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Short Communication

Enantioselective hydrogenation of activated ketones in the presence of Pt–cinchona catalysts. Is the proton transfer concept valid?

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ABSTRACT

Experimental evidences related to the proton transfer in the catalytic system Pt–cinchona alkaloids for enantioselective hydrogenation of activated ketones were collected and analyzed. Both new and earlier results indicate that in aprotic media direct transfer of proton from platinum to the substrate with the involvement of quinuclidine nitrogen as a general rule can be questioned.

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1. Introduction

Heterogeneous catalytic asymmetric hydrogenation of activated ketones over Pt–cinchona catalysts (Fig. 1) has been widely investigated [1–4].

In one of the new mechanistic considerations the protonation of the quinuclidine moiety of cinchonidine (CD) by hydrogen adsorbed on Pt was suggested [5]. Based on these results it has been assumed that "the protonated modifier always is the interacting species and it is unnecessary to postulate the stabilization of the half-hydrogenated state of the ketone by the amine modifier" [3]. In addition, experimental evidences using FTIR techniques were obtained on the protonation of CD under the condition of enantioselective hydrogenation [6,7], however these results do not answer the question whether the protonated form is an "actor" or a "spectator" in aprotic solvents. The proton transfer concept supports the electrophilic character of substrate–modifier interaction even in aprotic solvents [3], although nucleophilic type interaction has been justified by experimental data and quantum chemical calculations under these conditions [8–13]. The generality of the protonation mechanism [5] can also be questioned as some of the substrates (ketopantolactone) have anomalous behavior in the presence of acetic acid [14].

It has also been demonstrated that both the first hydrogen transfer from the platinum surface to the quinuclidine N of CD and the second one of the same hydrogen atom to the substrate occur without a transition state [5,15]. Accordingly, a simplified scheme of hydrogen transfer was suggested (Scheme 2 in Ref. [5]).

The aim of this study was to investigate the validity of proton transfer mechanism upon using different activated ketones and CD in the presence of various types of amine additives depicted in Fig. 2.

According to a new molecular modeling simulation [16] trimethylamine can also activate the hydrogen on the surface. However, the interaction of the hydrocarbon part and the metal hinders the basic effect because H atoms are more numerous than N atoms (ratio = 1:9). In case of CD, the strong adsorption via its quinoline part inhibits the hydrocarbon interactions of its quinuclidine part [16]. Nevertheless, if trimethylamine could generate this type of base interaction, other amines especially those having rigid structure and higher N:H ratio, such as quinuclidine and 1,4-diazabicyclo-[2.2.2]octane (Dabco; ratio = 1:6), would also able to create proton in some extent. In other words they would be able to transfer hydrogen from the Pt site to the prochiral substrate. Consequently, the proton transfer would be an intrinsic property of certain tertiary amines. This assumption can be based on the rate acceleration observed in the presence of both cinchona alkaloids and different achiral tertiary amines [17,18]. If certain tertiary amines were involved in the above transfer, the addition of these compounds to the reaction mixture containing CD would decrease the enantioselectivity because two competitive catalytic cycles would operate simultaneously (see Fig. 3). The decrease of enantioselectivity should also be observed upon using various activated ketones.

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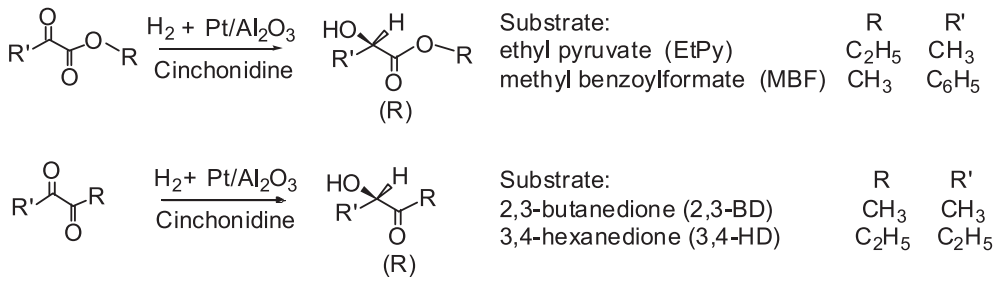

Fig. 1. Enantioselective hydrogenation of activated ketones.

