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# INSIGHT INTO PHOSPHINE EFFECTS ON THE HOMOGENEOUS HYDROGENATION OF AVERMECTINS TO IVERMECTIN CATALYZED BY *IN-SITU* FORMED RHODIUM COMPLEXES

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**Abstract**

A kinetic study of the homogeneous catalytic hydrogenation of avermectins is reported for a series of isosteric *p*-substituted arylphosphines as ligands. The activity of the rhodium complexes formed in situ from $[RhCl(COD)]_2$ increased with increasing the electron-donor capacity of the $P(p\text{-}XC_6H_4)_3$: $P(p\text{-}ClC_6H_4)_3 < P(C_6H_5)_3 < P(p\text{-}CH_3C_6H_4)_3 < P(p\text{-}OCH_3C_6H_4)_3$. As expected, this trend was also observed when using preformed complexes thereof. Linear correlations based on Hammett and Kabachnik treatments are provided as useful tools to guide the exploration work towards improved $[RhCl(COD)]_2/P(p\text{-}XC_6H_4)_3$ catalytic systems.

*Keywords*: Homogeneous hydrogenation, rhodium, phosphine, avermectin, ivermectin

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## INTRODUCTION

Ivermectin (IVM) is widely used in current anthelmintic therapy in livestock due to its safety profile and broad-spectrum activity against endoparasites such as the gastrointestinal nematodes *Cooperia pectinata* in cattle and *Haemonchus contortus* in sheep, and ectoparasites such as *Boophilus spp* ticks in cattle [1]. It is also used to control *Haematobia irritants* (horn fly) populations affecting the health of bovines and consequently their productivity [2]. Recently, IVM has been used for the treatment of onchocerciasis, lymphatic filariasis known as Elephantiasis, and scabies in humans [3]. IVM is obtained by the selective hydrogenation of the 22,23-carbon-carbon double bound of avermectins $B_{1a}$ and $B_{1b}$ (AVM), without affecting the remaining four double bonds. Wilkinson´s catalyst has been the first Rh-based catalytic system used for this purpose [4]. Since the primary patent expired, a strong competitiveness has depressed the price of IVM while that of Rh has continued to rise. In this scenario, the development of more efficient hydrogenation processes becomes relevant because the costliest industrial productions will be withdrawn from the market.

In order to develop less costly alternatives without the need to separately synthesize and purify each complex, the *in situ* synthesis of the catalytic species is (so far) present in all the attempts to improve Chabala´s pioneering process. However, there is scant kinetic information since it has been made available mainly from patents [5]. Only a few papers have approached the topic. Indeed, after reporting the kinetic modeling of the AVM hydrogenation with Wilkinson´s catalyst [6], we have recently studied the hydrogenation kinetics in homogeneous and biphasic systems catalyzed by complexes formed in situ from the common precursor $[RhCl(COD)]_2$ with triphenylphosphine and with sulphonated triphenylphosphines, respectively [7, 8]. S-shaped concentration profiles exhibiting very prolonged induction periods revealed that the above mentioned systems based on catalytic complexes formed in situ under mild hydrogenation conditions are not too good for IVM production.

A study providing some insight into the phosphine effects on the AVM hydrogenation rate with the simultaneous synthesis of the Rh complexes in homogeneous systems might be useful in the search for improved hydrogenation systems. It is well known that the donor properties of phosphine ligands can be modulated by varying the electronic and steric parameters. Even though these factors are not easily separated, a common approach is made to examine such effects while maintaining one of the two factors constant. Therefore, as part of our ongoing studies, here we present results comparing the performance of the AVM hydrogenation catalyzed by complexes *in situ* formed from $[RhCl(COD)]_2$ and *p*-substituted arylphosphines belonging to an isosteric

series varying in electron-donor capacity, i.e., P(*p*-$ClC_6H_4$)$_3$, P($C_6H_5$)$_3$, P(*p*-$CH_3C_6H_4$)$_3$, and P(*p*-$OCH_3C_6H_4$)$_3$. Useful correlations to guide the choice of *p*-substituted arylphosphines are given in terms of tabulated parameters for this type of phosphines.

