Opposite Chemoselectivity (Hydrogenation versus Carbonylation) Shown by 4-Vinylpyridine with Respect to 3-Vinylpyridine under Hydroformylation Conditions with $Rh_4(CO)_{12}$

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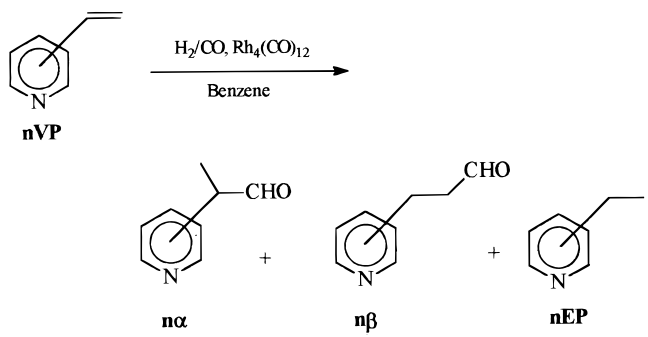
Summary: In the $Rh_4(CO)_{12}$-catalyzed hydroformylation of the vinylpyridine isomers, a very different chemoselectivity between 3- and 4-vinylpyridine is observed: whereas the former is fully transformed into the corresponding branched aldehyde, the latter only undergoes hydrogenation to 4-ethylpyridine. A different behavior of the corresponding branched alkylmetal intermediates related to the different polarization of the Rh−C bond has been suggested to explain the above results.

It is well-known that in the rhodium-catalyzed hydroformylation of vinyl compounds the nature of the substrate plays a key role in determining the chemo- and regioselectivity of the reaction.[1] In the case of simple 1-alkenes the hydroformylation produces mainly the linear aldehyde (β-regioselectivity).[2] On the contrary, in the hydroformylation of vinylaromatics the formation of the branched aldehyde is largely favored (α-regioselectivity). Most of the investigations in this field have been carried out on simple aromatic substrates (styrene,[3] nitrostyrene,[4] pentafluorostyrene,[1a] etc.); so far vinylheteroaromatic analogues such as vinylfurans,[5] vinylpyrroles,[6] and vinylpyridines[7] have received some attention. Our preliminary study on the hydroformylation of 2-vinylpyridine with $[Rh(CO)_2Cl]_2$/PMe_2Ph as catalyst precursor showed that the reaction occurs with almost complete chemoselectivity into aldehydes and high regioselectivity, the branched isomer being formed almost exclusively (α/β > 99:1).[8] Analogous results for 2-vinylpyridine have been obtained by Botteghi et al.[9] using rhodium catalytic precursors modified with bidentate ligands.

Scheme 1



No attempt to hydroformylate 3- or 4-vinylpyridine in the presence of rhodium catalyst has been reported so far.

In this contest, it seemed interesting to investigate the hydroformylation of all the vinylpyridine isomers, i.e., 2-vinylpyridine (**2VP**), 3-vinylpyridine (**3VP**), and 4-vinylpyridine (**4VP**), in the presence of $Rh_4(CO)_{12}$, an excellent catalytic precursor for the hydroformylation of simple and functionalized olefins,[10] which we have also successfully employed in the hydroformylation of 1-hexene,[2] styrene,[3a] unsaturated ethers,[11] and the vinylpyrrole isomers[6b,c] (Scheme 1).

The main aim of the above investigation is to compare the regio- and chemoselectivity in the hydroformylation of the vinylpyridine isomers, electron-poor heteroaromatic substrates, with the selectivities shown by styrene and vinylpyrroles.

In contrast to that observed with the other substrates, the three heteroaromatic vinylpyridines surprisingly show, under hydroformylation conditions, a very differ-

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Table 1. Hydroformylation of Vinylpyridine Isomers, *n*VP, with $Rh_4(CO)_{12}$, at Partial and Complete Substrate Conversion[a,b]

substrate	Rh:sub	*T* (°C)	react. time (h)	conversion (%)	hydrogenation[b] (yield %)	hydroformylation[b] (yield %)	α:*β*[c]
2VP	1:50	60	10	40	42	58	99:1
2VP	1:50	60	24	100	43	57	99:1
2VP	1:300	100	5	37	25	75	99:1
2VP	1:300	100	12	100	27	73	99:1
3VP	1:50	60	5	57	<1	>99	96:4
3VP	1:50	60	10	100	<1	>99	96:4
3VP	1:300	100	0.7	43	<1	>99	86:14
3VP	1:300	100	2	100	<1	>99	86:14
4VP	1:50	60	5.5	35	>98	<2	
4VP	1:50	60	12	100	>98	<2	
4VP	1:300	100	1.2	38	>98	<2	
4VP	1:300	100	4	100	>98	<2	

