

# Role of the Solvent in the Adsorption–Desorption Equilibrium of Cinchona Alkaloids between Solution and a Platinum Surface: Correlations among Solvent Polarity, Cinchona Solubility, and Catalytic Performance

Zhen Ma and Francisco Zaera\*

Department of Chemistry, University of California, Riverside, California 92521

Received: September 3, 2004; In Final Form: October 21, 2004

The role that the nature of the solvent plays in defining the extent of cinchona alkaloid adsorption–desorption equilibrium on platinum surfaces has been studied both by testing their solubility in 54 different solvents and by probing the stability of adsorbed cinchona in the presence of those solvents. The solubilities vary by as much as 5–6 orders of magnitude, display volcano-type correlations with solvent polarity and dielectric constant, and follow a cinchonine < cinchonidine < quinine, quinidine sequence. The adsorption–desorption equilibrium shifts toward the solution with increasing dissolving power of the solvent. The relevance of these results to the behavior of cinchona as chiral modifiers in hydrogenation catalysis is discussed.

## 1. Introduction

At present, most of the industrial processes used to produce chiral pharmaceuticals, agrochemicals, flavors, and many organic building blocks rely on homogeneous catalysts, often expensive and highly toxic organometallic complexes.<sup>1</sup> It would be highly desirable to replace those with heterogeneous catalysts, which are easier to separate, handle, and reuse.<sup>2</sup> One promising approach is the use of chiral modifiers to impart enantioselectivity to regular solid catalysts. Perhaps the best example of this is the cinchona-modified platinum catalysts in the enantioselective hydrogenation of  $\alpha$ -ketoesters, a process pioneered by Orito et al.<sup>3,4</sup> and further advanced by others.<sup>5–10</sup> However, although the initial research in this area has been progressively expanded to new modifiers,<sup>7,11,12</sup> new reactions,<sup>13–15</sup> new catalysts,<sup>16–19</sup> and new catalytic processes<sup>9,20,21</sup> and even though more basic issues such as the kinetics<sup>22,23</sup> and mechanisms of enantioselective hydrogenation<sup>24–30</sup> and the characterization of the adsorption of the modifiers<sup>31–37</sup> have been scrutinized as well, a good fundamental knowledge underlying the empirical behavior of this catalysis is still lacking.

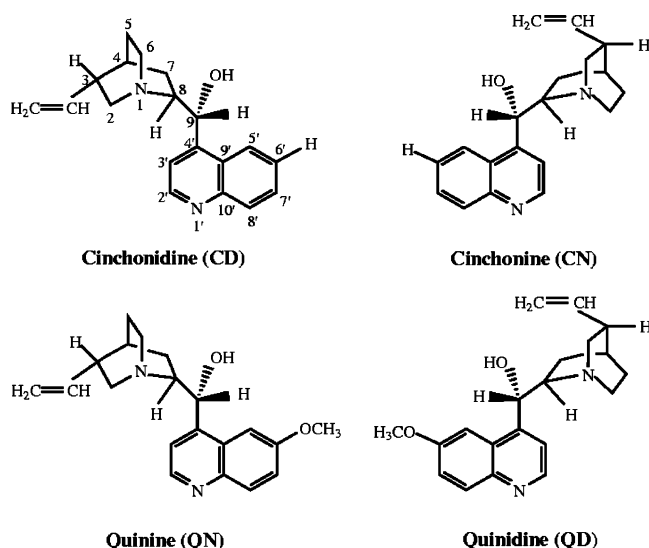
Solvent effects in organic synthesis are pervasive but not fully understood.<sup>38</sup> In the cinchona-modified Pt catalyst system, solvents play a complex role in determining both reaction rates and enantioselective excesses (ee).<sup>5</sup> For example, although it has been reported that the optimum ee from the hydrogenation of C=O bonds is often accomplished in solvents with dielectric constants around 2–10, no similar trends have been identified for C=C hydrogenation reactions.<sup>5,39</sup> Also, the ee in ethyl pyruvate hydrogenation appears to decrease with empirical solvent polarity ( $E_T^N$ ), except that higher-than-expected ee's are obtained in acetic acid or ethanol,<sup>6,40,41</sup> and no clear  $E_T^N$ –ee correlations have been observed with other reactants such as pyruvic acid oxime,<sup>42</sup> 4-hydroxy-6-methyl-2-pyrone,<sup>43</sup> and 2-oxoglutaric acid.<sup>14</sup> Finally, it has been reported that in fixed-bed reactors the ee sometimes decreases gradually with solvent flow if no supplementary modifier is added during the conversion, a behavior that in fact depends on the nature of the solvent

used.<sup>20,44</sup> To date, no convincing explanation has been provided for these observations.