## EXPERIMENTAL

### Chemicals

Avermectin $B_1$ ($B_{1a}$ > 94.50% and $B_{1b}$ > 4.25%) was obtained by the purification of commercially available AVM, as reported in [6]. Compounds [RhCl(COD)]$_2$ (98%), P(*p*-$OCH_3C_6H_4$)$_3$ (95%), P(*p*-$CH_3C_6H_4$)$_3$ (98%), P($C_6H_5$)$_3$ (99%), P(*p*-$ClC_6H_4$)$_3$ (97%), and RhCl(P($C_6H_5$)$_3$)$_3$ (99.99%), were all purchased from Sigma-Aldrich and used as received. Toluene (Cicarelli, puriss. p.a.) was dried and degassed prior to use. $N_2$ gas (AgaGas, 99.999%) and $H_2$ gas (AgaGas, 99.999%) were flowed through a Deoxo unit and a drying column before use.

### Equipment and operating conditions

Reactions were performed with a specially conditioned Parr reactor. The experimental setup and reactor details were illustrated and described in our previous contributions [6-8]. All air sensitive manipulations were carried out in the reaction device in an oxygen-free atmosphere. The study was carried out in the 313-343 K range, at 275.7 $kNm^{-2}$ of hydrogen pressure. The mechanical stirring speed was settled at 750 rpm to ensure a practically negligible gas-liquid resistance for the hydrogen mass transfer, as evaluated elsewhere [6].

### Experimental procedure

Each kinetic experiment consisted of two consecutive stages: First, the AVM hydrogenation was carried out with the simultaneous synthesis of the catalytic complexes from [RhCl(COD)]$_2$ and P(*p*-$XC_6H_4$)$_3$ (X = Cl, H, $CH_3$, $OCH_3$) (stage *I*). Second, when nearing a 98% conversion to IVM, a fresh AVM toluene solution was immediately added to perform a further hydrogenation under the same operating conditions used in stage *I*. In this way, the hydrogenation run was carried out once again, and finally stopped when no hydrogen gas uptake was noticeable (stage *II*). Kinetic experiments using pure crystalline RhCl($PPh_3$)$_3$ were also performed to compare the concentration-time profiles with those of stage *II*. As no significant differences were observed after

comparison, the kinetic behavior characterizing stage *II* was taken as representative of the intrinsic catalytic activity of the Rh complexes.

A typical experiment was as follows: Precise amounts of $[RhCl(COD)]_2$ and $P(p\text{-}XC_6H_4)_3$ to obtain 2/100 (mol/mol) $Cl[P(p\text{-}XC_6H_4)_3]_3$/AVM were placed into a cup mounted on the upper part of a CAC device consisting of a fixed cover (cap) and a loose vase (cup) mounted on the reactor shaft [9]. Toluene (90 mL) was charged into the reaction vessel, which was degassed by mild vacuum, purged with $N_2$, flushed with $H_2$, and finally $H_2$ pressurized to 275.7 $kNm^{-2}$. A stirring speed of 750 rpm was applied. Then, by a sudden interruption of mechanical stirring, the cup containing the catalyst precursors was fully immersed into the toluene and, while heating, the powdered precursors were dissolved and reacted to form the mononuclear complex $RhCl(PPh_3)(COD)$ in the absence of AVM (30-45 min). On the other hand, an AVM toluene solution (30 mL, 10.35 wt.%) was charged into the feeder reservoir, degassed, pressurized with $H_2$, and heated up to the reaction temperature. After stabilization, the hydrogenation reaction was allowed to start by a fast transfer of the AVM toluene solution to the reaction vessel by opening a connecting one-way valve. Zero time was taken just at that moment. As soon as no detectable $H_2$ consumption occurred, a fresh solution of AVM was added to proceed with stage *II*. Liquid samples of the reaction medium were withdrawn to be analyzed by HPLC with resolution of AVM analogues $B_{1a}$ and $B_{1b}$, and hydrogenated derivatives [6].

