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Review

Investigation of alkyl metal intermediate formation in the rhodium-catalyzed hydroformylation: Experimental and theoretical approaches

Raffaello Lazzaroni[a,*], Roberta Settambolo[b], Giuliano Alagona[c,**], Caterina Ghio[c]

[a] DCCI, University of Pisa, Via Risorgimento 35, I-56126 Pisa, Italy
[b] ICCOM-CNR (Pisa Section), Via Risorgimento 35, I-56126 Pisa, Italy
[c] Molecular Modeling Lab, IPCF-CNR, Via Moruzzi 1, I-56124 Pisa, Italy

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This review is dedicated to Prof. Fausto Calderazzo to whom the authors are bound by a long-lasting and strong personal and professional relationship.

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ABSTRACT

This review describes experimental results obtained for regioselectivities and diastereoselectivities in rhodium-catalyzed hydroformylations and deuterioformylations of a variety of unsaturated substrates with unmodified Rh catalysts and compares them with values computed in the density functional theory (DFT) framework. Deuterioformylation experiments pointed out that under mild reaction conditions isomeric alkyl metal intermediate formation is non-reversible; hence the selectivity for alkyls reflects the selectivity for the aldehydes. The stability of the relevant alkyl rhodium transition states (TS) has been determined with computational methods at the B3P86/6-31G* level (employing effective core potentials for Rh in the LanL2DZ valence basis set). Theoretical results turn out to be in good agreement with the experimental ones obtained under mild reaction conditions. Significant differences between theory and experiment are conversely obtained for hydroformylations of vinylidenic olefins, such as 1,1-diphenylethene, carried out at high temperature, where β-hydride elimination takes place. To clarify the reaction mechanism under those reaction conditions, it was necessary to compute the whole reaction mechanism, including zero point and thermal corrections also. The calculations, performed on the hydroformylation of 1,1-diphenylethene (yielding almost exclusively linear aldehydes), allowed us to put forward a novel explanation for that behavior: the addition of the fourth CO group to the tricarbonyl intermediate to give the tetracarbonyl one is prevented in the branched isomer, but not in the linear isomer.

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1. Introduction

The formation of the alkyl metal intermediates via metal hydride addition to the olefinic double bond as well as the reverse reaction, i.e. β-hydride elimination, is a well-known process in organometallic chemistry [1,2]. In the rhodium-catalyzed hydroformylation of olefins, isomeric rhodium alkyls play a crucial role in determining the different aspects of the selectivity (chemo-, regio- and stereo-) [3]. Direct experimental evidence for the formation of alkyl rhodium intermediates is, however, unavailable, because these species are present in a very low concentration in the reaction mixtures and very reactive under typical hydroformylation conditions. In the last decade deuterioformylation experiments showed to be the best possible experimental probe to investigate the nature

* Corresponding author. Tel.: +39 0 502219227; fax: +39 0 502219260.
** Corresponding author. Tel.: +39 0 503152450; fax: +39 0 503152442.
E-mail addresses: lazza@dcci.unipi.it (R. Lazzaroni), G.Alagona@ipcf.cnr.it (G. Alagona).

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and the fate of the intermediates involved in the reaction [4]. ^{2}H NMR investigations of crude deuterioformylation mixtures allowed the reversibility or non-reversibility of the alkyl metal intermediate formation to be established via identification of the position of the incorporated deuterium atoms into unconverted substrates. In this way, the behavior of vinyl- and allyl-ethers [5], vinyl- and vinylidenic olefins [6] as well as of styrene [7] and pyridines [8], under rhodium-catalyzed hydroformylation conditions, has been rationalized by our research group. In the last years, theoretical investigations have also contributed significantly to clarify the aforementioned aspects [9–14]. In particular, regioselectivities and diastereoselectivities in non-reversible rhodium-catalyzed hydroformylations of a variety of unsaturated substrates have been elucidated with computational methods by examining the stability of the relevant alkyl rhodium transition states (TS) [12a]. The theoretical results turn out to be in good agreement with the experimental ones obtained in mild reaction conditions, i.e. regioselectivities and diastereoselectivities determined on the alkyl formation TS correspond to those determined on the final aldehyde products. On the contrary, experiment and theory produce remarkably different results in the hydroformylation of vinylidenic olefins, such as 1,1-diphenylethene, carried out at high temperature (100 °C), where β-hydride elimination occurs. In order to explain this behavior, the whole reaction mechanism has been investigated. This review reports the most significant examples concerning both reversible and non-reversible processes using unmodified rhodium catalysts.

2. Rhodium-catalyzed hydroformylation of olefins: general remarks

The hydroformylation reaction or "oxo" synthesis provides the formal addition of CO and H_2 to an olefinic double bond catalyzed by transition metal-based precursors. In the case of terminal olefins, two aldehydic isomers are obtained, the branched (*b*) and the linear (*l*) ones (Chart 1), as the largely prevalent products.

An adapted scheme of the generally accepted mechanism [15] for hydroformylation processes of vinylic substrates catalyzed by unmodified rhodium precursors, proposing the rhodium–carbonyl hydride [$HRh(CO)_3$] as the catalytic active species of the reaction, is reported in Chart 2.

The rhodium hydride tricarbonyl species easily coordinates the vinyl substrate generating the π complex (**1**), which is converted into the alkyl rhodium intermediates (**2**) through insertion of the alkene into the Rh–H bond. Addition of CO to the tricarbonyl species **2** gives the tetracarbonyl one. Migratory insertion of the alkyl moiety onto a CO molecule coordinated to the metal center provides the acyl-rhodium species **3**, which, at the end of the catalytic cycle, interacts with molecular hydrogen, giving rise to aldehydic products and regenerating the rhodium tricarbonyl hydride catalytic species.

The alkene insertion into the Rh–H bond gives rise to the alkyl metal intermediates. This step can be reversible or non-reversible, depending on the substrate nature and the reaction conditions. Under mild conditions, i.e. at room temperature, the insertion is a non-reversible step; this is very important because the regioselectivity for the formation of the branched and the linear rhodium alkyl

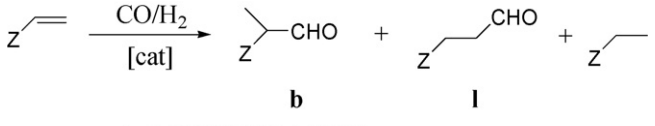

Chart 1. Schematic hydroformylation reaction of terminal olefins.

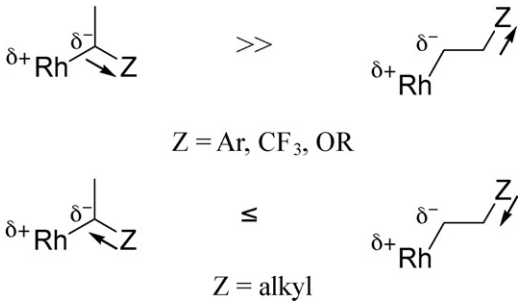

Fig. 1. Stabilization of alkyl-rhodium intermediates arising from the hydroformylation of different alkenes.

(Fig. 1) intermediates determines the regioselectivity for the formation of the final aldehydes. On the contrary if the alkyl formation is reversible, the selectivity determining step will occur later.

Both electronic and steric effects determine the regioselectivity for the formation of rhodium alkyls. Indeed, the hydroformylation under mild conditions of vinyl aromatic substrates such as styrene [16], vinylfurans [17], vinylthiophenes [18], vinilpyrroles [19] and vinylpyridines [8,20], always provides a large predominance of the branched isomer over the linear one (*b*/*l* = 95/5 for styrene). As far as oxygen containing substrates are concerned, vinyl ethers provide a regioisomeric ratio *b*/*l* ≥ 80/20 [5]. Under the same conditions, alkenes with α hydrogens (i.e. linear 1-alkenes) give the two regioisomers in almost 1:1 molar ratio [21]. An oxygen in β position to the vinyl group favors the formation of the branched isomers as observed for (allyl)ethyl ether (*b*/*l* = 70/30) and similar substrates [5]. The linear isomer largely predominates over the branched ones in the hydroformylation of 3-alkyl substituted vinyl alkenes (i.e. 3-methylbut-1-ene) [22] (Table 1).

