Chemical Physics Letters 458 (2008) 200–204

Contents lists available at ScienceDirect

Chemical Physics Letters

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Mechanistic theoretical insight of Ru(II) catalysts with a meridional–facial *bpea* fashion competition

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ARTICLE INFO

Article history:
Received 11 March 2008
In final form 23 April 2008
Available online 30 April 2008

ABSTRACT

A novel mechanistic insight for the interconversion between two octahedral ruthenium isomers, *trans-mer*-[$Ru^{II}Cl_2$(*bpea*)(dmso)], **2a**, and *cis-fac*-[$Ru^{II}Cl_2$(*bpea*)(dmso)], **2b**, (*bpea* = *N*,*N*-bis(2-pyridylmethyl)ethylamine) is reported. The isomer **2a** displaying the *bpea* ligand in a *meridional* fashion is kinetically favoured with respect to **2b**, with the *bpea* ligand in a *facial* fashion, which is the thermodynamically favoured one. The dissociative mechanism with the cleavage of a chloro ligand as starting point becomes more feasible with respect to the intramolecular mechanism. However, DFT calculations make competitive the mechanism which dissociates first the dmso ligand. Thus, a further characterisation of all the reaction pathways for the interconversion **2a** → **2b** has been fulfilled.

1. Introduction

From the seventies, the coordination chemistry of Ru complexes has experienced a large boost in the fields of catalysis [1–4], photochemistry and photophysics [5–15], and more recently in supramolecular [16–19] and bio-inorganic [20] chemistry. However, the most interesting and promising applications of Ru complexes are as chemotherapeutic agents [21–23]. A major challenge in this field is to understand the mechanism of action through which those complexes bind to DNA's tumour cells, involving π-stacking interactions and/or the substitution of Cl and/or dmso ligands so that a binding interaction can take place. Furthermore [$RuCl_2$(dmso)$_4$] is one of the most widely used starting materials for the synthesis of other Ru complexes [24–26] through the substitution of the labile Cl and dmso ligands by the desired ligand.

Because of the role of the Ru–Cl–dmso complexes as catalysts, [27–29] Llobet et al. [34] prepared a family of complexes containing Cl^-, dmso and the tridentate *bpea* ligand (*bpea* = *N*,*N*-bis(2-pyridylmethyl)ethylamine), displayed in Scheme 1 [30]. This ligand interestingly generates a very rich chemistry [3,31–33] given three factors: two different types of coordinating N atoms (aliphatic vs. aromatic) which generate different *trans* effects/influences with the corresponding consequences in the reactivity; the non-equivalence of the three N atoms that in an octahedral environment generate different kinds of geometrical isomers and the flexibility of the ligand that allow both a facial and a meridional type of coordination with the possibility of generating different isomers.

As described in Scheme 2, reaction of *fac*-[$RuCl_2$-(dmso-O)-(dmso-S)$_3$], **1** with *bpea* produces the kinetically favoured *trans-mer* **2a** complex in moderate yield [34]. Additional reflux to 12 h generates the thermodynamically favoured *cis-fac* isomer **2b**. Thus, the *bpea* ligand can potentially adopt a facial or meridional coordination mode due to its flexibility. The former mode is the most commonly found in the literature and it is in agreement with the fact that **2b** is thermodynamically favoured. On the other hand, the *trans-mer* isomer **2a** was the first Ru complex crystallographically characterised with the *bpea* ligand acting in a meridional manner. Reaction of **2a** with excess of dmso generates the bis-dmso complex **3** that is formed through **2b**. Complexes **2a, 2b** and **3** present a distorted octahedral type of geometry around the metal centre, as expected for low spin d^6 Ru ion [35,36]. DFT calculations show that isomer **2a** is 5.9 kcal mol^{-1} less stable than **2b** [34]. The H-bonds involving the oxygen atom of the dmso group in **2b** help to explain this energetic difference. Those results corroborated the experimental finding that **2a** is the kinetically favoured isomer, whereas **2b** is the thermodynamically preferred one.