2. Experimental

Ethyl pyruvate (EtPy, different batches from Fluka) was distilled under vacuum, and 2,3-butanedione (2,3-BD, Fluka) and 3,4-hexanedione (3,4-HD, Fluka) were purified by activated carbon. Methyl benzoylformate (MBF), CD, achiral tertiary amines (ATAs) such as quinuclidine, 1,4-diazabicyclo-[2.2.2]octane (Dabco), and triethylamine were purchased from Fluka and used as received. The 2S,4R,5R-2-hydroxymethyl-5-vinyl-quinuclidine (quincorine), 2R,4S,5R-2-hydroxymethyl-5-vinyl-quinuclidine (quincoridine) originated from Buchler Gmbh, ethylmethylamine (Fluka) and cis-2,6-dimethyl-piperidine (Aldrich) were used as received. Aromatic amine additives (quinoline, pyridine (Reanal)) were purified by distillation. Commercial 5 wt.% Pt/Al_2O_3 (E4759 Engelhard) catalyst was pretreated in hydrogen at 400 °C [19–21] while CatASium F214 (Degussa) were used as received [19,22].

Hydrogenations were carried out in a 300 cm^3 SS-autoclave at 20 °C and 50 bar H_2 pressure in dried toluene. CD was injected into the reaction system, pyridine and quinoline were premixed [23], and all other additives were co-injected with CD [21]. The reaction conditions are summarized in Table 1.

Samples were analyzed by a GC using a capillary column (Supelco BETA DEX 225). The enantioselectivity is expressed as ee = ([R − S] / [R + S]). In a given reaction ee_{max} was the highest ee value; the ee_{end} was the final one. First order rate constants k_1 and k_2 were calculated from experimental points obtained in the first 3–10 min and 25–60 min, respectively as described earlier [21]. The k and ee values were reproducible within 3–4 and 2%, respectively. The slope of dependencies in the [R − S] vs. 2[S] coordinates gives the rate enhancement in the form of k_e/k_r ratio, where k values belong to the enantioselective and raceme hydrogenation running parallel in the same experiment [20].

3. Results

3.1. Enantioselective hydrogenation of EtPy

Results obtained in enantiomeric hydrogenation of EtPy in the presence of ATAs and quinuclidine-derivatives (entries 1–9 in Table 2) show that all ATAs, except triethylamine, resulted in significant ee-increase contrary to the expected ee-decrease.

No decrease of ee was observed upon using triethylamine and optically active quinuclidine-derivatives (entries 5 and 6–9, respectively in Table 2). The latter give (R)-lactate (ee = 2–3%, [24]) and a slight rate increase (compare entries 1 and 6, 8 in Table 2) in the absence of CD.

In the presence of CD the rate increase induced by ATAs, quincorine and quincoridine is very pronounced. Achiral secondary amine additives resulted in similar tendency (compare entries 10 and 11–12 in Table 2). Both cyclic and aliphatic secondary amines enhanced the ee and rate constants. In these experiments in situ formation of ATAs was