In the case of hydroformylation of vinylidenic substrates reacting only at high temperatures (>80 °C), the linear isomer is almost exclusively produced whatever kind of Z substituent is present (dialkyl, arylalkyl, diaryl) [23].

At higher reaction temperature (>90 °C) and decreasing the CO and H_2 partial pressure, the amount of linear aldehyde generally increases. Under these conditions, the step of formation of the isomeric alkyl rhodium intermediates becomes reversible via a β-elimination process involving mainly the branched species. Thus the whole process brings about a partial isomerization of the branched alkyl isomer into the linear one and hence determines an increase in the linear aldehyde content. In the case of styrene, for instance, a strong increase in the linear aldehydic isomer (*b*:*l* = 98/2 at 20 °C to 64/36 at 130 °C) is observed [24]. For (ethyl)vinyl ether the above increase is lower, the percentage of linear aldehyde rang-

Table 1
Selected values of regioisomeric ratio in the hydroformylation of unsaturated substrates in the presence of unmodified rhodium precursors.[a]

Substrates	*T* (°C)	*P* (bar)[b]	Reaction times (h)	*b*:*l*[c]
Fluoroethene	80	110	6	100/0
3,3,3-Trifluoropropene	80	110	6	97/3
Substituted styrenes	20	60	16	95/5–98/2
(Vinyl)ethyl ether	20	100	9	83/17
3,3-Dimethylbutene	20	60	16	0/100
Vinyl acetate	20	60	16	>99/1
1-Hexene	15	100	6	52/48
(Allyl)ethyl ether	20	100	6	70/30
2-Phenylpropene	100	100	3	<1/99
1,1-Diphenylethene	100	100	20	<1/99
2-Methylpropene	100	100	1	0/100

[a] At complete substrate conversion.
[b] CO/H_2 = 1:1.
[c] Regioselectivity.

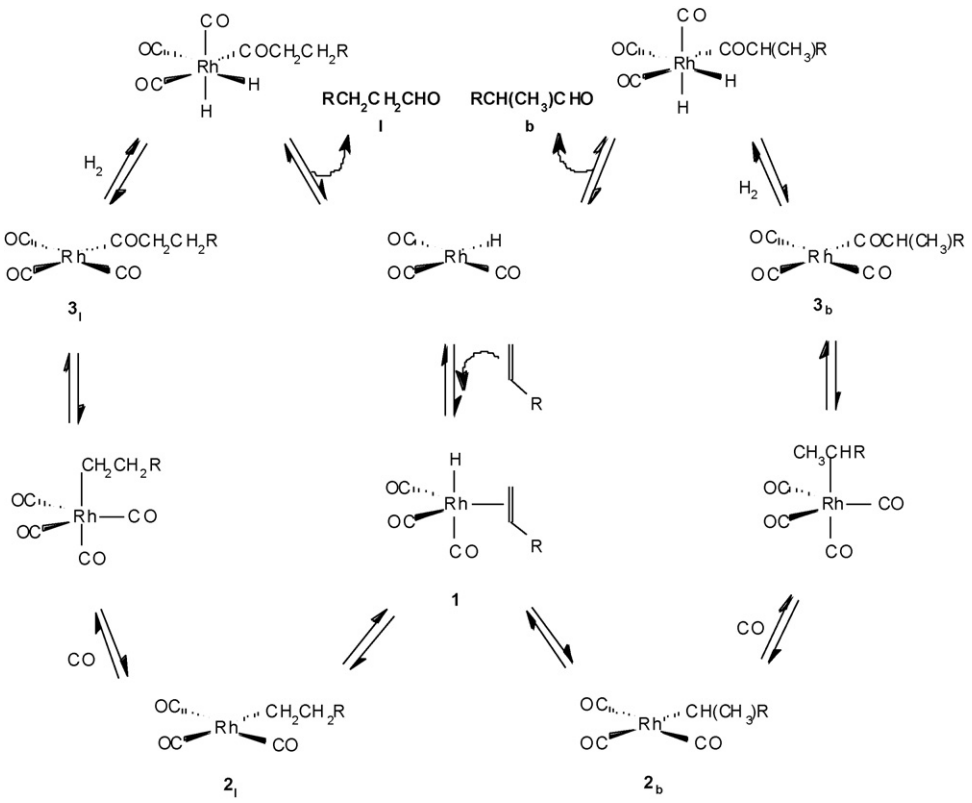

Chart 2. Wilkinson's catalytic cycle (originally proposed for the hydroformylation of alkenes with $HRh(PR_3)_2CO$).

ing from 12% at 20 °C to 24% to 100 °C [5]. In the case of vinylidenic alkenes, the linear aldehyde isomer is obtained with a complete selectivity at any temperature (80–130 °C) [23].

3. Investigation of alkyl metal intermediate formation

The investigation of the hydroformylation reaction can be carried out via well-established experimental approaches. The last years, however, besides synthesis and structural/spectroscopic characterization of the reaction outcomes, have witnessed the development and application of computational methods to elucidate the alkyl metal intermediate formation step using unmodified Rh catalysts. In what follows, we separately summarize experimental and theoretical results, pointing out their mutual interplay.

3.1. Experimental approach: rhodium-catalyzed deuterioformylation experiments both at room and high temperature

Deuterioformylation experiments carried out at partial substrate conversion have proved to be an excellent tool to investigate the alkene insertion step and then the nature and the fate of the involved alkyl intermediates [25–27]. Interestingly the regioselectivity values observed for hydroformylation experiments were very similar to the regioselectivity values obtained under deuterioformylation conditions for all substrates examined. Thus the above results strongly suggest that the information arising from deuterioformylation runs can be extended to hydroformylation ones.

As shown in Chart 3 for vinyl substrates, if a deuterated alkyl species undergoes a β-hydride elimination process, the elimination of Rh–H is favored over that of Rh–D, because of the well-documented kinetic isotope effect observed in this kind of process [2]. Thus β-hydride elimination from the linear alkyl species gives rise to an alkene deuterated at the carbon atom in position 2, while the analogous process for the branched alkyl intermediate generates an alkene deuterated at the terminal position of the double bond. Examination by ^2H NMR spectroscopy of the crude deuterioformylation mixture at partial substrate conversion gives direct information, both qualitative and quantitative, on the occurrence of a β-elimination process, i.e. on the reversibility of formation of the alkyl intermediates, and the nature of involved alkyls.

At 20 °C no signals due to the deuterated alkene are present in the ^2H NMR referred to the case of (ethyl)vinyl ether [5] (Fig. 2), indicating that no β-elimination process takes place and hence the formation of the alkyl intermediates is a non-reversible step.

Analogous experiments carried out at room temperature with styrene (Fig. 3) as well as 1-hexene [25] and (allyl)ethyl ether [5], clearly show that no β-hydride elimination occurs under these mild

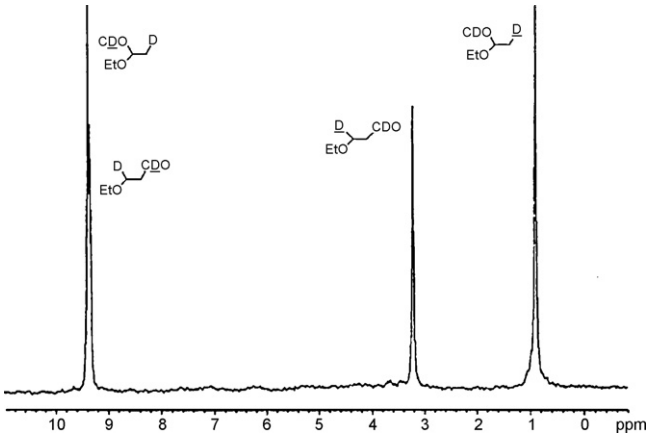

Fig. 2. ^2H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude mixture resulting from deuterioformylation of (ethyl)vinyl ether at 20 °C.