## RESULTS AND DISCUSSION

All four phosphines are isosteric according to their cone angle of 145°, and they have different electron-donor capacities as follows from Giering´s electronic parameters: $P(p\text{-}ClC_6H_4)_3$ = 10.5, $P(C_6H_5)_3$ = 11.5, $P(p\text{-}CH_3C_6H_4)_3$ = 13.3, and $P(p\text{-}OCH_3C_6H_4)_3$ = 16.8 [10]. Thus, the phosphine effects on the reaction kinetics can mainly be attributed to the electronic ligand contributions. In what follows, unless otherwise indicated, results from varying the *p*-substituent group X will be discussed with reference to the $[RhCl(COD)]_2/P(C_6H_5)_3$ system reacted with 1:6 (mol/mol) equivalent. Reactions were conducted at 313, 328 and 343 K, but since the relative trend of activity observed among the four phosphines was not changed by temperature, results are discussed in the light of those obtained at 328 K.

### AVM hydrogenation with $[RhCl(COD)]_2/P(C_6H_5)_3$ system

Figure 1 displays the AVM and IVM concentration profiles during two consecutive hydrogenations carried out as described in the Experimental procedure

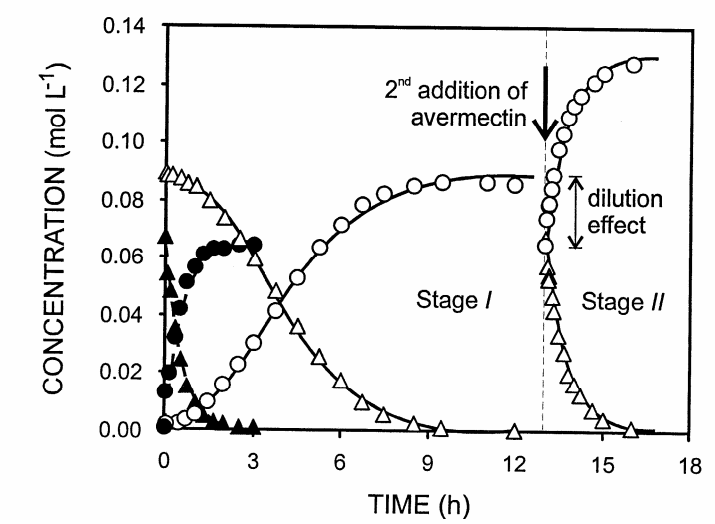


**Fig. 1.** AVM (Δ) and IVM (○) concentration profiles for two successive additions of AVM, at 328 K and 275.7 $kNm^{-2}$ of hydrogen pressure. Stage *I*: Hydrogenation with *in situ* formed catalytic species from $[RhCl(COD)]_2/P(p\text{-}C_6H_5)_3$ (1:6 mol/mol) in the presence of $RhCl[P(p\text{-}C_6H_5)_3]_3$/AVM (2:100 mol/mol) in toluene solution. Stage *II*: Addition and hydrogenation of fresh AVM solution (q.s. to 2:100 mol/mol $RhCl[P(p\text{-}C_6H_5)_3]_3$/AVM) with the catalytic complexes formed in Stage *I*. Black symbols denote hydrogenation with performed Wilkinson catalyst

