]Cl (C).

Although the [PtCl₂((*E*)-ime)₂] complex is very stable in solution, the phosphine-substituted complex [PtCl((*E*)-ime)₂(PPh₃)]Cl undergoes isomerization.⁵

In D₂O solution (pH = 6.5; Figure 1), the initial *EE* isomer (A) (peaks at 2.25 (C–Me) and 3.44 (O–Me) ppm), gradually converts to the *EZ* isomer (B) (peaks at 1.82 and 2.11 (C–Me) ppm and at 3.49 and 3.59 (O–Me) ppm), which, in turn, converts to the *ZZ* isomer (C) (peaks at 1.85 (C–Me) and 3.55 (O–Me) ppm). The equilibrium composition is reached in ca. 6 days and contains the three isomers (*EE*, *EZ*, and *ZZ*) in 0.2:1:1 ratios.

Because a downfield shift is expected for protons that come closer to platinum,^{23,24} upon conversion from the *E* to the *Z* configuration, the C–Me signal shifts upfield whereas the O–Me signal shifts downfield. The shift is greater (twice as much) for the C–Me protons, which are stereochemically more rigid than the O–Me protons.

It can be observed how the *E* to *Z* conversion of each iminoether ligand causes an upfield shift (shielding) of the platinum resonance of about 16 ppm (Figure S1, Supporting Information). Also, the Pt–P coupling constant increases upon moving from the *EE* to the *EZ* isomer (ΔJ = 100 Hz) and from the *EZ* to the *ZZ* form (ΔJ = 135 Hz), paralleling the upfield

shift of the ¹⁹⁵Pt resonance. Less important are the changes in ³¹P chemical shifts (Figure S2, Supporting Information). A small downfield shift is observed only on passing from the *EE* (2.5 ppm) to the *EZ* isomer (2.8 ppm) whereas the *ZZ* isomer is isochronous with the *EZ* form.

The *E/Z* isomerization of the iminoether ligands, which was quite slow in D₂O (pH 6.5), became much faster in acetone. Therefore, [PtCl((*E*)-ime)₂(PPh₃)]Cl, dissolved in acetone-*d*₆, undergoes fast isomerization (5 min) with formation of a white precipitate of pure *ZZ*. The *ZZ* isomer was filtered off and fully characterized by ¹H and ³¹P{¹H} NMR spectra.

Having at our disposal the pure *ZZ* isomer, we wanted to check if in D₂O it would undergo reverse isomerization with formation of the *EZ* and *EE* forms. After 6 days, the *EE*/*EZ*/*ZZ* ratios were 0.2:1:1 (Figure S3, Supporting Information), coincident with those obtained at equilibrium starting from pure *EE* isomer.

The much faster rate of isomerization observed in acetone with respect to water (the two solvents characterized by a very different dielectric constant) led us to investigate the possible role of the counterion. Therefore, we substituted ClO₄[–] for Cl[–] by precipitation of [PtCl((*E*)-ime)₂(PPh₃)](ClO₄) from a water solution of [PtCl((*E*)-ime)₂(PPh₃)]Cl and HClO₄.