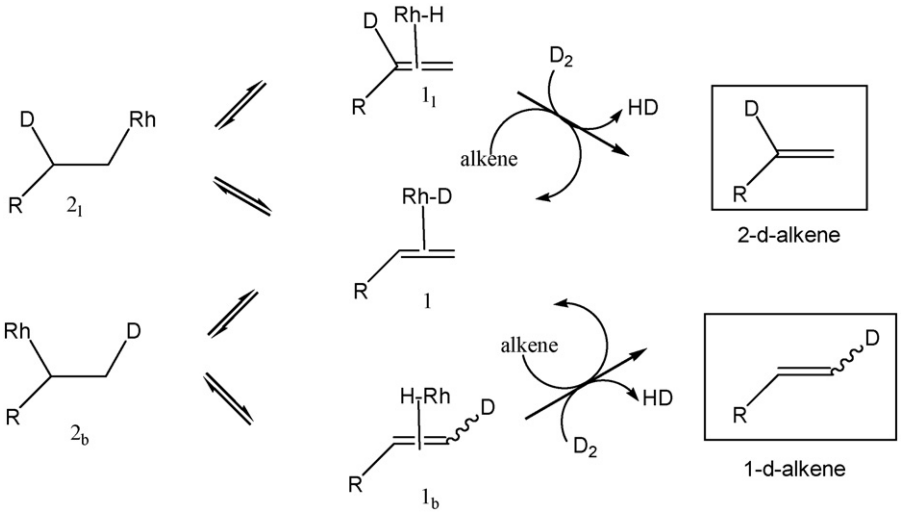

Chart 3. Schematic representations of deuterioformylation experiments.

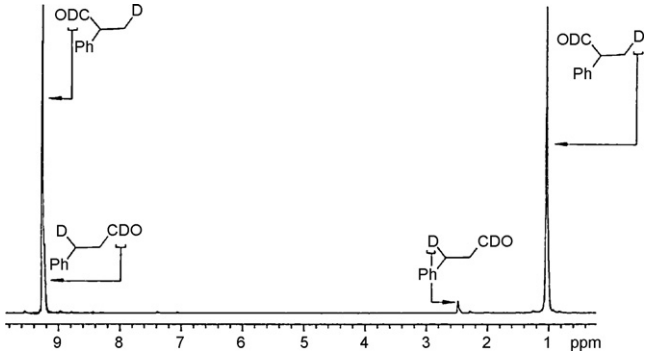

Fig. 3. ^{2}H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude mixture resulting from deuterioformylation of styrene at 20 °C.

conditions. This means that the alkene insertion into the Rh–H bond is non-reversible and hence the isomeric alkyl rhodium intermediates are directly transformed into the acyl species to give isomeric aldehydes.

On the contrary, the ^{2}H NMR spectrum of a mixture resulting from deuterioformylation of (ethyl)vinyl ether at 100 °C and 30% substrate conversion (Fig. 4) [5] shows the presence of

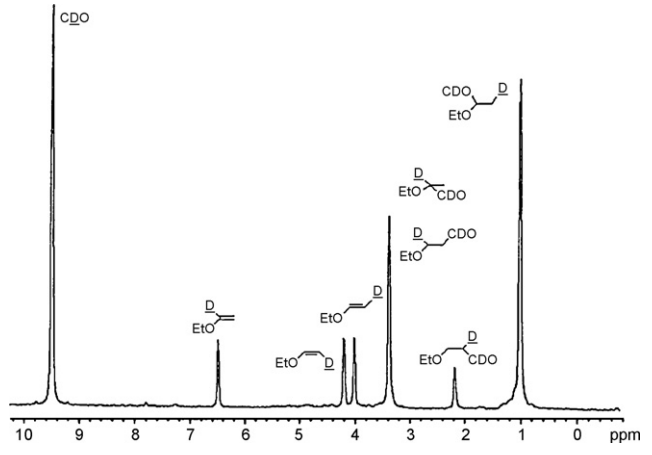

Fig. 4. ^{2}H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude mixture resulting from deuterioformylation of (ethyl)vinyl ether at 100 °C.

Et–O–CH=CHD (signals at 4.14 and 3.97 ppm) and of Et–O–CD=CH_2 (signal at 6.44 ppm).

These species clearly come from the branched alkyl rhodium intermediate and the linear one respectively, via β-hydride elimination. In particular, β-hydride elimination occurs more readily for the branched alkyl intermediate than for the linear one, as shown by the lower intensity of the signal at 6.44 ppm with respect to those at 3.97–4.14 ppm, accounting for the increase, although to a low extent (12% to 24%), of the linear aldehyde. Analogous behavior has been observed also for allylic substrates, e.g. 1-hexene and (allyl)ethyl ether. In these latter cases, the β-hydride elimination from the branched alkyl intermediate gives mainly the isomeric internal alkene deuterated at the terminal position (Z–CH=CH–CH_2D).

In contrast, in the case of styrene and other aromatic substrates [24,19], β-hydride elimination occurs selectively for the branched intermediate, at least at temperatures lower than 100 °C, since the signal at low fields, typical of deuterated alkene, is of a very low intensity into ^{2}H NMR spectrum (Fig. 5).

A case where the deuterioformylation played a crucial role was that of 1,1-diphenylethene [27]. In the ^{2}H NMR spectrum relative to the experiment carried out at 100 °C and at 15% conversion, together with the signals at 9.07 and 4.08 ppm due to deuterium atom of the aldehyde group and the deuterium atom on the carbon in α-position to the phenyl groups, respectively, a resonance of high intensity was present at 5.16 ppm (Fig. 6).

This resonance can be assigned to a deuterium atom bonded to the terminal carbon atom of 1,1-diphenylethene. On the basis of the relative intensities of the deuterium signals of the olefin and aldehydic species, we can conclude that ~2 mol of olefin are formed for each mole of aldehyde. Thus it can be assumed that the branched intermediate is formed to a larger extent with respect to the expected linear isomer, but the formation of the acyl-rhodium intermediate from the tertiary alkyl to give the corresponding branched aldehyde is not equally favored. In fact there are no traces of the quaternary aldehyde deriving from migratory insertion of this alkyl group onto the CO moiety and subsequent oxidative addition of H_2. At higher conversion, the deuterated olefin competes with the undeuterated one: already at 34% of conversion it becomes the substrate preferentially hydroformylated, as showed by the signal at 2.38 ppm, due to a deuterium atom bonded to the carbon atom in α-position to the carbonyl group. It must be stressed that the classical approach based on the sole analysis of regioisomeric ratios would have led to the erroneous conclu-

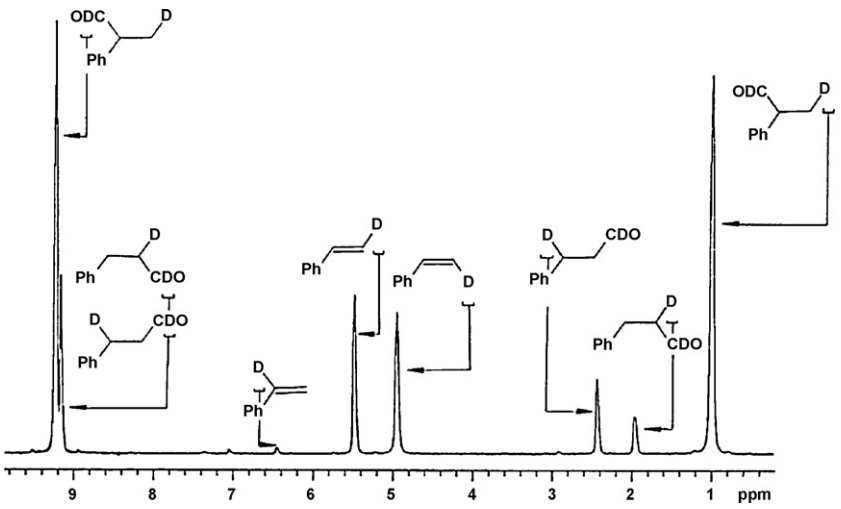

Fig. 5. ^{2}H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude mixture resulting from deuterioformylation of styrene at 100 °C.

sion that no tertiary metal-alkyl intermediate was formed in the hydroformylation of 1,1-diphenylethene, as no branched aldehyde is obtained. Deuterioformylation experiments carried out on vinylidenic alkenes containing two alkyl groups [23] show that the formation of a tertiary alkyl-metal intermediate occurs only to a very low extent (2-methylpropene) or that it does not occur at all (2,3,3-trimethylbutene).