(stages *I* and *II*). Stage *I* provides an S-shaped curve evidencing an induction phenomenon, which have some precedents in rhodium chemistry. But a too prolonged initial delay was certainly unexpected. The hydrogenation periods differ more than 2.5-fold between stages *I* and *II*. After analyzing the possible causes of this behavior, we concluded that the catalytic complexes are slowly formed under mild reaction conditions, such as those used here. Moreover, the remarkable coincidence between profiles of stage *II* (Δ symbol) with those obtained using an equivalent amount of pure crystalline Wilkinson´s catalyst (▲ symbol) revealed complexes entirely formed in finalizing stage *I*, and the absence of catalytic deactivation phenomena. Thus, during stage *I*, the hydrogenation regime progressively changes from an initial one having the synthesis of the rhodium complexes as RDS to another with the catalytic hydrogenation as RDS. From a kinetic viewpoint, the absence of AVM in the synthesis medium and high temperatures would be meaningful conditions to reduce both the induction periods and hydrogenation times [8]. Nevertheless, from an industrial viewpoint, both conditions are quite unsuitable because the advantages of the *in situ* synthesis are lost under the former, and detrimental effects on the selectivity toward IVM would appear under the latter. Therefore,

the need for intrinsically more active catalytic systems is apparent. The challenge is to deal with them comprehensively. Next, we focused on studying the ability of a series of isosteric *p*-substituted arylphosphines of different electron-donor capacities for varying both the in situ generation rate of the catalytic complexes and the AVM hydrogenation rate.

## AVM hydrogenation with $[RhCl(COD)]_2/P(p\text{-}XC_6H_4)_3$ systems

Figure 2 shows the AVM concentration-time profiles obtained when using $P(p\text{-}ClC_6H_4)_3$, $P(p\text{-}CH_3C_6H_4)_3$, and $P(p\text{-}OCH_3C_6H_4)_3$ as ligands. The equivalent profile for $P(C_6H_5)_3$ is also depicted for comparison purposes. All reactions were conducted under identical conditions, as described in the figure caption. All profiles exhibit similar patterns, which are characterized by induction phenomena while the rhodium complexes are synthesized. As the synthesis process was RDS at the beginning of stage *I*, the initial hydrogenation rate was expected to be representative of the synthesis activity. Thus, upon examining

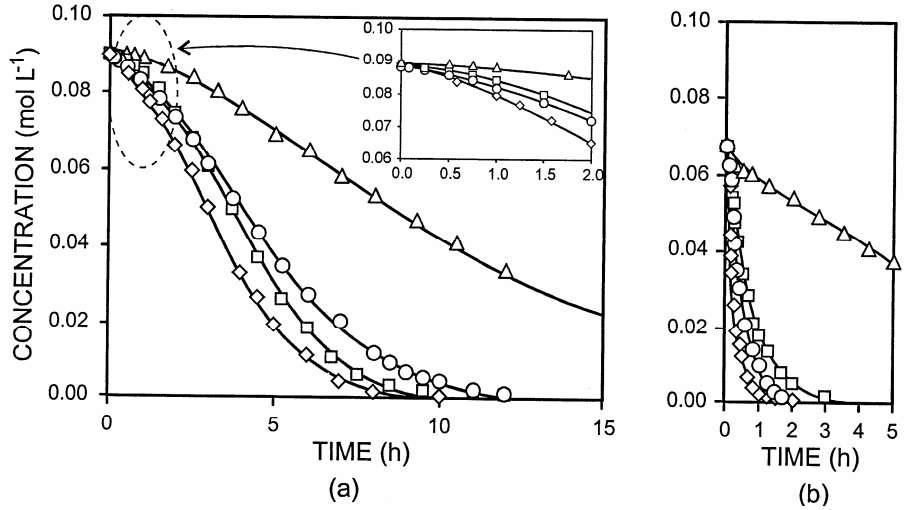


**Fig. 2.** AVM concentration–time profiles during stage *I* and *II* obtained for $P(p\text{-}ClC_6H_4)_3$ (Δ); $P(C_6H_5)_3$ (–), $P(p\text{-}CH_3C_6H_4)_3$ (○), and $P(p\text{-}OCH_3C_6H_4)_3$ (◊) as ligands, under the same operating conditions given in Fig. 1 (a) Stage *I*. (b) Stage *II*