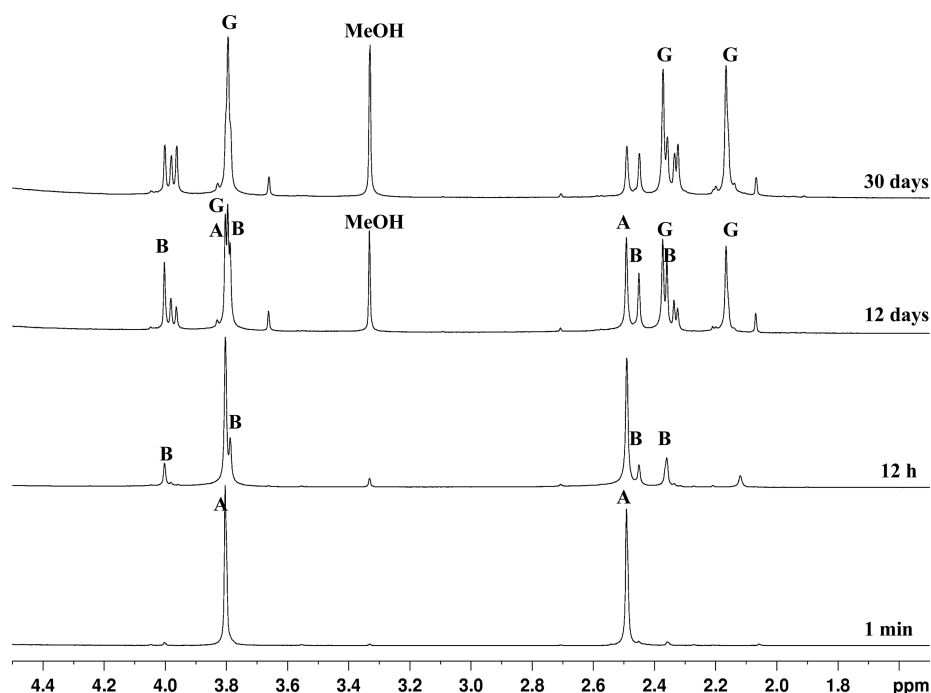


Figure 2. ^1H NMR spectra taken at various times for $[\text{Pt}((E)\text{-ime})_2(\text{thiourea})_2]\text{Cl}_2$ dissolved in D_2O at 295 K and pH 6.5. Isomer EE (A), isomer EZ (B), cyclic product (G).

$[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)](\text{ClO}_4)$, dissolved in acetone- d_6 or CDCl_3 , does not show signs of isomerization (^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR) even after several days. Moreover, the chemical shift of the iminic protons (6.55 ppm in CDCl_3 , Table 3 and Figure S4, Supporting Information) was considerably upfield with respect to the corresponding signal in $[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$ (7.94 ppm in CDCl_3 , Table 3) and in the usual range for iminic protons of neutral iminoether complexes, which do not have counterions. The downfield shift ($\Delta\delta = 1.39$) of the iminic proton in the case of the chloride counterion points to a specific interaction between the chloride anion and the iminic proton. We will come back to this point later on in the discussion. When Cl^- was added to the acetone- d_6 solution of the perchlorate complex, the isomerization of the iminoether ligands became fast.

Reaction of $[\text{PtCl}_2((E)\text{-ime})_2]$ with AsPh_3 . The reaction between $[\text{PtCl}_2((E)\text{-ime})_2]$ and AsPh_3 , carried out in CHCl_3 , yielded the $\text{trans}-[\text{PtCl}\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{AsPh}_3)]\text{Cl}$ complex, $[\text{PtCl}((E)\text{-ime})_2(\text{AsPh}_3)]\text{Cl}$. This compound is stable in CDCl_3 solution only in the presence of excess AsPh_3 . In the absence of free arsine, partial displacement of AsPh_3 by Cl^- takes place, affording $[\text{PtCl}_2((E)\text{-ime})_2]$ and free AsPh_3 . Such a reverse reaction does not take place in D_2O solution.

Similarly to complex $[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$, complex $[\text{PtCl}((E)\text{-ime})_2(\text{AsPh}_3)]\text{Cl}$ undergoes an isomerization equilibrium to EZ and ZZ forms in D_2O at pH 6.5 (Figure S5, Supporting Information). Therefore, the signals of the EE isomer (A) (peaks at 2.23 (C–Me) and 3.39 (O–Me) ppm) decrease with time with a simultaneous increase of the signals of the EZ isomer (B) (peaks at 1.77 and 2.08 (C–Me) and at 3.38 and 3.45 (O–Me) ppm) and of the ZZ form (C) (peaks at 1.81 (C–Me) and 3.39 (O–Me) ppm). After 6 days, a composition equilibrium was reached with the three isomers EE , EZ , and ZZ , present in 0.15:1:1 ratios, respectively. The greater stability of the Z form, with respect to the E form, appears to be a common feature of the iminoether ligand in

compounds in which a neutral ligand (PPh_3 or AsPh_3) has substituted a chlorido ligand.

Reaction of $[\text{PtCl}_2((E)\text{-ime})_2]$ with DMSO. $[\text{PtCl}_2((E)\text{-ime})_2]$ reacts with DMSO in water affording $\text{trans}-[\text{PtCl}\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{DMSO})]\text{Cl}$, $[\text{PtCl}((E)\text{-ime})_2(\text{DMSO})]\text{Cl}$. Unlike PPh_3 and AsPh_3 , DMSO can be used in large excess (even pure DMSO) without formation of the bis adduct. The reaction is quite slow and can be accelerated by using $\text{trans}-[\text{PtCl}(\text{NO}_3)\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2]$, $[\text{PtCl}(\text{NO}_3)((E)\text{-ime})_2]$, instead of $[\text{PtCl}_2((E)\text{-ime})_2]$, as the starting substrate. The nitrate ligand is known to be a much better leaving group than chloride.