For the isomerisation of **2a** into **2b**, two different mechanistic scenarios were envisaged [34]: the so-called 'intramolecular rearrangement mechanism', which does not involve any bond breaking and the 'dissociative mechanism', which involves the breaking and formation of a Ru–Cl bond. The intramolecular mechanism was

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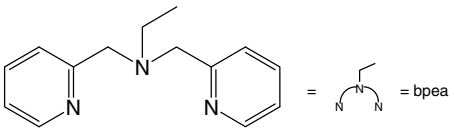
doi:10.1016/j.cplett.2008.04.110



Scheme 1. Schematic structure of the *bpea* ligand.

investigated, being key the N3-Ru-N2-N1 dihedral angle that changes from 180° to 90° while going from the **2a** isomer to the **2b** isomer. The energy profile obtained in this way presents a transition state revealing an energetic barrier of 43.1 kcal mol^{-1}. For the dissociative mechanism, the breaking of a Ru–Cl bond as suggested by a kinetic analysis is followed by ligand reorganisation including the facial to meridional conformation for the *bpea* ligand, and finally Ru–Cl bond formation requires 26.0 kcal mol^{-1}. Thus theoretically this dissociative mechanism is favoured with regard to the intramolecular rearrangement, in excellent agreement with the kinetic experiments.

Here we report the interconversion of the meridional and facial conformations of the [Ru^{II}(Cl)$_2$(*bpea*)(dmso)] complex through a dmso dissociative mechanism, *i.e.* completing a detailed analysis of its substitution and isomerisation reactions through DFT calculations. Furthermore the key role of the *bpea* ligand in the stability of isomers **2a** and **2b** is further analysed.

2. Experimental details

Cyclic voltammetric (CV) experiments were performed in an IJ-Cambria IH-660 potentiostat using a three electrode cell. Glassy carbon disk electrode (3 mm diameter) was used as working electrode, platinum wire as auxiliary and SSCE as the reference electrode. All cyclic voltammograms were recorded under nitrogen atmosphere. The complexes were dissolved in previously degassed solvents containing the necessary amount of *n*-Bu$_4$N$^+$PF$_6^-$ (TBAH) as supporting electrolyte to yield a 0.1 M ionic strength solution. All $E_{1/2}$ values were estimated from cyclic voltammetric experiments as the average of the oxidative and reductive peak potentials $(E_{p,a} + E_{p,c})/2$. The concentration of the complexes was approximately 1 mM.