Deuterioformylation experiments have been precious also in elucidating the unusual process giving ethylpyridine in the rhodium-catalyzed hydroformylation of 4-vinylpyridine [28]. The analysis of the isolated 4-ethylpyridine derived from deuterioformylation mixtures showed that, with the use of unmodified $Rh_4(CO)_{12}$, 4-ethylpyridine contained two deuterium atoms (Fig. 7), one for each of the two carbons belonging to the ethyl moiety (Fig. 7a), while in the case of a phosphine-modified $Rh_4(CO)_{12}$ catalyst at low substrate conversion the corresponding product contained about one deuterium atom, almost exclusively on the β-carbon of the ethyl group (Fig. 7b).

In the case of unmodified $Rh_4(CO)_{12}$, a slow oxidative addition of D_2 to the branched alkyl rhodium intermediate accounts for the formation of the expected dideuterated product. Interestingly a cleavage of the rhodium–carbon bond in the branched alkyl metal intermediate by the hydroxyl proton of the branched aldehyde in its enolic form accounts for the formation of monodeuterated 4-ethylpyridine together with the trideuterated aldehyde (Chart 4).

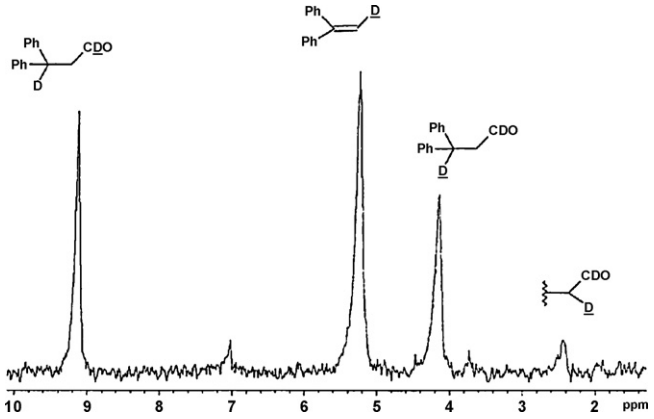

Fig. 6. ^{2}H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude reaction mixture obtained by deuterioformylation of 1,1-diphenylethene at 100 °C and 15% substrate conversion.

This hypothesis was confirmed by the reaction between deuterated enolic form (–OD) and not deuterated alkyl giving an ethylpyridine monodeuterated in α position [28].

3.2. Theoretical approach: DFT studies (B3P86/6-31G* and effective core potentials on Rh coupled with the LanL2DZ valence basis set)

3.2.1. Vinyl olefins

Our first theoretical investigation carried out on hydroformylation reactions using an unmodified rhodium catalyst (H–Rh(CO)$_3$) addressed only the regioselectivity issue, but on a large set of substrates (such as propene, 2-methylpropene, 1-hexene, 3,3-dimethylbutene, fluoroethene, 3,3,3-trifluoropropene, vinylmethylether, allylmethylether, and styrene) at the B3P86/3-21G level for preliminary surface scans and eventually at the B3P86/6-31G* level, while Rh was described with effective core potentials, that include some relativistic effects for the electrons near the nucleus, in the LanL2DZ valence basis set. That study represented the first attempt to explore in a comprehensive way the hydroformylation regioselectivity from a theoretical point of view [12a]. Earlier theoretical studies focused on the hydroformylation of ethylene with modified catalysts [9,10] or used propene as the model olefin and pure density functional theory (DFT) [29] or hybrid DFT/molecular mechanical (QM/MM) methods [30] to account for steric effects when bulky phosphines are considered. An unmodified catalyst (a cobalt–carbonyl species) was employed in Ref. [29a], whereas only catalytic precursors modified with phosphines were considered elsewhere [29b,30]. With the exception of Ref. [30], the simplest phosphine was in general used as a ligand, although PH_3 is not suited as a model of triphenylphosphine or other phosphines [31]. A thorough examination of the various possible H–Rh(CO)$_3$–olefin complexes was performed with extensive comparisons to the adducts with modified catalysts, such as H–RhPH$_3$(CO)$_2$ or H–Rh(PH$_3$)$_2$CO. The computed geome-

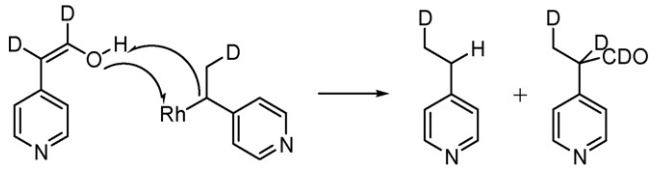

Chart 4. Acidic cleavage of the Rh–C bond by the enolic form of the branched aldehyde.

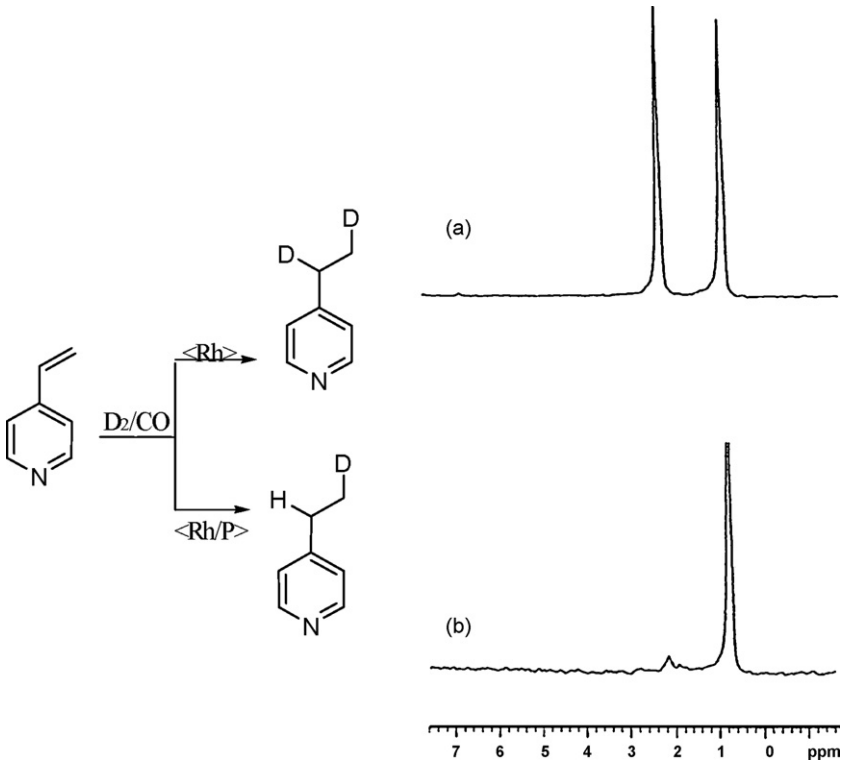

Fig. 7. ^{2}H NMR spectrum (46 MHz) of 4-ethylpyridine recovered by distillation from (a) deuterioformylation of 4-vinylpyridine at total substrate conversion with $Rh_4(CO)_{12}$; (b) deuterioformylation of 4-vinylpiridine at 26 % substrate conversion with $Rh_4(CO)_{12}/PMe_2Ph$ (1:4).

tries turned out to be in satisfactory agreement with the X-ray ones.