The ^1H NMR spectrum of $[\text{PtCl}((E)\text{-ime})_2(\text{DMSO})]\text{Cl}$ in D_2O (signals at 2.54 (C–Me), 3.46 (S–Me), and 3.91 (O–Me) ppm) shows a set of minor peaks belonging to the hydrolyzed mono adduct $\text{trans}-[\text{Pt}\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{H}_2\text{O})(\text{DMSO})]\text{Cl}_2$, $[\text{Pt}((E)\text{-ime})_2(\text{H}_2\text{O})(\text{DMSO})]\text{Cl}_2$ (Figure S6, Supporting Information). This assignment is supported by the observation that addition of NaCl converts $[\text{Pt}((E)\text{-ime})_2(\text{H}_2\text{O})(\text{DMSO})]\text{Cl}_2$ into $[\text{PtCl}((E)\text{-ime})_2(\text{DMSO})]\text{Cl}$.²⁵ The $^{195}\text{Pt}\{^1\text{H}\}$ NMR spectrum gives a singlet at -3000 ppm.

Unlike compounds $[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$ and $[\text{PtCl}((E)\text{-ime})_2(\text{AsPh}_3)]\text{Cl}$, compound $[\text{PtCl}((E)\text{-ime})_2(\text{DMSO})]\text{Cl}$ was stable in D_2O solution at neutral pH and room temperature and did not show signs of isomerization to EZ and ZZ isomers during a period of 1 week (Figure S6, Supporting Information). In a recent paper Arnesano, Liu, et al. found a similar behavior in the reaction of $[\text{PtCl}_2((E)\text{-ime})_2]$ with AcMet or Met .²⁶ However, by changing the solvent (DMSO- d_6 instead of water) the initially former $[\text{PtCl}((E)\text{-ime})_2(\text{DMSO})]\text{Cl}$ complex undergoes isomerization with formation of the EZ and ZZ forms. After 6 days, the equilibrium ratios of the three isomers, EE , EZ , and ZZ , were 1:2:0.7 (Figure S7, Supporting Information).

Scheme 2. Formation of the Cyclic Species G

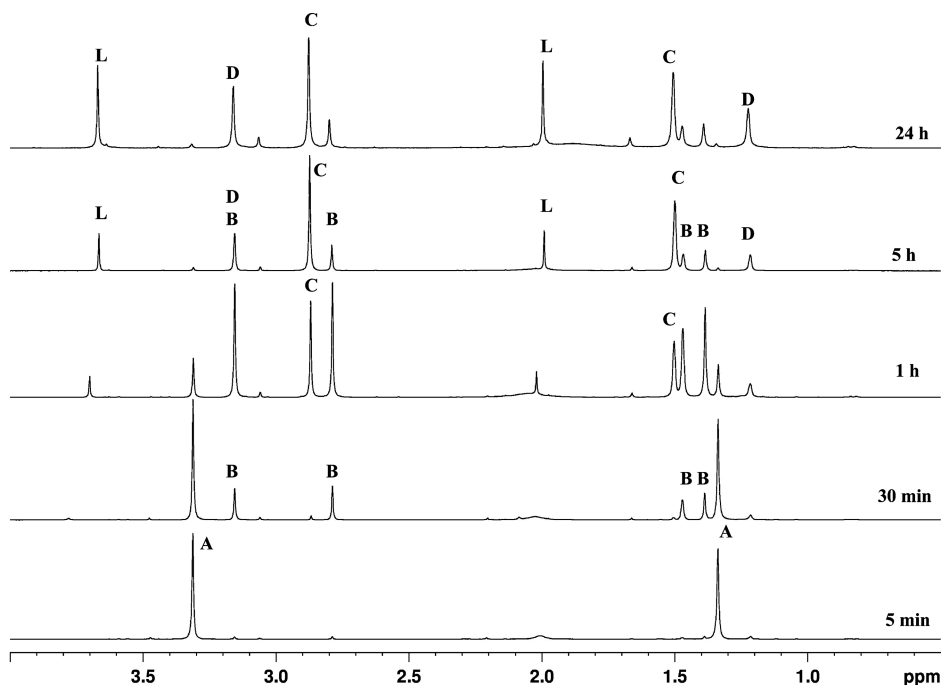
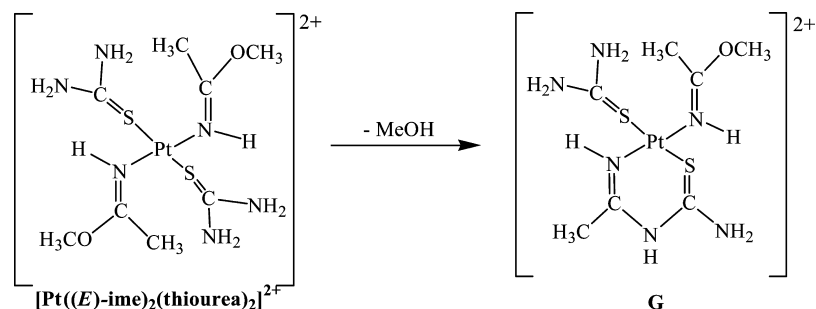