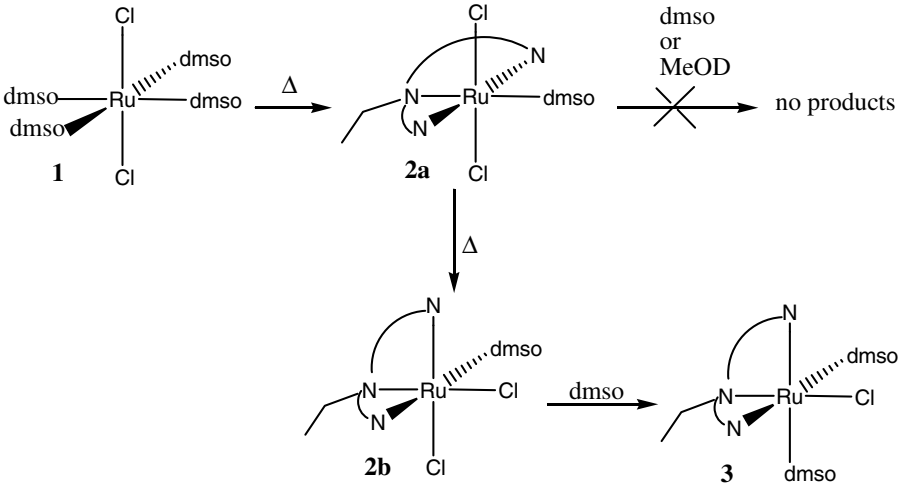
3. Computational details

Density functional theory (DFT) calculations have been carried out with the B3PW91 hybrid density functional [37,38], as implemented in the Gaussian 03 package [39]. The Ru atoms have been represented with the quasi relativistic effective core pseudopotentials (RECP) of the Stuttgart group and the associated basis sets augmented with a polarization function ($\alpha = 1.235$) [40,41]. The remaining atoms (C, N, O, S, Cl, and H) have been represented with 6-31++G(d,p) basis sets [42]. The solvent effect of ethanol was introduced by the polarizable continuum model (PCM) [43,44].

4. Results and discussion

DFT results are validated through several publications using the same methodology [34,45–47] and displaying a constant and good trend for ruthenium complexes [34,47]. The present study started from a detailed analysis of the role of the *bpea* ligand. Single-point energy calculations of the isolated *bpea* at the geometry of the ligand in isomers **2a** and **2b**, either with meridional or facial conformation, respectively, give as a result that the facial conformation is less stable in 5.7 kcal mol^{-1} with respect to the meridional conformation. Therefore, the stability of the isolated ligand is opposite to that of the ruthenium isomeric complexes **2a** and **2b**. However, the number of possible conformations of *bpea* is very large, being the most stable facial conformation 4.6 kcal mol^{-1} more stable than the most stable meridional conformation. Taking into account the solvent effect, complex **2b** presents an entropy value lower by 7.8 cal mol^{-1} with respect to complex **2a**. Overall, the facial *bpea* gains energetic stability as compared to the meridional ligand when it complexes the metal, loosing entropy. The study of the transition state (TS) between both isolated *bpea* conformations gives a TS situated only 1.2 kcal mol^{-1} higher in energy with respect to the meridional *bpea* conformation. This means that the potential energy surface is very flat, and that any conformation can be adopted when the *bpea* ligand is free; more interestingly, the interconversion between them is energetically inexpensive, which differs from what is found when is bonded to a metal.

To investigate whether the chelate ligand plays a key role, we replaced the *bpea* ligand by three ammonia units, obtaining **2a$_s$** and **2b$_s$** isomers. The results indicate that the most stable conformation is the coordination of the three N atoms in a meridional way, in contrast to the facial conformation, more stable with the chelated *bpea* ligand. These two isomers, **2a$_s$** and **2b$_s$**, present only another isomer, **2a$_{s'}$**, higher in energy (see Fig. 1). This simplification allows the demonstration that the chelation of *bpea* plays a key role with respect to the *trans* effect between ligands, typical of square planar and octahedral complexes. Furthermore, linking the ammonia units with ethylene groups, i.e. forming ethylendiamines the results are very similar to the *bpea* ones as expected



Scheme 2. Schematic overview of the reactions according to available experimental results.