[a] Reaction conditions: 4.64 mmol of vinylpyridine, 5 mL of benzene; 0.023 mmol (at 60 °C) or 0.004 mmol (at 100 °C) of $Rh_4(CO)_{12}$; autoclave volume 25 mL; 110 atm total pressure (1:1 H_2/CO) in benzene. [b] Determined by GC analysis of the crude reaction product employing *o*-xylene as internal standard. [c] Determined by GC and ^{1}H NMR analyses.

ent behavior: whereas 3-vinylpyridine (**3VP**) is fully transformed into the corresponding aldehydes **3α** and **3*β***, 4-vinylpyridine (**4VP**) gives only the hydrogenation product 4-ethylpyridine (**4EP**). An intermediate behavior is observed in the case of 2-vinylpyridine (**2VP**), this isomer giving both hydrogenation and hydroformylation products.

Results

The hydroformylation reactions were carried out in benzene at 60 and 100 °C under 110 atm of H_2/CO total pressure. The reaction products were analyzed by GC−MS and ^{1}H NMR spectroscopy at partial and complete conversion. The results obtained in the hydroformylation runs are presented in Table 1.

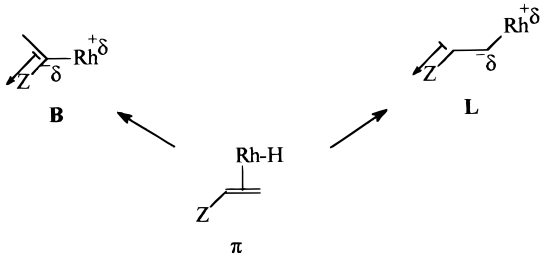
The hydroformylation of **3VP** chemoselectively (>99%) produces the isomeric aldehydes **3α** and **3*β***, with a large predominance of the branched isomer **3α**. An increase of the linear isomer is observed with increasing temperature, as previously found for styrene.[3a]

4VP undergoes almost complete hydrogenation of the double bond, giving **4EP** both at partial and total substrate conversion, the amount of aldehydes produced being less than 2%.[12]

In the case of **2VP** the chemoselectivity into aldehydes is much lower than for **3VP**, the proportion of hydrogenation product ranging from 27 to 43%. The α-regioselectivity is very high, both at 60 and 100 °C. In the case of **3VP** and **2VP** the chemo- and regioselectivity are the same at partial and total conversion.

Aldehydes **3α** and **3*β***, derived from **3VP**, are both new compounds. 2-(3-Pyridyl)propanal, **3α**, the predominant isomer, has been identified from the ^{1}H NMR spectrum of the crude hydroformylation mixture.[13] 3-(3-Pyridyl)-propanal, **3*β***, the minor product of the reaction, has been characterized by comparison with an authentic sample obtained by oxidation of 3-(3-pyridyl)propanol.[14]

Scheme 2



The characterization of the reaction products **2α**, **2*β***, and **2EP** has been reported in a previous paper.[7]

Discussion

According to the generally accepted mechanism of the rhodium-catalyzed hydroformylation,[15] $Rh_4(CO)_{12}$[10a] undergoes degradation, under typical experimental conditions (high temperature and pressure), to the "transient" active species $HRh(CO)_3$ that, via a Markovnikov or anti-Markovnikov addition to the olefinic double bond, generates both the branched (**B**) and the linear (**L**) alkylrhodium intermediates (Scheme 2).

As previously reported for styrene[3a] and vinylpyrroles,[6b] in the case of the vinylpyridines the **B** and **L** rhodium-alkyl intermediates should also form. In particular, the branched intermediate **B** should be largely favored, with respect to the linear **L**, by electronic factors connected with the electron-withdrawing character of the heteroaromatic ring. According to this hypothesis a high regioisomeric ratio α/*β* was observed (Table 1) in the case of **3VP** and **2VP**. Analogous evidence was not accessible in the case of **4VP**, this substrate giving mainly hydrogenation product under hydroformylation conditions.