Figure 3. ^1H NMR spectra taken at various times for $[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$ dissolved in CDCl_3 at 295 K. Isomer *EE* (A), isomer *EZ* (B) (peaks at 1.38 and 1.45 ppm (C—Me) and at 2.83 and 3.16 ppm (O—Me)), isomer *ZZ* (C) (peaks at 1.50 (C—Me) and 2.89 (O—Me) ppm), *trans*- $[\text{PtCl}\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}(\text{PPh}_3)_2]\text{Cl}$ (D) (peaks at 1.23 (C—Me) and 3.16 ppm (O—Me)), free iminoether (L) (peaks at 2.02 (C—Me) and 3.70 ppm (O—Me)).

Reaction of $[\text{PtCl}_2((E)\text{-ime})_2]$ with Thiourea. $[\text{PtCl}_2((E)\text{-ime})_2]$ reacts with thiourea in water, as well as in organic solvents, forming always the bis-substituted species *trans*- $[\text{Pt}\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{thiourea})_2]\text{Cl}_2$, $[\text{Pt}((E)\text{-ime})_2(\text{thiourea})_2]\text{Cl}_2$, even when a defect of entering ligand (0.5 or 1 equiv) is used. This compound is very soluble in water but insoluble in chloroform or acetone, from which it precipitates as a white solid.

In D_2O solution, $[\text{Pt}((E)\text{-ime})_2(\text{thiourea})_2]\text{Cl}_2$ (A, ^1H signals at 2.49 (C—Me) and 3.80 (O—Me) ppm, Figure 2) undergoes isomerization to the *EZ* form. However, concurrent to the isomerization of the iminoether ligand, another unexpected rearrangement takes place: methanol is released and a new species (G), with two signals in the C—Me region (2.17 and 2.37 ppm), and only one signal in the O—Me region (3.79 ppm) is formed (Figure 2).

The release of a methoxy group from one iminoether ligand, not observed in the previous experiments, could be fostered by an aminic group of thiourea displacing the methoxyl group of a *cis*-iminoether and forming a cyclic product (G, Scheme 2). This hypothesis was fully confirmed by multinuclear NMR

(Figure S8, Supporting Information) and ESI-MS analysis. The latter one showing a molecular peak at m/z : 460.0 Da corresponding to $[\text{G} - \text{H}]^+$ (exact mass for G: $\text{C}_7\text{H}_{18}\text{N}_6\text{OPtS}_2$, 461.0).

Formation of the Bis(phosphine) Adduct *trans*- $[\text{Pt}\{(E)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{PPh}_3)_2]\text{Cl}_2$, $[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$. The reaction between $[\text{PtCl}_2((E)\text{-ime})_2]$ and excess PPh_3 , performed in Et_2O , affords only the 1:1 adduct $[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$, which separates out of solution soon after formation. However, if the reaction is carried out in CHCl_3 , the $[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$ complex is formed in quantitative yield (95%). Upon passing from the monophosphine ($[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$) to the bisphosphine derivative ($[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$), the iminic nitrogen undergoes a remarkable downfield shift ($\Delta\delta = 1.24$ ppm), whereas the methyl protons undergo an upfield shift, which is much greater for C—Me ($\Delta\delta = 0.86$ ppm) than for O—Me ($\Delta\delta = 0.15$ ppm) (Table 3). The upfield shift of the C—Me and O—Me protons could be due to a shielding effect exerted by the phenyl groups of the phosphine ligands, whereas the downfield shift of the iminic proton could be due to H bond interaction with the