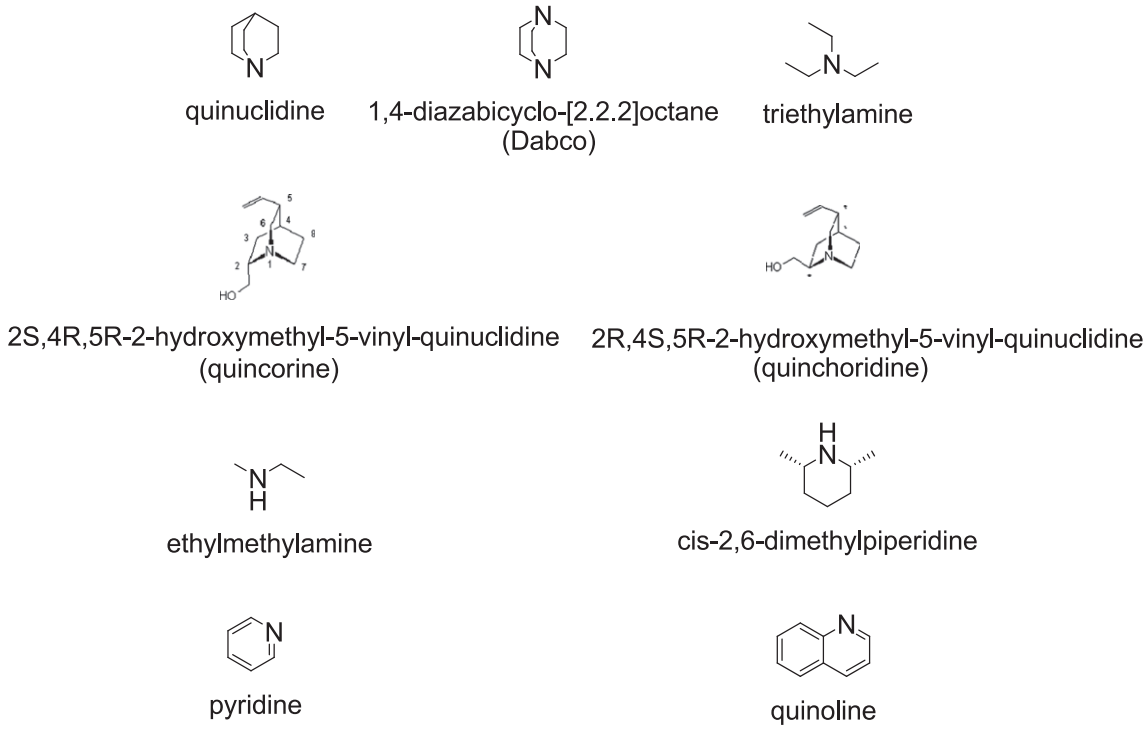

Fig. 2. Amine additives.

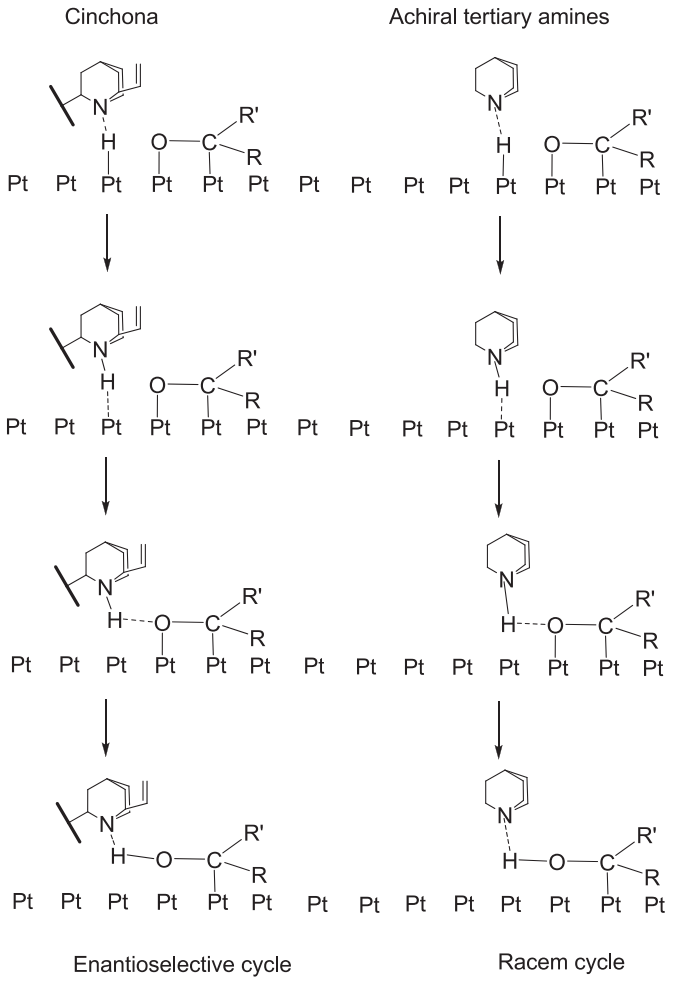

Fig. 3. Reaction scheme for reaction mixture containing both CD and ATAs.

evidenced by MS. The effect of ATAs can be related to the shift of the CD dimer–monomer ratio [21,22].

Enantioselective hydrogenation of EtPy was also investigated in the presence of nitrogen containing aromatic additives. Pyridine and quinoline increased both rate constants and ee (compare entries 13 and 15–16 in Table 2), too. In an earlier study a similar phenomenon attributed to some sort of base effect of quinoline [25].