the subfigure showing the profiles at short reaction times, it can be envisaged that the synthesis activity increases as the electron-donor capacity of the phosphines increases, *i.e.*, $P(p\text{-}ClC_6H_4)_3 < P(C_6H_5)_3 < P(p\text{-}CH_3C_6H_4)_3 < P(p\text{-}OCH_3C_6H_4)_3$. Likewise, as determined by the AVM profiles during stage *II*, the

higher the electron-donor capacity of the phosphines, the higher the catalytic activity, as in the case of simple olefins. Both orderings can be better visualized from the values summarized in Table 1, which also shows that among the four catalyst systems, the initial rates of reaction differ about 9-fold between the slowest and the fastest rate. This fact reveals the significant effects that the phosphine ligands have on the nature of the catalytic complexes, and thereby on the *in situ* synthesis and hydrogenation rates. Among the four phosphines the P(*p*-$OCH_3C_6H_4)_3$ as ligand showed the best performance, as expected from its stronger electron-donor capability.

**Table 1**

AVM initial reaction rates with *in situ* synthesized and preformed rhodium complexes from $[RhCl(COD)]_2$ and isosteric P(*p*-$XC_6H_4)_3$ [a]

| X group | $-r^{o}_{synthesis}$ [b] [mol $L^{-1}$ $s^{-1}$] | $-r^{o}_{hydrogenation}$ [c] [mol $L^{-1}$ $s^{-1}$] | $\frac{r^{o}_{synthesis}}{r^{o}_{hydrogenation}}$ |
|---|---|---|---|
| Cl | 2.52 | 94.32 [d] | $2.67 \times 10^{-2}$ [e] |
| H | 7.92 | 316.42 | $2.50 \times 10^{-2}$ |
| $CH_3$ | 16.20 | 507.60 | $3.19 \times 10^{-2}$ |
| $OCH_3$ | 28.44 | 840.60 | $3.38 \times 10^{-2}$ |

[a] Conditions: $T$ = 328 K; $P(H_2)$ = 275.7 $kNm^{-2}$; $[RhCl(COD)]_2$/P(*p*-$XC_6H_4)_3$ = 1/6 (mol/mol) equivalent; Cl[P(*p*-$XC_6H_4)_3]_3$/AVM = 2/100 (mol/mol). [b] Value calculated by fitting the concentration-time profile of stage *I* with a second-order polynomial. [c] Value calculated by fitting the concentration-time profile of stage *II* with an exponential function. [d] Low value due to the deactivation of the catalytic species during stage *I*. [e] High value due to (*d*).

An attempt to provide some quantitative orientation on the effects of the structure of the isosteric P(*p*-$XC_6H_4)_3$ ligands on the reactivity was made on the basis of the Hammett and Kabachnik treatments, which have been applied to many organic chemical reactions [11, 12]. Our experimental data for X = Cl, H, $CH_3$, and $OCH_3$ were found to fit very well in the framework provided by Hammett, and less accurately in Kabachnik's, as shown in Fig. 3. The linear equations obtained by fitting the initial reaction rates with the tabulated Hammett and Kabachnik constants are given in Table 2, for 95% confidence limits. Setting the values of the σ and κ parameters for a given X group, reaction rates can be predicted for AVM hydrogenations that have not yet been carried out using such group. Therefore, the equations obtained provide a useful tool to facilitate the search of more effective X groups, the values of σ and κ being