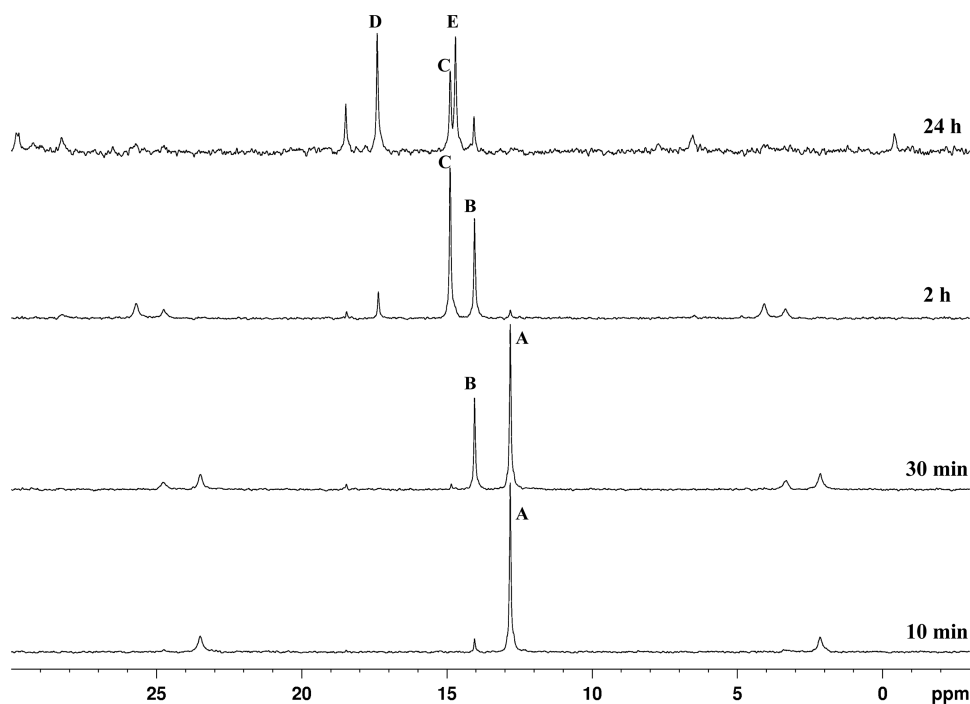


Figure 4. $^{31}\text{P}\{^1\text{H}\}$ NMR spectra taken at various times for $[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$ dissolved in CDCl_3 at 295 K. Isomers: *EE* (A) (peak at 12.8 ppm with platinum satellites, $^1J_{\text{P-Pt}} = 2598$ Hz), *EZ* (B) (peak at 14.0 ppm, $^1J_{\text{P-Pt}} = 2600$ Hz), *ZZ* (C) (peak at 14.8 ppm, $^1J_{\text{P-Pt}} = 2630$ Hz), *trans*- $[\text{PtCl}\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}(\text{PPh}_3)_2]\text{Cl}$ (D) (peak at 17.4 ppm, $^1J_{\text{P-Pt}} = 2641$ Hz), *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$ (E) (peak at 14.2 ppm, $^1J_{\text{P-Pt}} = 3668$ Hz).

