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Stereoselective Hydrogenation of Methacycline to Doxycycline Catalysed by Rhodium-Carborane Complexes

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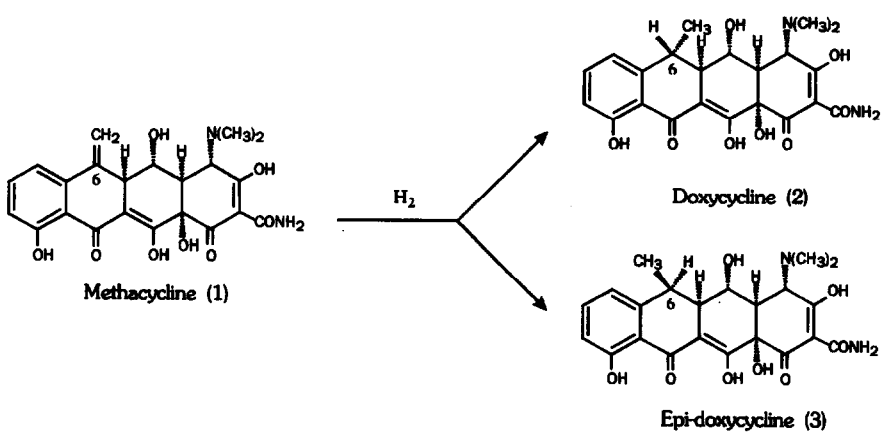
Abstract : Doxycycline (2), a tetracycline antibiotic extensively used in chemotherapy, was obtained stereoselectively from the hydrogenation of methacycline (1), catalysed by novel rhodium-carborane complexes.

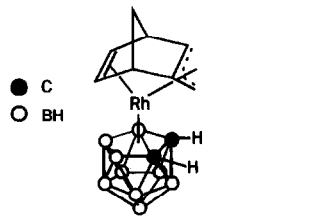
α-6-Deoxy-5-hydroxytetracycline (2) (doxycycline) is a tetracycline antibiotic extensively used in chemotherapy because of its increased antibacterial effectiveness, its stability, its improved pharmacokinetic properties and less severe adverse reactions compared to other tetracyclines. Doxycycline is moreover the only tetracycline that can be used safely in patients with renal insufficiency.[3]



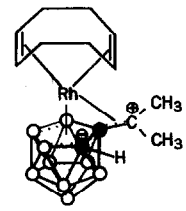
Doxycycline has generally been prepared by semisynthetic procedures, especially from the catalytic stereoselective hydrogenation of 6-demethyl-6-deoxy-5-hydroxy-6-methylene-tetracycline (1) (methacycline). As illustrated in the scheme, the reduction of the exocyclic methylene moiety of (1) may lead to the formation of two diastereoisomers, the most active α-epimer, doxycycline (2), and the β-epimer, 6-epi-doxycycline (3).

So far, some rhodium-based catalysts including Wilkinson-type catalysts $RhCl(PR3)_3$[4] and systems produced by treatment of rhodium salts (or complexes) with hydrazine(s) or a salt thereof in the presence of triphenylphosphine,[5] were reported to be the most active ones for the stereoselective hydrogenation of methacycline (**1**) into doxycycline (**2**).

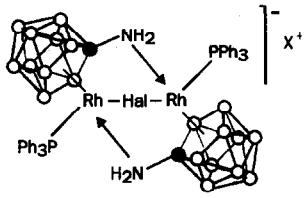
During the course of a project designed to extend the range of rhodium catalysts effective for the title reaction,[6] we focused our attention upon rhodacarborane clusters and related species as potential catalytic systems. Within the rhodacarborane family, a number of *closo*- and *exo-nido*-bisphosphinerhodacarboranes have been demonstrated to be effective alkene hydrogenation and isomerisation catalyst precursors,[7] and their mechanisms have been examined in detail.[8] In order to study this particular reaction, we have chosen two Rh(III) and Rh(I) complexes **A**, **B** as representatives of a new type of recently discovered neutral and zwitterionic 18-electron *closo*-dien(yl)rhodacarboranes[9] which have not previously been tested as hydrogenation catalysts (or catalyst precursors). Complexes **C**-**E**[10] are regarded as rare types of *closo*-rhodacarbaborane clusters[11] wherein the metal centres formally possess the 18- (**C**, **D**) and 16-electron (**E**) configuration. The exceptionally high efficiency of complex **A** prompted us to report these preliminary results.



[A]

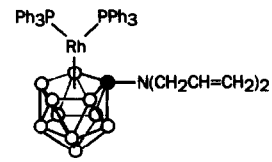


[B]



[C] X^+ : $(C_4H_9)_4N^+$, Hal = Cl

[D] X^+ : $[(C_6H_5)_3P{=}]_2N^+$, Hal = Br



[E]

Under our experimental conditions,[12] cluster **A** [*closo*-3,3-(η^2,η^3-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$][9] was found to catalyse the hydrogenation of methacycline in quantitative yield depending on the temperature, the catalyst concentration (Figure 1**A** and Table) and the reaction time. We observed indeed that increased concentration of catalyst **A** led to higher yields of desired product (**2**) (Table; for a reaction time of 4h). Under these unoptimized conditions, the selectivity in the formation of doxycycline was close to 95%, a value comparable to the best results reported up to now.[4-6] Reaction temperatures close to 60°C proved to be the most favorable whereas temperatures higher than 80°C led to partial decomposition of the starting methacycline (**1**) and/or the reduced products (**2**) and (**3**) into unidentified compounds [Figure 1 (catalysts **A** and **B**) and Table (catalysts **C**-**E**)]. The present study also demonstrated the crucial influence of the nature of cage ligands associated to the rhodium atom in the catalyst moleculars on their activity. Independent of electron configuration and nuclearity, the rhodium-monocarbaboranes **C**, **D** and **E** bearing an amino

Table 1. Rhodium-catalysed Hydrogenation of Methacycline (1) to Doxycycline (2).