The opposite chemoselectivity shown by 4-vinylpyridine with respect to 3-vinylpyridine could be caused, in principle, by different factors as (a) formation of rhodium metal responsible for the hydrogenation of **4VP**, (b) formation of a different catalytic species from **4VP** with respect to **3VP**, the former undergoing hydrogenation, the latter hydroformylation, and (c) intrinsic electronic differences between the two substrates. The aspect of the reaction mixtures recovered at partial and

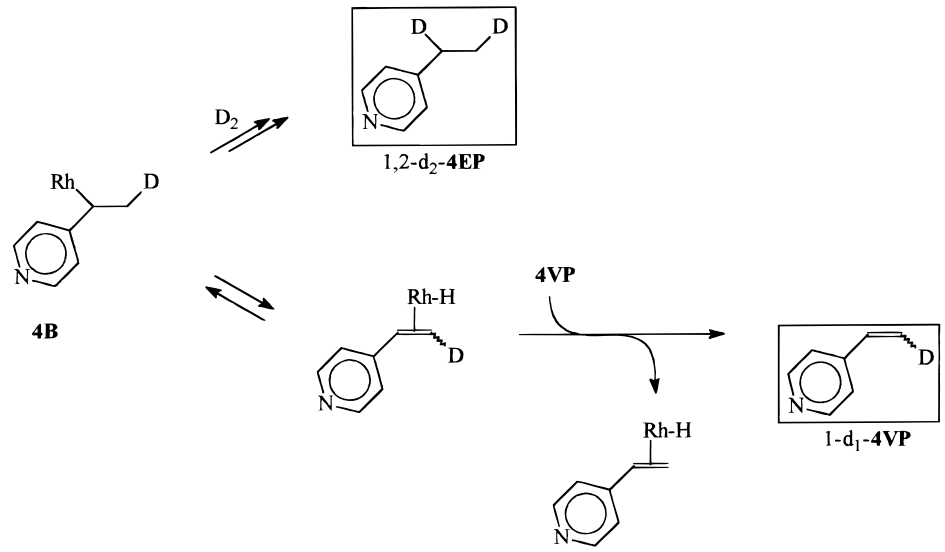
(12) The branched aldehyde seems to predominate also in the case of 4-vinylpyridine, but the aldehydes are produced in such a small quantity that no accurate determination of the isomeric ratio was possible. 4-Ethylpyridine and 2-ethylpyridine have been determined by comparison with authentic samples commercially available.

(13) ^{1}H NMR spectrum of **3α** in C_6D_6 shows, as characteristic signals, a doublet at 0.95 ppm (CH_3), a quartet at 2.79 ppm (CH), and a doublet at 9.1 ppm (CHO).

(14) ^{1}H NMR spectrum of **3*β*** in $CDCl_3$ shows, as characteristic signals, a multiplet at 2.82 ppm (CH_2), a triplet at 2.96 ppm (CH_2), and a triplet at 9.83 ppm (CHO).

(15) (a) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1961**, *83*, 4023. (b) Garland, M.; Pino, P. *Organometallics* **1991**, *10*, 1693.

Scheme 3



complete substrate conversion was carefully observed: it was homogeneous and weakly yellow in color in all the cases. Therefore the formation of rhodium metal must be excluded. As far as the second hypothesis is concerned, a hydroformylation experiment on an equimolecular mixture of the vinylpyridine isomers **4VP** and **3VP** was carried out at 100 °C, the reaction being stopped at partial and total substrate conversion. 4-Vinylpyridine and 3-vinylpyridine were transformed with a similar rate, the former giving only the hydrogenation product **4EP** and the latter giving only the hydroformylation products **3α** and **3*β***, exactly as occurs with the two substrates separately. Therefore the hypothesis b must also be excluded. If no different catalytic centers are involved, it can be likely concluded that also in the case of **4VP** the catalytic pathway occurs via the formation of the **B** and **L** rhodium−alkyl intermediates. Experimental evidence has been obtained by deuterioformylation[16] of **4VP** at 100 °C at partial substrate conversion. The ^{2}H NMR spectrum (Figure 1) of the crude reaction mixture, in addition to the signals at 2.04 and 0.77 ppm (−CHD- and $-CH_2D$, respectively) of 4-(1,2-dideuterioethyl)pyridine (1,2-d_2-**4EP**), showed two resonances at 4.99 and 5.48 ppm due to the *Z* and *E* isomers of *β*-deutero-4-vinylpyridine (1-d_1-**4VP**). This last compound clearly arises from the branched alkylrhodium intermediate **B** via a *β*-hydride elimination process (Scheme 3).