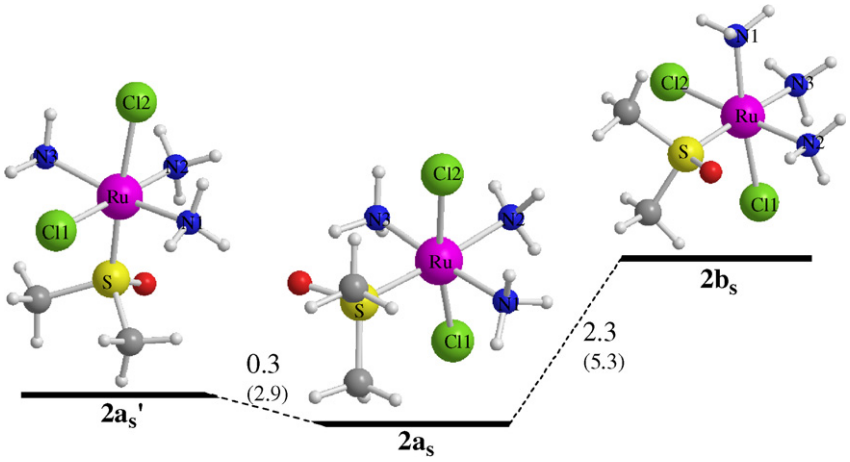


Fig. 1. Energetic diagram of isomers **2a$_s$**, **2b$_s$**, and **2a$_s$'** in gas phase (and solvent phase) in kcal mol^{-1}.

[48]. Therefore, the steric role of the triaza ligand is stronger than its electronic influence.

Through the computation of complex **3** (see Fig. 2) we discover an energetic stabilisation of about 1.5 kcal mol^{-1} with respect to isomer **2b**, thus anticipating a higher thermodynamic stability bonding a dmso ligand instead of a chloride anion. Furthermore, in order to validate the thermodynamic stability of both isomers, **2a** and **2b**, and complex **3**, their redox properties were investigated by means of experimental cyclic voltammetric techniques [34]. The cyclic voltammograms of **2a**, **2b**, and **3** exhibit quasi-reversible electrochemical waves assigned to the Ru(III/II) couples. For the complexes **2a** and **2b** these waves appear at $E_{1/2}$ = 0.53 V vs. SSCE (ΔE_p = 190 mV) and $E_{1/2}$ = 0.56 V vs. SSCE (ΔE_p = 220 mV) respectively, whereas for the complex **3** this wave is anodically shifted to $E_{1/2}$ = 1.04 V (ΔE_p = 260 mV). This anodical shift is in good agreement with the fact that complex **3** has two dmso ligands and one chloride ligand coordinated instead of two Cl$^-$ and one dmso as in **2a** and **2b** cases.

It is also interesting to observe that in the voltammogram of **2a** in acetonitrile solution, this complex exhibits a quasi-reversible monoelectronic wave at $E_{1/2}$ = 0.52 V vs. SSCE. However irradiation with a 200 W UV–vis lamp, the initial waves were gradually replaced by new reversible ones at $E_{1/2}$ = 0.25 V, Fig. 3.

As it can be seen in Scheme 3, the low values reported above indicate the substitution of the dmso ligand by the acetronitrile ligand, due to the lower π-backdonation presented by acetonitrile with regard to dmso. This reinforces the idea of the possible competition between both dissociative mechanisms, chloro and dmso, and the fact that the lability of dmso must be taken into account. However, this photo-induced substitution of acetonitrile for dmso is not simply correlated with the different π-backbonding nature of both ligands. And the photo-chemically lability nature of dmso ligand does not directly ensure its thermal lability.

Here the **2a** → **2b** interconversion is further analysed through the dmso dissociative mechanism displayed in Scheme 4 together with the chloride dissociative mechanism as well as the intramolecular mechanism.

The dissociation of dmso costs only 2.8 kcal mol^{-1}. The solvent does not stabilise strongly the complex because after eliminating the dmso ligand the molecule is not charged, and the low stabilization for this dmso dissociation is mainly due to the empty site of the ruthenium. The overall barrier of 22.3 kcal mol^{-1} is due to the first decoordination of the dmso ligand and a reorganisation that costs 19.5 kcal mol^{-1} (see Fig. 4). Furthermore, the reorganisation takes place in two steps. The first one requires that the two chloro ligands that are in *trans* position move to the *cis* location and the second one is reflected by the N3-Ru1-N2-N1 dihedral angle, which should move approximately from 180° to 90°. The first step of the reorganisation presents a similar barrier compared to the second one, 10.4 and 10.7 kcal mol^{-1}, respectively. This second one is also lower than in the intramolecular process studied before [34], because the steric hindrance is smaller, due to the lack of one of the six coordinating ligands of ruthenium.