The B3P86/3-21G potential energy surfaces for the olefin insertion reactions leading to intermediates along the pathways to branched or linear aldehydes were considered using styrene as a model olefin. The activation energies for the alkyl rhodium transition states, computed at both the B3P86/3-21G and 6-31G* levels, leading to $Rh(CO)_3$ alkyl intermediates along the pathways to branched or linear aldehydes, allow the regioselectivity ratios to be predicted, since they are in very good agreement with the experimental ones evaluated on the isomeric aldehydes (Fig. 8).

After gaining a deep insight into the reaction mechanisms from the accurate investigation of the PES carried out for two test cases, it was possible to focus the attention only on the stationary points of the various surfaces. The regioselectivity was then estimated making use of a formula, which takes into account only the relative energies of the *b* and *l* transition states:

$$b : l = k_b : k_l = \sum e^{-\Delta G_b^{\neq}/RT} : \sum e^{-\Delta G_l^{\neq}/RT}$$

$$= \sum e^{-\Delta\Delta G^{\neq}/RT} \approx \sum e^{-\Delta\Delta E^{\neq}/RT}$$

This assumption is viable when the olefin insertion occurs irreversibly. An evaluation of the isomeric ratios for the various compounds can thus be performed, by using the transition state barriers ($\Delta E^{\neq}$) determined for all the possible conformers. Since both basis sets produce analogous regioselectivities, only the 6-31G* results are reported in Table 2, as compared to the proper experimental results, already mentioned above at least in part.

The agreement between computed and experimental data is in general very good, although ratios close to 50:50 are much more sensitive to small energy differences than those largely favoring an isomer over the other (i.e. 100:0 or 0:100). Furthermore, the use of the internal energy is preferable to the use of the free energy when the substrates are prone to internal rotations, hindered or free, because rotations are considered as true vibrations in the harmonic vibrational analysis, thus significantly affecting the thermodynamic functions for propene and primarily for 1-hexene.

In contrast, when the reaction is reversible, marked differences between computed and experimental ratios are observed, requiring a theoretical investigation extended to the whole reaction paths (*vide infra*).

3.2.2. Vinylidenic olefins

Aryl or alkyl 1,1-disubstituted olefins, as stated above, are known to afford the linear aldehyde as the only product [23,32–33]. Interestingly enough, this result is fairly well reproduced for 2-methylpropene using the TS relative stabilities (Table 2). Conversely, for other substrates (for which the reaction is probably reversible), the theoretical *b*:*l* ratios turn out to be about 50:50 (or even 72:28 as in the case of 1,1-diphenylethene [34]), instead of decidedly favoring linear aldehydes.

Experimental findings arising from deuterioformylation runs actually support that a tertiary alkyl-Rh intermediate is formed in

Table 2
Regioselectivity (*b*:*l*) for the complexes with unmodified rhodium catalysts, obtained from the B3P86/6-31G*/LanL2DZ activation energy, $\Delta E^{\neq}$, and free energy, $\Delta G^{\neq}$. Experimental ratios are shown for comparison.

Substrate	*b*:*l* [$\Delta E^{\neq}$]	*b*:*l* [$\Delta G^{\neq}$]	*b*:*l* [exp]
Propene	56:44	59:41	50:50
1-Hexene	50:50	10:90	48:52
3,3-Dimethylbutene	15:85	9:91	10:90
F-Ethene	98:2	97:3	100:0[a]
3,3,3-Trifluoropropene	98:2	97:3	97:3[a]
Vinylmethylether	86:14	95:5	83:17
Allylmethylether	87:13	88:12	70:30
Styrene	98:2	98:2	98:2
2-Methylpropene	9:91	10:90	1:99

[a] From Ref. [16].

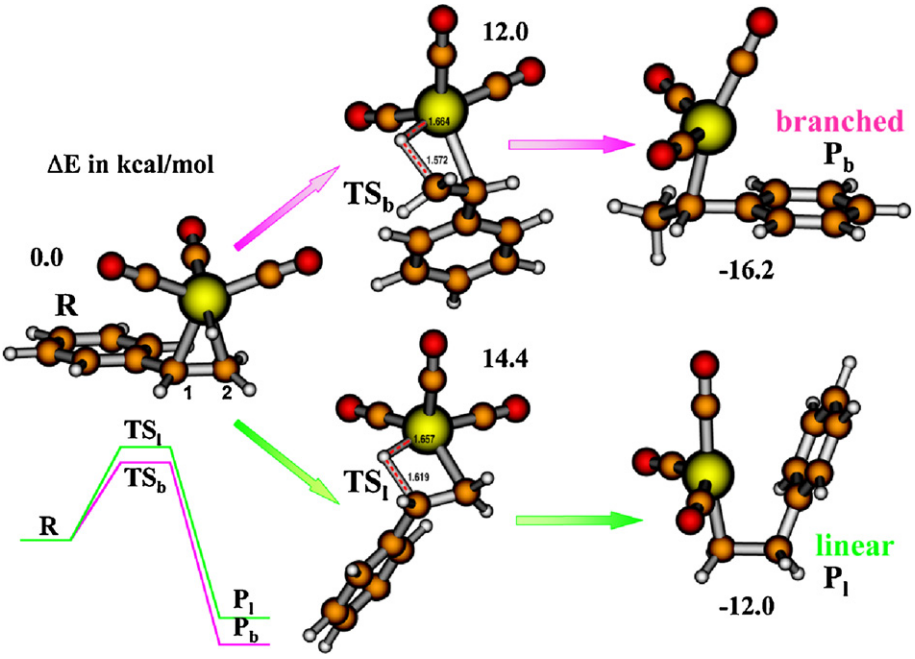

Fig. 8. Structures and energies along the branched and linear reaction paths (step **1** to steps $\mathbf{2}_b/\mathbf{2}_l$ in Chart 2) for the Rh-catalyzed hydroformylation of styrene.

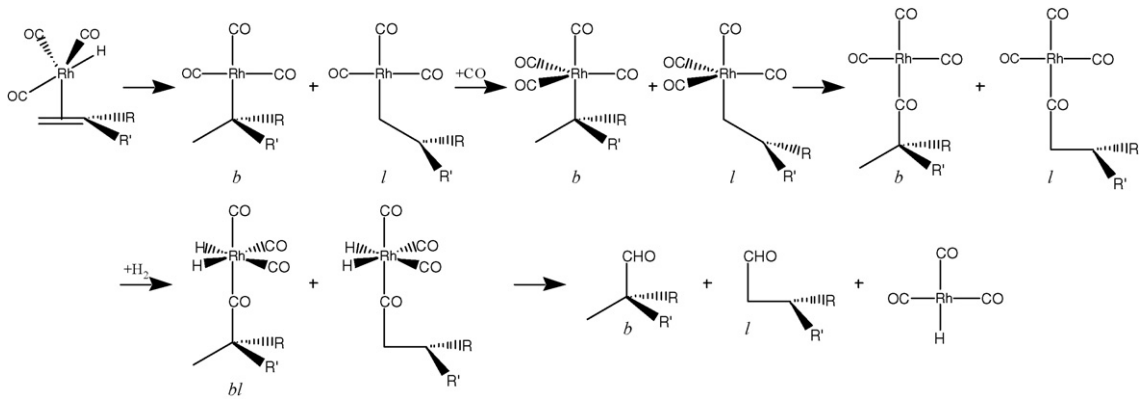

Chart 5. The Rh-catalyzed hydroformylation reaction for 1,1-diphenylethene ($R = R' = \Phi$).

a larger amount than the linear isomer under hydroformylation conditions of 1,1-diphenylethene in the early stage of the reaction (in agreement with our aforementioned theoretical results [34]), but without formation of the branched aldehyde [27]. This was attributed to the different behavior of the alkyl $Rh(CO)_4$ branched species during the migratory insertion step, probably prevented by steric reasons, rather than in their formation step. Consequently the branched intermediate was considered to undergo β-elimination only [27]. Despite the merits of deuterioformylation experiments in rationalizing mechanistic aspects, especially at partial substrate conversion, it is however difficult, relying only on them, to fully clarify the reasons for the reaction outcomes. Therefore, a thorough computational investigation of the complete reaction pathway (Chart 5) has been carried out on 1,1-diphenylethene as a test case, in order to understand the origin and the fate of the various species [34].