If it is assumed that the catalyst species are very similar for all the pyridine isomers, the differences of chemoselectivity observed in the hydroformylation of the three substrates must be attributed to intrinsic differences in the substrate nature (hypothesis c). In this light, the electronic characteristics of starting olefins have been carefully examined. It is well-known that the carbon atoms of the pyridine ring are characterized by different charge densities.[17] In particular the carbon atoms in the 2, 4, and 6 ring positions present a positive charge whereas the carbon atoms in the 3 and 5 position show a negative charge. Semiempirical calculations

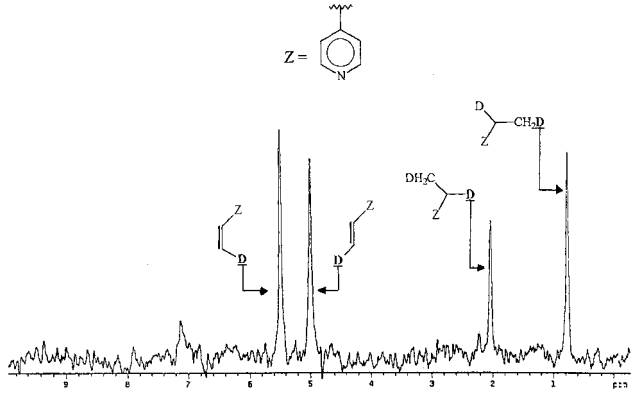


Figure 1. ^{2}H NMR spectrum (46 MHz, 25 °C, C_6D_6 as external standard) of the crude reaction mixture in benzene, obtained by deuterioformylation of 4-vinylpyridine, **1a**, at 100 °C and 15% substrate conversion.

(CNDO)[18] carried out on the three vinyl substrates ***n*VP** confirms a large positive charge density on the carbon atom bound to the vinyl group for **4VP** (4 position) and **2VP** (2 position), whereas this charge is very small in the case of **3VP** (3 position)[19] (Chart 1).

Therefore, the opposite chemoselectivity shown by 4-vinylpyridine with respect to 3-vinylpyridine must be related to the different fate of the respective branched alkylrhodium intermediates under hydroformylation conditions: the former mainly gives oxidative addition of hydrogen, the latter, migratory insertion[20] on a CO bound to the rhodium atom to form the acylrhodium species. The different pathways for the two isomers can be attributed to the fact that the negative charge on the carbon atom bound to the metal will be much more delocalized in the alkylmetal intermediates arising from **4VP** than for the one originating from **3VP** (Scheme 4).

(16) Lazzaroni, R.; Uccello-Barretta, G.; Scamuzzi, S.; Settambolo, R.; Caiazzo, A. *Organometallics* **1996**, *15*, 4657.

(17) Fusco, R.; Rosnati, V.; Bianchetti, G. *Chimica Organica*; Guadagni: Milan, 1980; Vol. 2, p 413.

(18) *Hyperchem Program*; Hypercube Inc.: 419 Phillip Street, Waterloo, Ont., N2L 3X2 Canada.

(19) The charge densities on the other atoms of the pyridyl ring as well as of the vinyl group are very similar in all the substrates. The nitrogen atom shows a negative charge as well as the carbon atom present in the position two of the double bond whereas a small positive charge is present on the vinyl carbon atom bound to the heteroaromatic ring.

(20) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; J. Wiley & Sons: New York, 1988; p 1201.