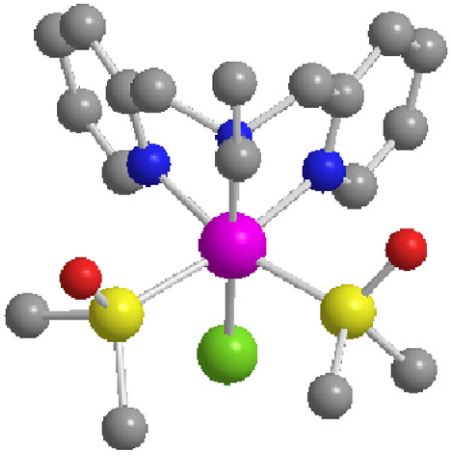


Fig. 2. B3PW91 optimised structure of complex **3** (hydrogen atoms have been omitted for clarity).

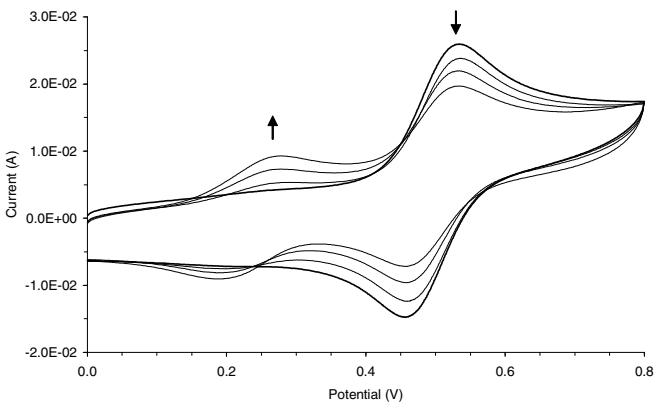
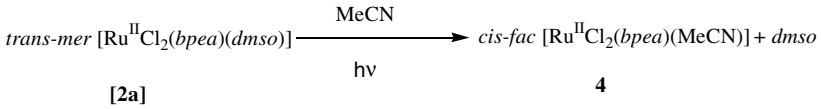
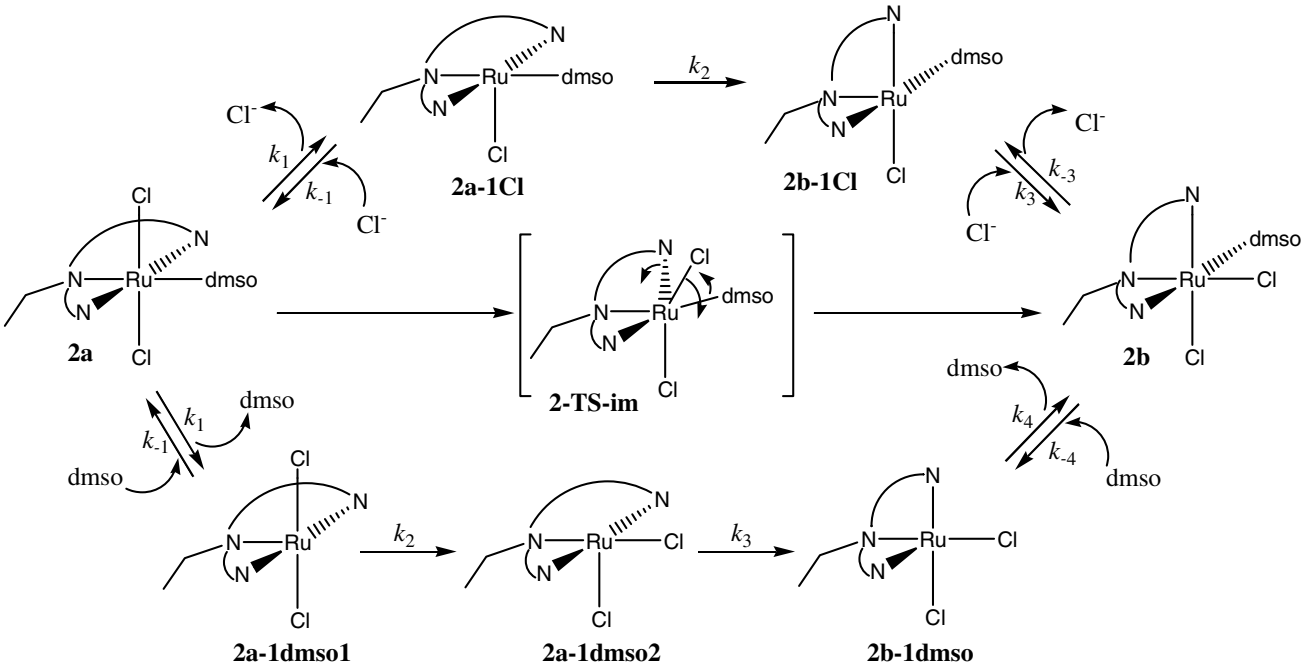