Catalyst/concentration (10^{-4} mol.L^{-1})	Temperature (°C)	Conversion (%) 1	Yields (%) 2	3
A/ 8.1	43	19	18.5	0.5
A/ 16.9	"	39	37.5	1
A/ 32.5	"	69	67.5	1.5
A/ 48.0	"	97.5	95.5	2
A/ 16.9	62	99.2	95.5	3.7
A/ 24.7	84	99.5	90	2
B/ 11.7	43	5	5	-
B/ 26.0	"	12	12	-
B/ 19.5	71	28	22	3.5
B/ 33.8	100	99	41	52.5
C/ 15.9_5	43	1	0.6_5	-
C/ 4.6	100	11	1.2	0.1
D/ 4.7	"	8	1.1	0.6
E/ 18.2	"	14.5	0.8	0.3

Reaction conditions : 2 mL of a 0.02 mol.L^{-1} solution of methacycline hydrochloride in methanol; P_{H_2}, 100 atm; reaction time, 4h.

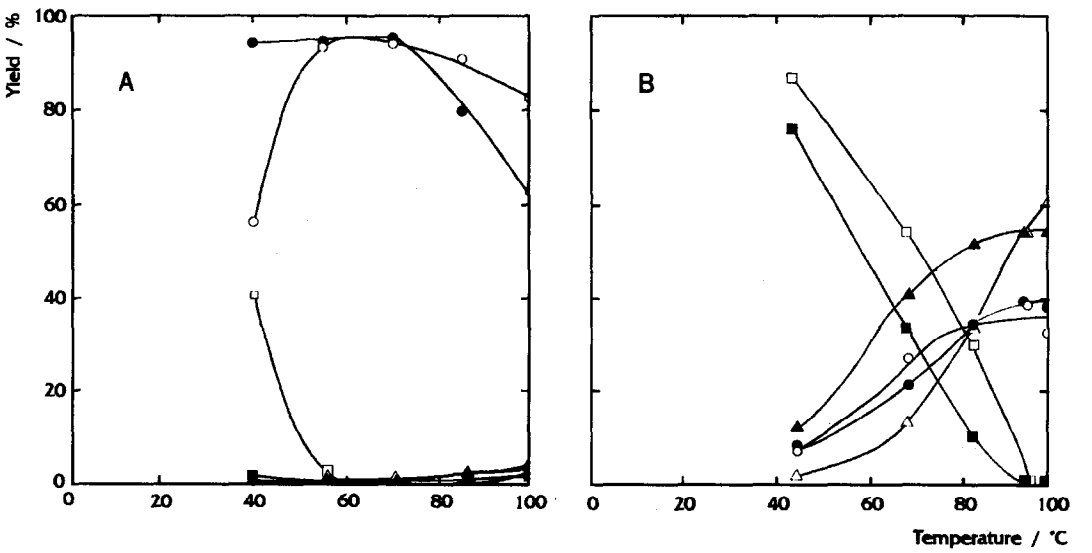


Figure 1. Temperature effect on the hydrogenation reaction of methacycline hydrochloride to doxycycline catalysed by rhodium-carborane complexes A and B [(□, ■) methacycline; (o, ●) doxycycline, and (Δ, ▲) 6-epi-doxycycline]. Reaction conditions : 2 mL of a 0.02 mol.L^{-1} solution of methacycline hydrochloride in methanol; P_{H_2}, 100 atm; reaction time, 4h; catalyst A, 17.1 (□, o, Δ) and 49.9 (■, ●, ▲) 10^{-4} mol.L^{-1}; catalyst B, 10.1 (□, o, Δ) and 35.9 (■, ●, ▲) 10^{-4} mol.L^{-1}, respectively.

substituent proved to be inactive for that process, even at higher temperatures. At the same time, rhodacarborane **B** gave fair to good yields of reduced products only at temperatures above 70°C (Figure 1**B**). It is noteworthy that in this particular case the β-epimer (**3**) was the major reaction product (up to 60% at 100°C), illustrating, therefore, the clear-cut effect brought about by modification of the carborane ligand and/or rhodium oxidation state in the catalysts on the stereochemical outcome of the hydrogenation reaction.

In conclusion, the novel *closo*-rhodacarborane [*closo*-3,3-(η^2,η^3-$C_7H_7CH_2$)-3,1,2-$RhC_2B_9H_{11}$] **A** proved to be one of the most active catalysts for the hydrogenation of methacycline into doxycycline. Further applications of **A** and related clusters as well as mechanistic study of these catalytic systems are currently under our active investigation.

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12. For experimental conditions see Table and Figure. The reaction mixture was thereafter analysed by H.P.L.C. using a Macherey-Nagel column (ET 125-8-4 Nucleosil 100-5 C18 AB). The mobile phase was a mixture of 500 mL of 0.1 M sodium phosphate buffer containing 0.01 M EDTA, 500 mL methanol H.P.L.C. and 6 mL N,N-dimethyloctylamine ajusted to pH 8 with 20% aqueous NaOH. Samples from the reaction mixtures and authentic samples were diluted with the mobile phase before injection (flow rate, 0.7 mL.min^{-1}; temperature, 38°C; wavelength, 280 nm).

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