Scheme 4

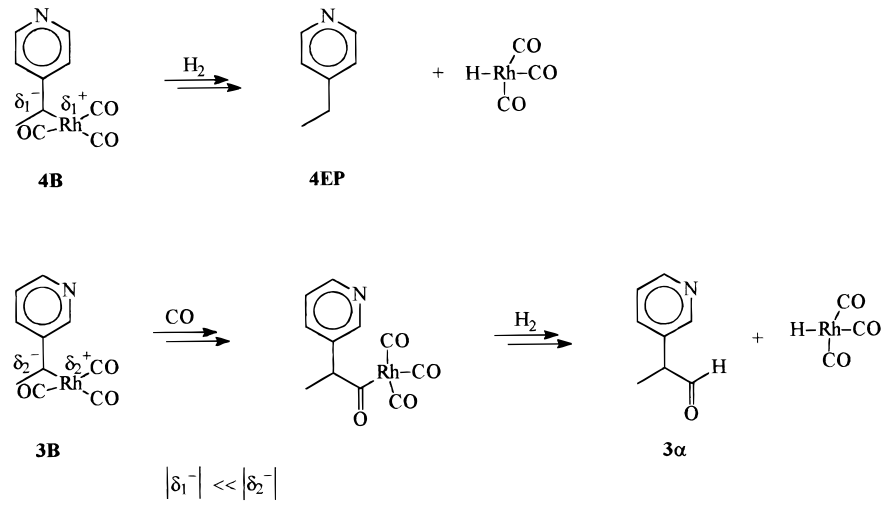


Chart 1

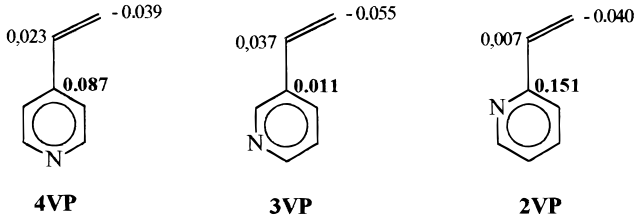
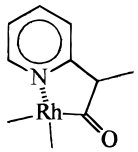


Chart 2



In this way, in the case of **3VP**, the alkyl carbon atom remains sufficiently nucleophilic to give intramolecular substitution on CO (migratory insertion), whereas, in the case of **4VP**, it is a very weak nucleophile and it is not able to give migratory insertion but it only undergoes oxidative hydrogen addition.

Behavior analogous to that of **4VP** could be expected for **2VP**. In this case, however, the proximity of the vinyl group to the nitrogen atom presumably generates, under hydroformylation conditions, a five-membered cyclic acylrhodium intermediate (Chart 2), which is likely the precursor of the branched aldehyde. A similar acyl intermediate has been isolated and characterized by Botteghi et al.[9] using a rhodium−diphosphine catalytic precursor.

The formation of this cyclic species favors, in the case of **2VP**, the conversion of the branched alkylrhodium intermediate into aldehydes rather than into the hydrogenation product. Such an intermediate is not allowed in the case of **3VP** and **4VP**, the vinyl group being in an unsuitable position to allow an intramolecular interaction between the rhodium and the nitrogen atoms.

In conclusion, the above findings clearly show the dramatic influence on the chemoselectivity of the reaction of electronic effects connected with the electron-poor character of the heteroaromatic ring as well as with the relative position of the vinyl group with respect to the nitrogen atom.

Experimental Section

Benzene was dried over molecular sieves and distilled under nitrogen. The starting compounds 2-vinylpyridine and 4-vinylpyridine were commercially available and were distilled before use. $Rh_4(CO)_{12}$[21] and 3-vinylpyridine[22] were prepared as reported in the literature. GC analyses of the reaction mixtures were performed on a Perkin-Elmer 8500 chromatograph equipped with a 12 m × 0.22 mm BP1 capillary column, using helium as carrier gas. ^1H and ^2H NMR spectra were measured on a Varian VXR 300 spectrometer (operating at 46 MHz for ^2H). Chemical shifts were referred to TMS in the ^1H NMR spectra and to C_6D_6 in the ^2H NMR spectra.

Hydroformylation or Deuterioformylation of Vinylpyridines 1a−c: General Procedure. A solution of ***n*VP** (0.5 mL, 4.64 mmol), $Rh_4(CO)_{12}$ (17 mg, 0.023 mmol, at 60 °C; 3 mg, 0.004 mmol, at 100 °C), and *o*-xylene (0.5 mL) in benzene (5 mL) was introduced by suction into an evacuated 25 mL stainless steel autoclave. Carbon monoxide was introduced, the autoclave was stirred and heated to the desired temperature (60 or 100 °C), and dihydrogen was rapidly introduced up to 110 atm total pressure (1:1 CO/H_2). When the gas absorption reached the value corresponding to the fixed conversion, the reaction mixture was siphoned out. The degree of conversion was measured by GLC analysis, using *o*-xylene as internal standard.

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(22) 3-Vinylpyridine was prepared from 3-pyridinecarboxaldehyde as reported in: Laborde, E. *Tetrahedron Lett.* **1992**, *33*, 6607.