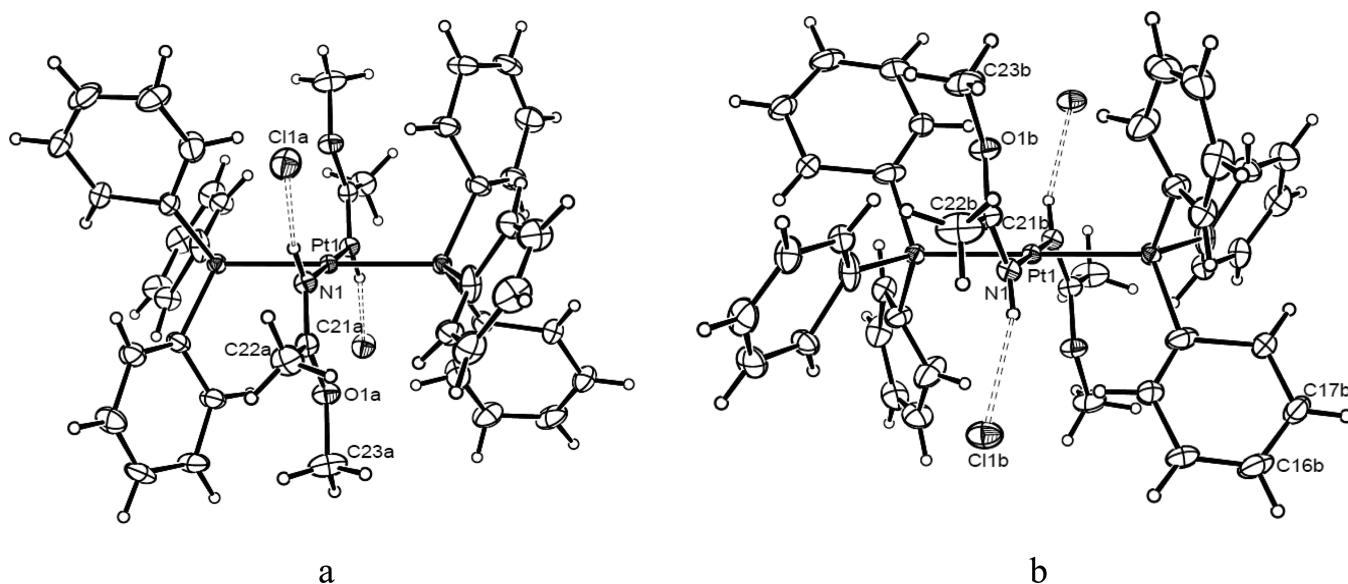


Figure 5. ORTEP drawing at 20% probability of $[\text{Pt}((Z)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$. The ligands ((*Z*)-ime and PPh_3) can assume two different conformations (labeled “a” and “b”), both conformations are shown. The chloride counterions are located near the iminoether ligands and form strong H bonds with N–H.

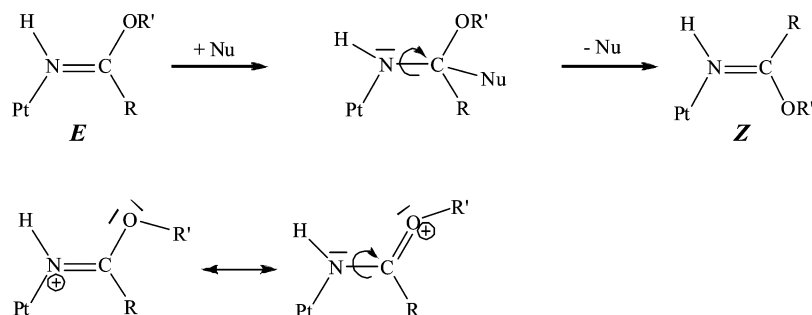
counterions, see following X-ray Structure section and the Discussion.

$[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$ undergoes fast isomerization to the *EZ* and *ZZ* forms not only in chlorinated solvent (CDCl_3) but also in water. Therefore, unlike the monophosphine derivative $[\text{PtCl}((E)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$, for which the isomerization in D_2O was very slow, the bisphosphine derivative $[\text{Pt}((E)\text{-ime})_2(\text{PPh}_3)_2]\text{Cl}_2$ undergoes fast isomerization into the *EZ* and the *ZZ* forms, with the equilibrium being almost completely shifted toward the *ZZ* form (^1H , ^{31}P , and ^{195}Pt

spectra in Figures S9, S10, and S11 (Supporting Information), respectively).

In CDCl_3 , the isomerization of the *EE* form (A) to the *EZ* form (B) and to the *ZZ* form (C) is also accompanied by displacement of the iminoether ligand by chloride and formation of *trans*- $[\text{PtCl}\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}(\text{PPh}_3)_2]\text{Cl}$ (D) and free iminoether (L) (Figure 3).

The ^{31}P NMR (Figure 4) also showed that, in addition to species A, B, C, and D, there is also formation of a species in which both iminoethers have been displaced by chloride, *cis*- $[\text{PtCl}_2(\text{PPh}_3)_2]$, E. That in the case of the bisphosphine

Scheme 3. Mechanism of Isomerization about the C=N Double Bond^a

^aFor the two limiting formulas, the formal charge on the ligand atoms is also indicated.

compound the equilibrium is completely shifted toward the ZZ form could be checked by monitoring (¹H NMR) a solution of [Pt((Z)-ime)₂(PPh₃)₂]Cl₂ in D₂O or CDCl₃. No sign of isomerization to the EZ and EE forms was observed (Figure S9–S11, Supporting Information).