The energy profiles for the first reaction steps, displayed in Fig. 9, do not shed light on the reaction experimental outcomes, since the transformation of a tricarbonylmetal-alkyl compound into a tetracarbonyl metal-alkyl one is generally considered to be spontaneous. Both tetracarbonyl species turn out to be more stable indeed than the tricarbonyl ones. Thus, the subsequent step, i.e.

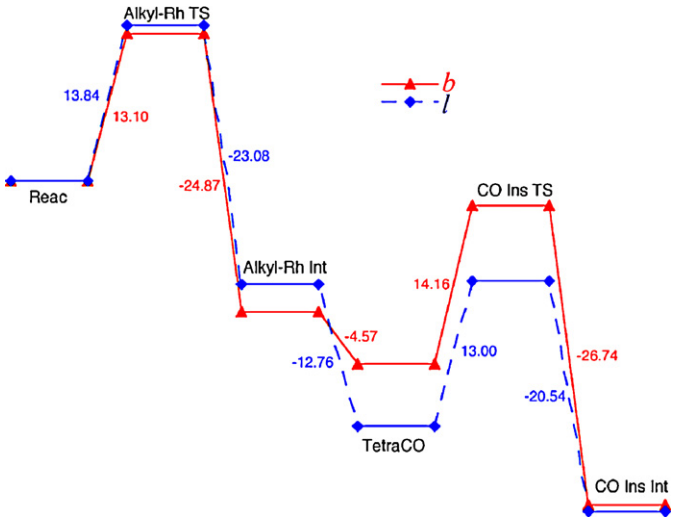

Fig. 9. Branched (*b*) and linear (*l*) reaction profiles (**1** to $\mathbf{3}_l/\mathbf{3}_b$) for 1,1-diphenylethene (a CO at infinite separation is included in the first three steps for the sake of comparison).

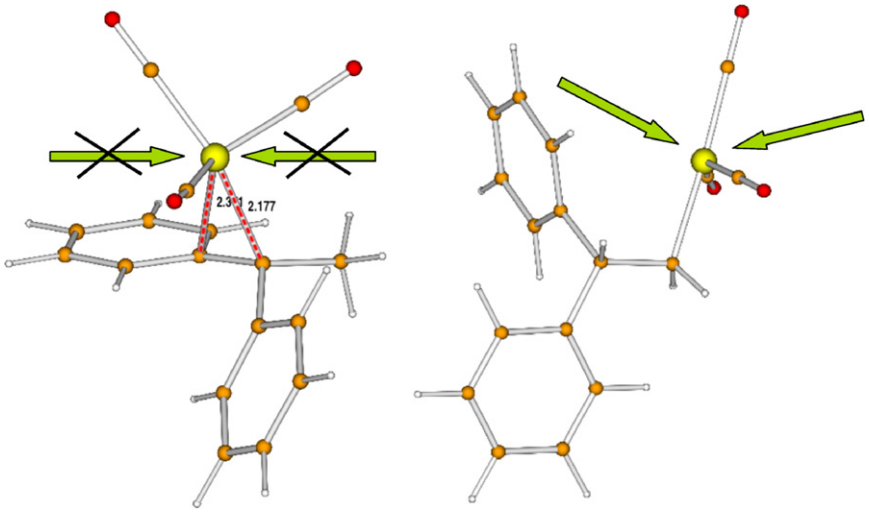

Fig. 10. B3P86/6-31G*/LanL2DZ structures of branched (left) and linear (right) Rh-tricarbonyl intermediates.

the migratory insertion of the tertiary alkyl onto the coordinated CO group, has invariably been regarded as the critical step [23a].

The *b* path, leading to the branched aldehyde, is initially more favorable than the *l* one: the TS differential stability produces a *b*:*l* ratio of 72:28, as mentioned above. The alkyl-Rh(CO)$_4$ branched complex is less stable than the linear one, but the difference in barrier heights for the CO migratory insertion is not dramatic (13 vs 14 kcal/mol). The striking difference between linear and branched tricarbonyl intermediates (displayed in Fig. 10) suggested to take into account the approaching paths to Rh of the incoming CO group, although this is generally considered in the literature a low energy step.

Actually, experimental evidence was interpreted in favor of a rate-determining H_2 oxidative addition step [15b and c] or CO migratory insertion step [27]. Interestingly, also theoretical studies making use of phosphine-modified catalysts indicated that CO insertion is rate-determining [10,14].

From the computed reaction profiles, it turns out evident that an additional CO can approach Rh easily from both faces in the case of the linear complex. In contrast, in the case of the branched one, there is a remarkable barrier. The barrier is due to the fact that the incoming CO has to overcome the agostic interaction (Fig. 10, left hand side) established in the branched tricarbonyl intermediate between Rh and the π density of one of the phenyl rings, whereas in the linear tricarbonyl intermediate the closest phenyl ring is farther than 3 Å from Rh. All the subsequent reaction steps leading to the aldehydes have been investigated, considering all the possible conformers of each isomer (linear or branched) not to miss the most stable ones. Again all the stationary points have been confirmed via frequency calculations, allowing the free energies to be calculated as well. Free energies (Fig. 11) are to be taken into account in reaction mechanisms where the number of molecules involved in the reaction changes along the pathway. The difference between the potential energy (*E*, lower part) and free energy (*G*, upper part) profiles is stunning indeed.

While the alkyl-Rh(CO)$_3$ TS barriers are almost insensitive to the inclusion of thermal corrections, the stabilities of the alkyl-Rh(CO)$_3$ intermediates remarkably decrease. Conversely, the barrier for the passage from the alkyl-Rh(CO)$_3$ intermediate to the alkyl-Rh(CO)$_4$ one actually increases from 3.3 to 15.7 kcal/mol at 373 K. An analogous shift in the free energies is maintained for the subsequent steps, as evident from Fig. 12, indicating that the real difference between the two pathways is the upward shift in the profile determined by the CO addition TS. The first obvious consideration is related to the overall trend of both profiles: the internal energy ones present high initial barriers for both linear and branched pathways, while all the other TS are in any case lower than the reactant level. In addition the branched alkyl-Rh TS is slightly more favorable than the linear one, thus confirming the experimental results obtained at partial substrate conversion [23a].

Therefore the β-regioselectivity in the hydroformylation of 1,1-diphenylethene is due to the remarkable activation free energy for the addition of the fourth CO group (obtained only in the case of the branched alkyl-Rh tricarbonyl intermediate) that causes the branched profile to become higher than the linear one by a nearly constant amount. This step, usually overlooked because of the stability of the tetracarbonyl Rh intermediates with respect to the tricarbonyl ones, turns out to be the critical step instead of the migratory insertion of the Rh–C(alkyl) moiety onto the coordinated CO, thus far considered responsible for this result in some experiments and in previous calculations using phosphine-modified catalysts, as mentioned above. Because of that free energy increase along the path leading to the branched aldehyde, the forward barriers are higher than the backward ones, and the branched path is early abandoned; thus, the branched alkyl-Rh intermediate returns to the reactant stage producing again branched and linear Rh-alkyls in the *b*:*l* proportion, until the olefin is completely consumed, yielding a product that practically consists only of the linear aldehyde.

One of the referees suggested a possible different mechanism for the final step, for instance metathesis. Our goal, however, was to assess whether the linear and branched profiles were similar or not and why. A different attack of H_2 in the last part of the mechanism should not affect the energetic of the CO addition and thus does not alter the conclusions of our recent investigation [34].

Hydro(deuterio)formylation experiments as well support a β-hydride elimination mechanism [6,23a,27], although they cannot indicate which step is responsible for that behavior.

Therefore in the case of reversible hydroformylation reactions any stationary points on the potential energy surface must be considered, because avoiding of doing so can lead to erroneous results irrespective that zero point energy and thermal corrections have been added.