Over CD-Pt/Al_2O_3 catalyst the highest ee value was obtained when aromatic basis (quinoline) and achiral tertiary amine (quinuclidine) were introduced together (entry 17 in Table 2). Fig. 4 represents the kinetic behavior of this experiment. The co-presence of quinuclidine and quinoline does not alter the general kinetic patterns (Fig. 4a), but increases the k_e/k_r ratio (Fig. 4b) in accordance with the ee-enhancement. This increase can be attributed to the virtual increase of CD concentration [21,23].

3.2. Enantioselective hydrogenation of other activated ketones

Enantioselective hydrogenation of 2,3-BD and 3,4-HD showed moderate or low ee values (see entries 18, 20, 22 in Table 2). The type of the solvent significantly influenced both the reaction rate and the ee (compare entries 20 and 22 in Table 2). In ethanol poorer results were obtained than in toluene due to the possibility of condensation type side reactions [4]. However, the addition of ATAs resulted in slight rate- and significant ee-increase even in ethanol (compare entries 22 and 23 in Table 2). *Accordingly, the observations found for EtPy are maintained completely*.

Upon hydrogenation of MBF, the CD itself caused fourfold increase in k_1 (compare entries 24 and 25 in Table 2). Addition of quinuclidine (entry 26 in Table 2) or quinoline (entry 27 in Table 2) to the reaction mixture further increased the k values, but no decrease in the enantioselectivity was observed.

4. Discussion

Results given in Table 2 and Fig. 4 clearly show that in the enantioselective hydrogenation of *four different substrates* neither the addition of ATAs nor the addition of nitrogen containing aromatic compounds has any negative effect on the ee values and the reaction rates. The most pronounced positive effect on the ee values and the reaction rates was obtained when quinuclidine and quinoline were added together. The lack of the negative effect of all additives contradicts to the proton transfer mechanism depictured in Fig. 3.

The above argumentation would be questionable since amine additives have no anchoring moieties, and consequently they cannot form strongly adsorbed surface species. Although the generally accepted view that strongly bonded CD to platinum via π-bonding with its quinoline ring is the "relevant" species in these asymmetric hydrogenation reactions, the weakly bound tilted form of CD is a "spectator" [26]. However, our previous [23] and present results (see entries 15–17, 27 in Table 2) clearly demonstrate that the strong adsorption of CD is not a prerequisite for obtaining both high enantio-discrimination and reaction rates. Data shown in Ref. [23], in accordance with those of Table 2 and Fig. 4, provide evidence that nitrogen containing aromatics have no negative effect either on the reaction rate or on the enantioselectivity. Pre-adsorbed quinoline and acridine cannot be fully replaced from the surface of platinum by CD [23], i.e. the strong adsorption of CD via its aromatic ring is not a requirement to get high ee values in the enantioselective hydrogenation of EtPy. Similar conclusion was obtained upon using MBF. The lack of ee decrease means that the pre-adsorbed quinoline has no influence on the enantio-differentiation ability of CD.

These experimental findings suggest that neither Scheme 2 in Ref. [5] nor the concept of "strongly bonded to the platinum CD via its quinoline ring" is working adequately.

5. Conclusion

In this contribution experimental evidences are summarized, which strongly contradict to the proton transfer mechanism [5,15] proposed for the catalytic system Pt–cinchona alkaloids. If the quinuclidine

Table 1
Reaction conditions.

Substrate	$[Substrate]_0$, M	Catalyst	$m_{catalyst}$, g	$V_{reaction}$, cm^3	$t_{reaction}$, min	Agitation, rpm
EtPy (batch1)	1.00	E4759	0.125	100	90	500
EtPy (batch2)	0.85	CatASium F214	0.040	40	60	1000
EtPy (batch3)	1.00	E4759	0.125	100	90	500
2,3-BD	1.00	E4759	0.125	100	240	500
3,4-HD	1.00	E4759	0.125	100	240	500
MBF	0.25	E4759	0.125	50	180	1000

Table 2
Influence of additives.