Fig. 3. CV performed during the photochemically induced substitution of dmso by acetonitrile ligand.



Scheme 3. Reaction of exchange between dmso/MeCN.



Scheme 4. Extrema (local minima or transition states) of the three possible paths of the **2a** → **2b** interconversion.

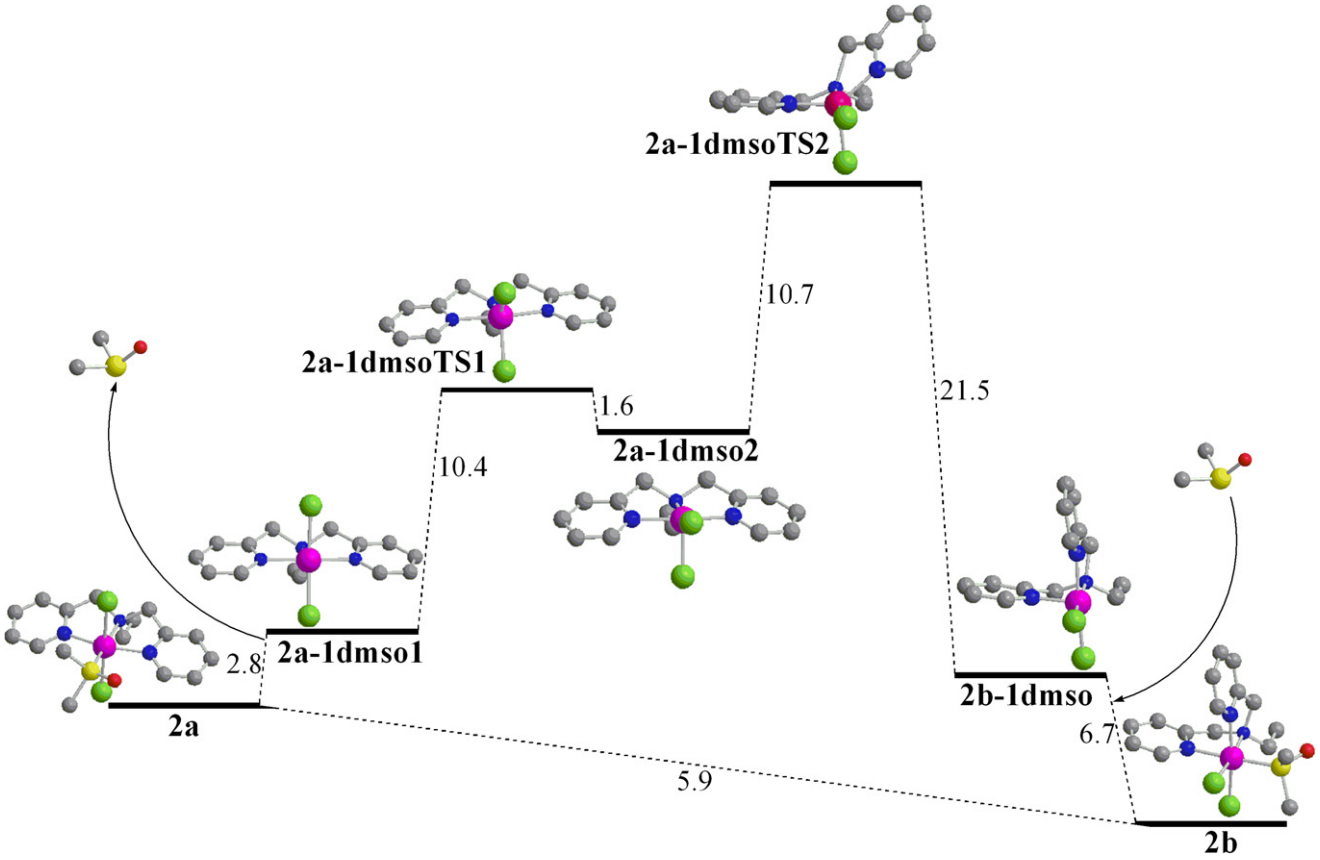


Fig. 4. Dissociative mechanism involving dmso elimination including solvent effects (Gibbs free energies in kcal mol^{-1}).

According to the results (*vide supra*), the dissociation of dmso has revealed to be even more feasible than the chloro dissociation because it costs only 2.8 kcal mol^{-1} (16.8 kcal mol^{-1} for the chloro dissociation) [35], and with an overall barrier of 22.3 kcal mol^{-1} (26.0 kcal mol^{-1} for the chloro dissociative mechanism). This refutes again the possible intramolecular mechanism (with an energetic barrier of 43.1 kcal mol^{-1}) but leaves two competing dissociative mechanisms. It must be pointed out that the dissociative barrier for charged species is known to be mostly overestimated, thus both dissociative mechanisms become competitive. The same dissociation in the simplified models with ammonia units shows a slight increase of the energetic barrier for chloro (29.2 kcal mol^{-1} compared to 26.0 kcal mol^{-1}) and especially for dmso (33.1 kcal mol^{-1} compared to 22.3 kcal mol^{-1}), taking into account the solvent effect in both cases. Thus, this model study reveals that, in this case, the chloro process would be favoured. Finally the dissociation of one of the coordinative atoms of the *bpea* ligand was also theoretically studied. However, the resulting systems were not stable enough and the subsequent re-bonding took place.