3.3. Regioselectivity and diastereoselectivity in the hydroformylation of chiral substrates

Deuterioformylations and theoretical calculations have been successfully employed in the elucidation of regioselectivity and diastereoselectivity of chiral substrates characterized by

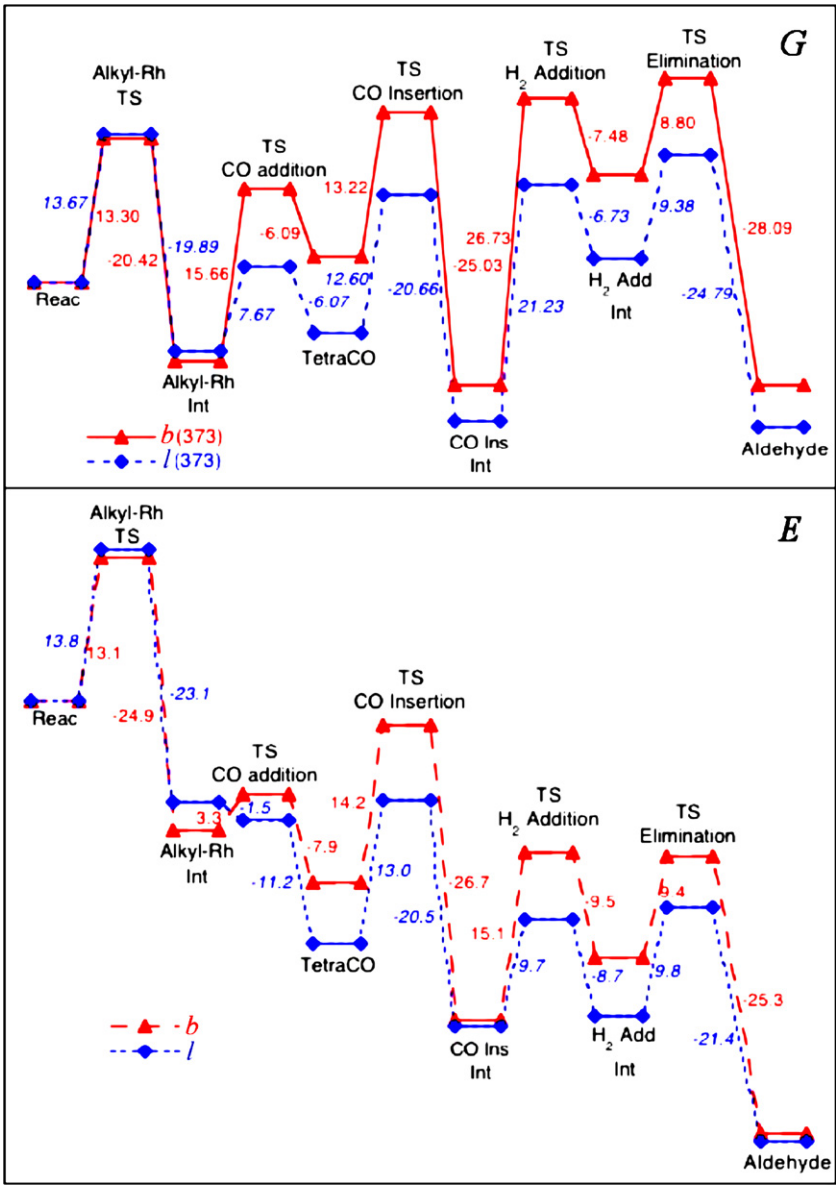

Fig. 11. Branched (*b*, triangles) and linear (*l*, diamonds) potential energy (*E*)/free energy (*G*, at 373 K) reaction profiles (kcal/mol) for 1,1-diphenylethene. Italic values refer to linear profiles.

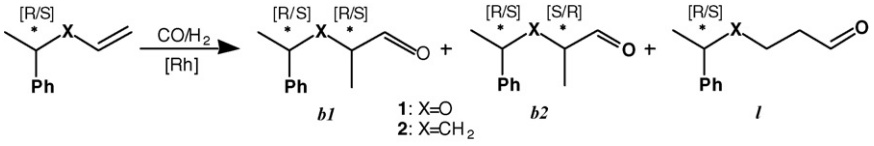

Chart 6. Hydroformylation reaction for (1-vinyloxy-ethyl)-benzene (**X** = O) and (1-methyl-but-3-enyl)-benzene (**X** = CH_2).

stereogenic center in β-position to vinyl moiety, namely (1-vinyloxy-ethyl)-benzene (**X** = O) and (1-methyl-but-3-enyl)-benzene (**X** = CH_2) (Chart 6). Also in the case of chiral substrates, deuterioformylation occur without β-elimination [35] and hence regioselectivity and diastereoselectivity originate at level of alkyl intermediate formation.

This fact should allow a quantitative evaluation of regio- and diastereo-isomeric ratios via computational approaches [36,37]. In order to estimate the diastereoselectivity, it is necessary to consider not just the total amount *b* of branched diastereomers obtained, but its individual components, *b1* and *b2*, as shown in Chart 6.

Indeed, the branched alkyl rhodium intermediates can be either RS or RR (by considering the chiral reactant as R only, for the sake of simplicity), corresponding to the RR (*b1*) and RS (*b2*) branched aldehydes, respectively.[1] The same holds for the linear alkyl rhodium

[1] The chirality of the developing chiral center for the alkyl rhodium TS is in this case opposite to that obtained for the aldehyde product. This is due to the formal change of chirality at the C_2 carbon atom occurring because of the Cahn-Ingold-Prelog priority rules (Rh > O > CH_2 and O > CHO > CH_3, for alkyls and aldehydes, respectively). However, to avoid misunderstandings, we refer to the aldehyde chirality, even when discussing about TS.

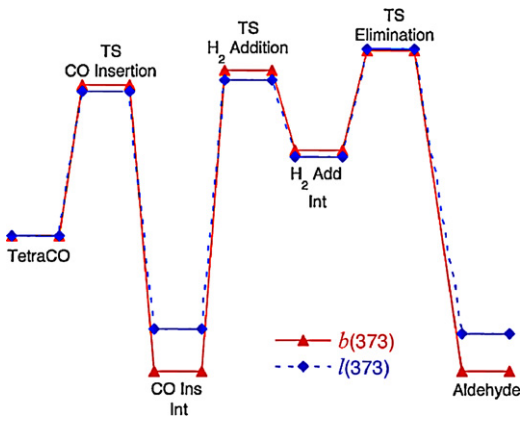

Fig. 12. Branched (*b*, triangles) and linear (*l*, diamonds) free energy reaction profiles at 373 K for 1,1-diphenylethene with the alkyl-Rh(CO)$_4$ intermediate (TetraCO) values superimposed.

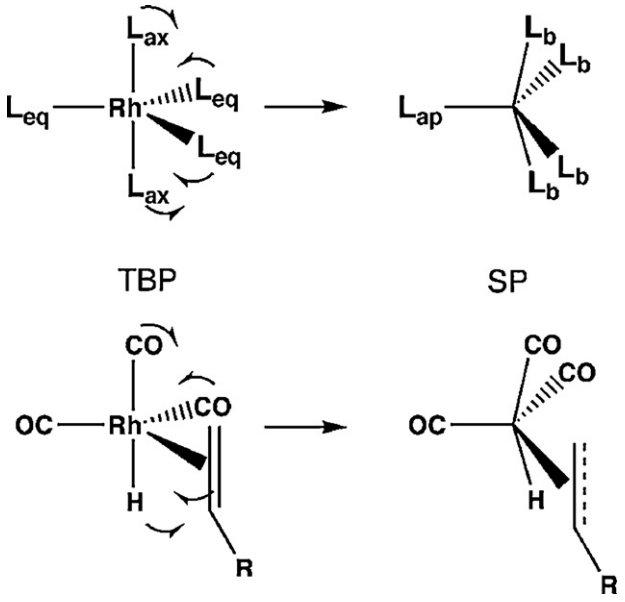

Chart 7. Berry pseudorotation mechanism going from the TBP reactant adduct to the SP transition state.