No	Substrate	Additive	[additive], 10^{-5} M	[CD], 10^{-5} M	k_1, min^{-1}	k_2, min^{-1}	ee_{max}	ee_{end}	$conv_{240}$
1	EtPy (batch1)	–	–	0	0.0036	0.0059	–	–	<0.95
2[a]		–	–	1.2	0.0236	0.0747	0.838	0.819	
3[a]		Quinuclidine	6	1.2	0.0482	0.0997	0.901	0.882	
4[a]		Dabco	6	1.2	0.0486	0.1267	0.909	0.905	
5[a]		Triethylamine	6	1.2	0.0300	0.0905	0.849	0.843	
6		Quincorine	10	0	0.0058	0.0150	0.051	0.038	
7		Quincorine	10	1.2	0.0526	0.1168	0.896	0.889	
8		Quincoridine	10	0	0.0071	0.0171	0.082[c]	0.082[c]	
9		Quincoridine	10	1.2	0.0459	0.0679	0.912	0.895	
10[b,c]	EtPy (batch2)	–	–	1.2	0.0998	0.0643	0.720	0.557	
11[b,c]		Ethylmethylamine	10	1.2	0.3128	0.0277	0.787	0.757	
12[c]		cis 2,6-Dimethyl-piperidine	10	1.2	0.1543	0.0250	0.755	0.671	
13	EtPy (batch3)	–	–	1.2	0.0265	0.0721	0.815	0.806	
14		Quinuclidine	10	1.2	0.0510	0.0895	0.839	0.825	
15		Pyridine	10	1.2	0.0537	0.1080	0.841	0.822	
16		Quinoline	10	1.2	0.0555	0.1125	0.861	0.842	
17		Quinuclidine + quinoline	10	1.2	0.0699	0.1287	0.916	0.899	
18[d]	2,3-BD	–	6	1.2	0.0102	0.0008	0.295	0.191	0.635
19[d]		Quinuclidine	6	1.2	0.0158	0.0005	0.430	0.366	0.656
20[e]	3,4-HD	–	6	1.2	0.0047	0.0006	0.327	0.269	0.426
21[e]		Quinuclidine	6	1.2	0.0067	0.0003	0.451	0.325	0.437
22[e,f]		–	6	1.2	0.0045	0.0002	0.095	0.070	0.300
23[e,f]		Quinuclidine	6	1.2	0.0101	0.0016	0.205	0.126	0.572
24[g]	MBF	–	10	0	0.0122[a]	0.0126	–	–	<0.95
25		–	10	5	0.0440	0.0159	0.755	0.621	
26		Quinuclidine	10	5	0.0485	0.0190	0.768	0.672	
27		Quinoline	10	5	0.0465	0.0182	0.759	0.660	

[a] From Ref. [21].
[b] From Ref. [22].
[c] Co-premixing of amine with CD.
[d] Yields of butanediols <6%.
[e] Yield of hexanediols <5%.
[f] Solvent = ethanol.
[g] From Ref. [19].

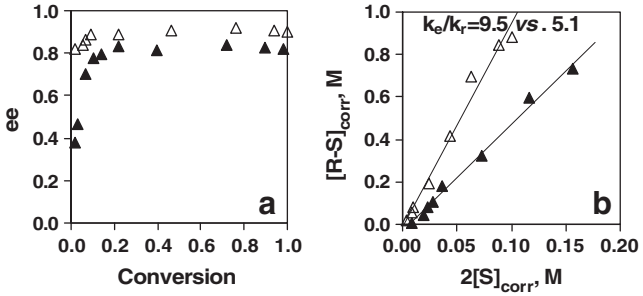

Fig. 4. Enantioselective hydrogenation of EtPy in the presence of quinoline and quinuclidine (1:1) additives. [CD] = 1.2×10^{-5} M, EtPy = batch 3 (see Table 1). ▲—no additives; Δ—[additives] = 1×10^{-4} M.

nitrogen of the CD is involved in the hydrogen transfer, other tertiary amines would accomplish similar job. If ATAs were involved in the above hydrogen transfer, their addition to the reaction mixture containing CD would decrease the enantioselectivity because two competitive catalytic cycles would operate simultaneously. The lack of the negative effect in the presence of amine additives suggests that the direct transfer of proton from platinum to the substrate with the involvement of quinuclidine nitrogen can be questioned. Our results also indicate that anchoring of CD to Pt by its quinoline ring is not really needed for the enantio-differentiation.

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