5. Conclusions

In the present work, we have shown that the formation and reactivity of complexes containing the flexible *bpea* ligand drive to a complicated scheme. Theoretical DFT calculations allow getting a deeper insight into complex reactivity, mechanisms and structure of reactive intermediates and transition states, as well as the identification of the structure of isomers which have not been experimentally obtained nor detected. The isomerisation of **2a** into **2b** changing the coordination of the chelated *bpea* ligand was the main scope of this study. As a result of the investigations carried out, the mechanism for the intramolecular rearrangement can be totally ruled out, while the two possible dissociative pathways are potentially operative. Further experimental work is required in order to establish clearly which is the dissociative mechanism that takes place or, in the case that both have a role, which one is postulated by now.

Acknowledgements

This research has been financed by the Spanish Ministerio de Educación y Ciencia (MEC) through projects CSD2006-003, CTQ2006-15634 and CTQ2005-08797-C02-01/BQU and by the Catalan Departament d'Universitats, Recerca i Societat de la Informació (DURSI) project No. 2005SGR-00238. Joaquim Mola and Albert Poater are grateful for the allocation of a pre-doctoral grant of the Generalitat de Catalunya and a postdoctoral contract of MEC, respectively. Antoni Llobet and Isabel Romero also thank Johnson and Matthey for a $RuCl_3 \cdot xH_2O$ loan.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cplett.2008.04.110 .

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