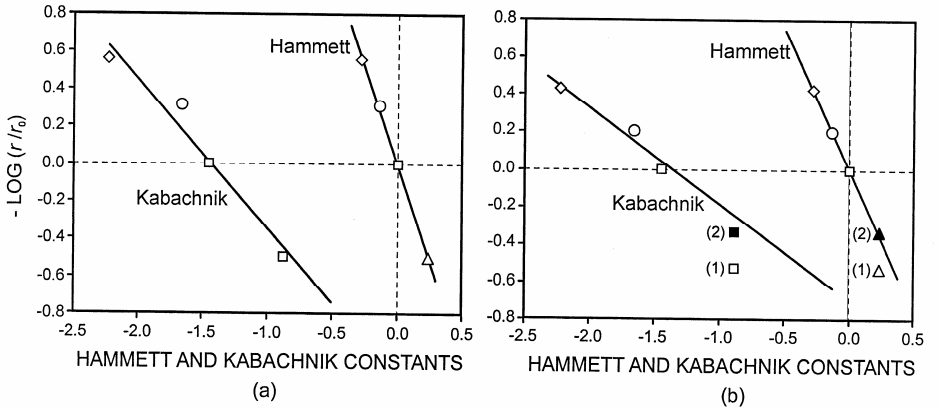


**Fig. 3.** Initial reaction rates as a function of Hammett and Kabacnik constants. (a) Stage *I*. (b) Stage *II*. (1) Experimental data with partial deactivation of the catalytic complexes. (2) Expected value without catalytic deactivation

**Table 2**

Hammett and Kabachnik equations for predicting the AVM initial reaction rates with *in-situ* formed (stage *I*) and preformed (stage *II*) rhodium complexes in $[RhCl(COD)]_2/P(p\text{-}XC_6H_4)_3$ systems [(a)]

| Stage | Hammett equation | Kabachnik equation |
|---|---|---|
| *I.* | $\log\frac{r}{r_0} = (-2.05 \pm 0.13)\,\sigma$ | $\log\frac{r}{r_0} = (-0.80 \pm 0.51)\,\kappa + (-1.14 \pm 0.83)$ |
| *II.* | $\log\frac{r}{r_0} = (-1.50 \pm 0.07)\,\sigma$ | $\log\frac{r}{r_0} = -(-0.51 \pm 1.60)\,\kappa + (-0.69 \pm 2.87)$ |

where $r_0$ and $r$ are the initial reaction rates for $P(C_6H_5)_3$ and any other isosteric $P(p\text{-}XC_6H_4)_3$ as ligands, respectively; σ and κ are the corresponding Hammett and Kabachnik constants for the *p*-substituent group X.

[(a)] Conditions: T = 328 K; $P(H_2)$ = 275.7 $kNm^{-2}$; $[RhCl(COD)]_2/P(p\text{-}XC_6H_4)_3$: 1/6 (mol/mol) equivalent. Values of the parameters are given for 95% confidence limits

available for many groups [13]. For example, under operating conditions as those referred to in section *3.1*, the use of $N(CH_3)_2$ as X group (σ = -0.63) would yield increases up to 20-fold and 10-fold in the intrinsic rates of synthesis and hydrogenation, respectively, relative to those obtained with the usual $P(C_6H_5)_3$ as ligand.

## CONCLUSIONS

We have quantified the extent to which differences in the *p*-substituent group X on isosteric P(*p*-$XC_6H_4)_3$ have effect on the activities of rhodium-based hydrogenation catalysts to produce IVM in reacting homogeneous systems. The trend in the generation rate of rhodium complexes formed *in situ* under hydrogenation conditions corresponds well to the increasing electron-donor capacity of the *p*-substituted arylphosphines, with P(*p*-$OCH_3C_6H_4)_3$ having the greatest effect and P(*p*-$ClC_6H_4)_3$ having the least effect relative to the value of the usual P$(C_6H_5)_3$. The same trend on the intrinsic catalytic activity is in agreement with that observed for small olefins. We have demonstrated that the resulting variations in hydrogenation rates can be reliably predicted in the framework provided by Hammett, and less accurately in Kabachnik's. Concerning the search and examination of X groups in isosteric P(*p*-$XC_6H_4)_3$ to deal with *p*-substituted arylphosphines more effective than the usual P$(C_6H_5)_3$, linear correlations in terms of tabulated parameters of substituent X have been provided as a useful tool to guide the exploration work.

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