To investigate the effect of the counterion upon the rate of isomerization of the iminoether ligand also in the case of the bisphosphine derivative, we prepared the tetrafluoroborate complex [Pt((E)-ime)₂(PPh₃)₂](BF₄)₂, which is insoluble in H₂O and in CHCl₃, but sufficiently soluble in CD₂Cl₂ and in acetone-*d*₆.

In CD₂Cl₂, a fast isomerization took place affording, after few minutes, a white precipitate of the pure ZZ isomer. The same fast isomerization was observed in acetone-*d*₆ where the [Pt((Z)-ime)₂(PPh₃)₂](BF₄)₂ compounds is also soluble (Figure S12, Supporting Information).

X-ray Structure of [Pt((Z)-ime)₂(PPh₃)₂]Cl₂. [Pt((Z)-ime)₂(PPh₃)₂]Cl₂ crystallizes, incorporating three molecules of CHCl₃ per molecule of complex. The asymmetric unit comprises half a molecule of the complex, and the structure is generated by inversion at the Pt1 center (Figure 5).

The platinum ion has a square-planar coordination geometry. As expected, also the iminoether ligands are planar (maximum deviation from the plane passing through N1, C21, C22, O1, and C23 0.03(1) Å). The dihedral angle between the coordination plane and the iminoether plane is ca. 81°. The two iminoether ligands have similar geometrical parameters. The N=C, C(sp²)—O, and O—C(sp³) bond distances (average values 1.29(1), 1.32(1), and 1.43(1) Å, respectively) and the Pt—N—C and N—C—C angles (average values 123.5(6) and 121.8(6)°, respectively) are similar to those previously observed in platinum-iminoether complexes (such as *trans*-[PtCl₂{(Z)-HN=C(*t*-Bu)OMe}₂]₂),¹¹ *trans*-[PtCl{(Z)-HN=C(Me)OMe}₂(PPh₃)]Cl,²⁷ and *cis*- and *trans*-[PtCl₂{(E)-HN=C(Me)OMe}₂]₂)²⁴ and indicate the presence of an extensive electron charge delocalization over the N—C—O moiety.

The iminoether ligands have the oxygen-bound Me group directed toward the C—Me (Z anti configuration), whereas in the other complexes with Z configuration of the iminoethers previously investigated, *trans*-[PtCl₂{(Z)-HN=C(*t*-Bu)OMe}₂], the oxygen-bound Me group was directed toward the metal core (Z syn configuration).¹¹ An electrostatic interaction between the lone pair of electrons on the oxygen of the iminoether ligand and the positively charged metal ion (Pt···O distance of ca. 3.04[1] Å, shorter than the sum of the van der Waals radii, which amounts to ca. 3.22 Å) could be responsible for the observed Z anti configuration.

Interestingly, the chloride counterion is located near the iminoether ligand and forms a strong hydrogen bond with NH (N1···Cl1b 3.180(2) Å, N1H1b···Cl1b 2.347 Å, N1—H1b···Cl1b 163.2(2)°; N1···Cl1a 3.247(4) Å, N1H1a···Cl1a 2.417 Å, N1—H1a···Cl1a 162.3(2)°).

DISCUSSION

For the series of *trans*-[PtCl₂{HN=C(R)OMe}₂] complexes (R = Me, Et, Ph, *t*-Bu), it was found that the stability of the *E* isomer decreases in the order Me > Et > Ph > *t*-Bu, indicating that an increase of steric bulk of the R group destabilizes the *E* isomer in which the R group is cis to the metal core with respect to the C=N double bond. Moreover, because the addition of the alcohol to the coordinated nitrile to form the iminoether takes place in *trans* positions, the *Z* isomer is always kinetically favored and isomerization to the thermodynamically preferred form takes place in a second step. In the case of R = *t*-Bu, the *Z* isomer is both kinetically and thermodynamically preferred.¹¹

Unexpectedly, some evidence indicated that the relative stability of the *E* and *Z* isomer could also be influenced by the nature of the ancillary ligands. Therefore, although in the dichlorido species *trans*-[PtCl₂{HN=C(Me)OMe}₂] the iminoether ligands have stable *EE* configuration (thermodynamically preferred configuration), in the complex [PtCl{(HN=C(Me)OMe)₂(PPh₃)}]Cl, both in protic as well as in aprotic solvents, the *E* configuration of the iminoether is no longer the most stable and an equilibrium composition containing the three isomers (*EE*, *EZ*, and *ZZ*) is established.