intermediates, where *l1* and *l2* diastereomers can be obtained from the calculations as well as from deuterioformylation experiments. The evaluation of diastereomeric ratios can be performed in analogy to regioisomeric ratios, by using the relevant relative stabilities of the transition states ($\Delta\Delta E^{\neq}$):

$$b1 : b2 = k_{b1} : k_{b2} = \sum e^{-\Delta G_{b1}^{\neq}/RT} : \sum e^{-\Delta G_{b2}^{\neq}/RT}$$
$$= \sum e^{-\Delta\Delta G^{\neq}/RT} \approx \sum e^{-\Delta\Delta E^{\neq}/RT}$$

From the computational viewpoint, one of the main problems for this kind of systems is due to the great number of conformers to be considered, as can be derived from the number of rotatable single bonds in the substrate. In addition, either one of the opposite equatorial CO groups in the trigonal–bipyramidal (TBP) reactant adduct (see Chart 7) can take the apical position in the square-planar pyramidal (SP) arrangement of the complex with the catalyst at the TS, producing distinct structures and energies. Failure of taking into account even one of the most stable TS rotamers can blur the overall theoretical picture of selectivity. Nonetheless, due to the difficulty of discriminating between real vibrations and hindered rotations, only internal energies have been used to calculate the ratios. This is perfectly acceptable in this case, because the number of species does not change during this reaction step.

An interesting outcome of this study is the significant difference in the internal geometries for the transition states for **1** between branched and linear structures as well as between the branched diastereomers themselves (shown in Fig. 13), because of the rigidity induced in the structure by the presence of the ethereal oxygen. Therefore, in the vinyl ether (**1**), the main chain atoms ($C_1C_2O_3C_4$) turn out to be roughly co-planar, while the main electronic stabilizing interaction in *b1*_0 is due to the ethereal O lone-pairs (lp) staggered with respect to the substituents at C_4. This arrangement is not attainable in the *b2* diastereomers, whose stability significantly decreases especially when the O lp are almost eclipsed to the groups at C_4. This fact, imposing a strong conformational constraint, is responsible for the marked diastereoselectivity in the alkyl formation, reflected in that observed for aldehydes.

By substituting the ethereal O with a CH_2 group (compound **2**), all the most favorable linear and branched transition states turn out to be fairly similar, thus accounting for the low regioselectivity and diastereoselectivity observed. The conformational flexibility about the C_2C_3 bond in the olefin (**2**) permits to relieve the steric hindrance. The asymmetric induction expected by the preexisting chiral center is thus almost completely absent in **2**. For a thorough discussion of structures and results the interested readers are referred to the original articles [36,37], where a comparison between different theoretical descriptions (B3LYP/6-31G*/SBK(d) vs B3P86/6-31G*/LanL2DZ), producing however fairly similar results, is also carried out. We summarize hereafter only the principal results.

In **1**, the branched diastereomeric aldehydes remarkably prevail over the linear *R*-aldehyde (experimental and computed *b*:*l* ratios are 85:15 and 89:11, respectively). Actually it is the branched RR diastereomer (*b1*) that prevails over the RS ones (*b2*), as shown in Fig. 13 (experimental and computed *b1*:*b2* ratios are 88:12 and 96:4, respectively). Conversely in **2**, i.e. when the ethereal O is substituted with a CH_2 group, nearly the same quantity of linear and branched structures is produced, and even the *b1* and *b2* diastereomers are obtained in an equal amount, in excellent agreement with the experiment (experimental and computed ratios are respectively: *b*:*l* = 49:51 and 48:52; *b1*:*b2* = 52:48 and 56:44).

Therefore, both regioselectivities and diastereoselectivities for hydroformylation reactions originate at the alkyl formation step in the case of non-reversible reactions according to the just mentioned results and to our previous theoretical investigations on the regioselectivity carried out on prochiral substrates [12a]. This fact elicited us to make predictions for the substrate without **X** separator, also considered in Ref. [37], although those theoretical results have not been confirmed as yet. Both the regioselectivity (*b*:*l*) and the diastereoselectivity (*b1*:*b2*)[2] turned out to be 44:56.

The importance of the organic part structure in organometallic complexes for hydroformylation reactions is evident from the cited studies as well as the valuable contribution of theoretical methods in exploring experimentally inaccessible species and in interpreting mechanistic aspects.

[2] In Fig. 3 and Table 4 of Ref. [37] as well as in the relevant text, *b1* (*b* therein, notice the different notation) is reported in place of *b2* (*b*′) and *l1* (*l*) in place of *l2* (*l*′) and *vice versa*. Therefore the regioselectivity, defined as *b* + *b*′:*l* + *l*′, is correct, whereas the diastereoselectivity should be inverted (as we did here).

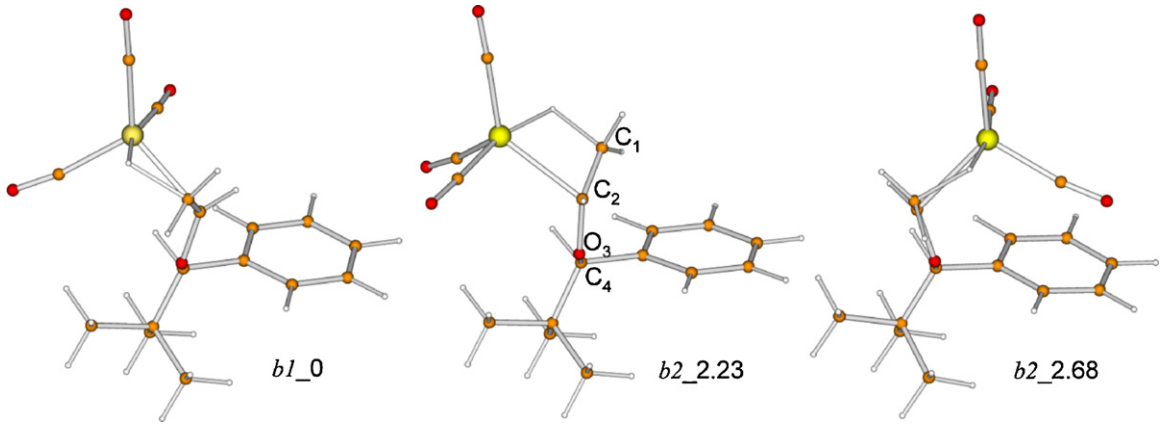

Fig. 13. View along the O_3–C_4 bond of the three most stable branched diastereomers of **1**. Structures named for short as type_ΔE (kcal/mol).

4. Concluding remarks

The investigation of the hydroformylations of a variety of unsaturated substrates (vinyl or vinylidenic olefins) catalyzed by an unmodified rhodium catalyst ($Rh_4(CO)_{12}$) pointed out the relevant role of the substrate structures in determining the selectivities (regio- and diastereo-) of the reaction.

Deuterioformylation experiments are of great importance in determining the behavior of alkyl metal intermediates and demonstrated that their formation is a non-reversible step under mild reaction conditions (20 °C).

Theoretical investigations are very useful under two respects: (i) the regioselectivity of the alkyl intermediate formation is in complete agreement with the regioselectivity of the aldehyde formation; (ii) the stereochemistry of the transition states obtained in this way can explain the regioselectivity and diastereoselectivity of the reaction.

Thus the origin of 1,3-substrate-directed diastereoselectivity in the hydroformylation of the chiral vinyl ether ((1-vinyloxy-ethyl)-benzene) must be related to the stereochemistry of diastereomeric transition states arising from theoretical calculations.

In addition the remarkable and unexpected activation free energy for the addition of the fourth CO group to the branched rhodium-tricarbonyl-alkyl intermediate in the hydroformylation of 1,1-diphenylethene accounts for the complete β-regioselectivity of that reaction.

From the above observations emerges the valuable contribution of theoretical approaches and deuterioformylation in exploring experimentally inaccessible species and in interpreting mechanistic aspects.

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