For the isomerization about the C=N double-bond, we can postulate a mechanism similar to that suggested for isomerization in basic conditions,²⁴ that is attack of an external nucleophile (Nu) upon the carbon atom of the imino residue leading to formation of an amido species which afterward eliminates the nucleophile restoring the iminoether ligand, but in an isomerized form (upper row of Scheme 3). The positive charge on the imino nitrogen should increase in the substituted products, relative to the dichlorido species, facilitating the nucleophilic attack at the imino carbon. In the latter mechanism we have also to contemplate the possibility of exchange between the alkoxy group and the attacking nucleophile. Such a substitution has not been observed in the present investigation.

For the latter reason, we cannot exclude the possibility that in the present case the isomerization could take place without the intervention of an external nucleophile. Previous and present X-ray investigations support the view that an oxygen lone pair of the iminoether gets involved in conjugation with the C=N π system. In other words, the iminoether moiety can

be described in terms of two limiting formulas as shown in the lower row of Scheme 3. The positive charge accumulated on the metal core by the effect of substitution of Cl^- by neutral ligands could stabilize the limiting formula on the right that, having a single N—C bond, could undergo rotation finally leading to E—Z isomerization of the iminoether.

The X-ray investigation, performed on the bis(phosphine) derivative (present work) as well as on the monophosphine derivative $[\text{PtCl}((Z)\text{-ime})_2(\text{PPh}_3)]\text{Cl}$,²⁷ has revealed, for the first time, a Z configuration for an iminoether with small C-alkyl substituents (Me). Moreover, this Z configuration differs from that previously observed for the *t*-Bu derivative for which the Z configuration was stabilized by the bulky *t*-Bu preferring to be trans to the bulky platinum residue with respect to the azomethine double bond. For the latter complex, the oxygen-bound Me group was directed toward platinum (approaching the metal from an apical position) so to avoid steric clash with the *t*-Bu group (Z syn configuration). In contrast, the phosphine substituted compounds, *trans*- $[\text{Pt}\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{PPh}_3)_2]\text{Cl}_2$ and *trans*- $[\text{PtCl}\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2(\text{PPh}_3)]\text{Cl}$, also having the Z configuration, have the oxygen-bound Me group directed not toward platinum but toward the C—Me group (Z anti configuration). The latter configuration could be favored by the smaller steric hindrance of the C—Me with respect to C—(*t*-Bu); however, we hypothesize that additional stability of the Z anti configuration comes from the electrostatic interaction between the oxygen lone pair and the platinum cation as witnessed by the rather short Pt...O distance. Such an interaction could be fostered by the net positive charge of the phosphine complexes, as opposed to the neutral dichlorido species, and possibly by the lower dielectric constant around the metal core provided by the hydrophobic phosphine environment. The same factors, net positive charge of the complex and reduced dielectric constant around the metal core, could favor formation of a strong H bond between the iminic proton and the chloride counterion. Such an interaction, observed in the solid state, is also present in solution of organic solvent as witnessed by the downfield shift of the iminic proton in the case of Cl^- counterion(s).

A particular case is that of the thiourea derivative in which an aminic group of thiourea displaces the methoxyl group of a *cis*-iminoether forming a cyclic product. Such a rearrangement, reminiscent of the McLafferty rearrangement, could play a role also in the interaction of iminoether compounds, such as *trans*- $[\text{PtCl}_2\{(Z)\text{-HN}=\text{C}(\text{Me})\text{OMe}\}_2]$, with target DNA. The latter drug gives prevalently monofunctional adducts with DNA (substitution of one chloride by a purinic base) which, contrarily to monofunctional adducts formed by other platinum complexes, are able to inhibit DNA and RNA polymerases. It is conceivable that, in addition to platinum coordination to a nucleobase, a McLafferty type rearrangement occurring between an iminoether ligand and an aminic residue could lead to cross-linking.

CONCLUSION

The present investigation has highlighted the role that ancillary ligands, formally not participating in a reaction, can play in determining the stereochemistry and the reactivity of a metal-coordination compound. We believe that the rearrangements/interactions taking place within the coordination shell of a platinum complex, as highlighted in the present work, have a general significance and can apply to several other cases.

ASSOCIATED CONTENT

Supporting Information

Crystallographic Data in CIF format. Additional ^1H , $^{31}\text{P}\{^1\text{H}\}$, and $^{195}\text{Pt}\{^1\text{H}\}$ NMR spectra and portion of 2D ^1H — ^{13}C HMBC spectrum. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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