Because of the complexity of the role that the solvent plays in chiral hydrogenation with heterogeneous catalysts, it is advisable to use model systems and study each possible pairwise interaction among reactants, products, catalyst, chiral modifier, and solvent separately.<sup>26</sup> In terms of reactant–solvent interactions, it has been found that the solubility of H<sub>2</sub> and those of many organic reactants do vary in different solvents.<sup>6,15,45</sup> In fact, ethyl pyruvate, a prototypical feedstock in the chiral catalysis mentioned above, can even isomerize to its hemiketal form in alcohols.<sup>40,46</sup> Different solvents also interact differently with the surface of the catalyst,<sup>6</sup> and some may even undergo destructive adsorption.<sup>13,47</sup> Perhaps more important for the systems addressed here is the interaction between the chiral modifier and the solvent, in part because the population of the different conformers of the cinchona on the surface can be affected by the liquid phase. In particular, the population of the so-called Open(3) conformer has been estimated to decrease with the dielectric constant of the solvent, a behavior in agreement with the changes in ee reported during the hydrogenation of 1-phenyl-1,2-propanedione,<sup>15</sup> ketopantolactone,<sup>48</sup> and butane-2,3-dione.<sup>49</sup> However, this correlation appears to be highly specific to the particular reactant and catalyst being considered.<sup>14,17,45,50</sup> It has also been speculated that a difference in the solvation of cinchonidine in polar versus nonpolar solvents may influence the adsorption equilibrium of the cinchona on the surface of the catalyst.<sup>45,51</sup> Nevertheless, neither quantitative solubility data nor in situ spectroscopic evidence were ever furnished to support this claim.

Following our previous work on the adsorption of cinchonidine and its analogues onto Pt surfaces, both under vacuum and from solution,<sup>33–35,52,53</sup> and to address some of the issues highlighted above, here we present results from our fundamental studies on the effect of the solvent on the interactions between cinchona chiral modifiers and the platinum surface. Both solubility tests and in situ spectroscopic studies were carried out on these systems. It was found that the solubility of cinchona in different solvents varies by as much as 5–6 orders of magnitude, and that subtle correlations can be drawn among

\* Corresponding author. E-mail: zaera@ucr.edu.



**Figure 1.** Molecular structures of the four cinchona alkaloids (cinchonidine (CD), cinchonine (CN), quinine (QN), and quinidine (QD)) studied here and often used as chiral modifiers for the enantioselective hydrogenation of  $\alpha$ -ketoesters.<sup>5,6</sup> The structural differences between CD and CN, and between QN and QD, are due to changes in stereo substitution at the C-8 and C-9 positions. On the other hand, the structural difference between CD and QN, and between CN and QD, is the additional methoxy group at the C-6' position of the quinoline ring present in the latter.

the polarity of the solvent, the solubility of the cinchona, the ease of removal of adsorbed cinchona from platinum surfaces, and the reported catalytic behavior for these systems.

## 2. Experimental Section

A total of 54 solvents was used in these studies. Cyclohexane (99%) (**1**), *n*-pentane (99+%) (**2**), *n*-hexane (99+%) (**3**), triethylamine (Fisher, 99%) (**4**), carbon tetrachloride (99.9%) (**5**), carbon disulfide (99.9%) (**6**), toluene (99.5%) (**7**), benzene (99.9+%) (**8**), ethyl ether (99.9%) (**9**), trichloroethylene (Fisher, 99.9%) (**10**), 1,4-dioxane (99+%) (**11**), chlorobenzene (99%) (**12**), tetrahydrofuran (EM, 99.5+%) (**13**), ethyl acetate (99.5%) (**14**), chloroform (Mallinckrodt, 99.8%) (**15**), cyclohexanone (99+%) (**16**), dichloromethane (EM, 99.8%) (**17**), ethyl formate (97%) (**18**), nitrobenzene (99+%) (**19**), acetone (EM, 99.99+%) (**20**), *N,N*-dimethylformamide (99.8%) (**21**), dimethyl sulfoxide (99.9%) (**22**), acetonitrile (EM, 99.99+%) (**23**), propylene carbonate (99.7%) (**24**), 2-butanol (99.9%) (**26**), 2-propanol (99.5%) (**27**), 1-butanol (Fisher, 99.8%) (**29**), ethyl lactate (98%) (**31**), acetic acid (99.99+%) (**32**), ethanol (99.5%) (**33**), *N*-methylformamide (99%) (**36**), methanol (99.9%) (**39**), formamide (Fluka, 99.5+%) (**41**), and ethyl pyruvate (98%) (**54**) were purchased from Aldrich unless otherwise indicated above and used as supplied. Additional aqueous solutions were prepared with dioxane (90 wt % (**25**), 70 wt % (**30**), 50 wt % (**35**), and 30 wt % (**42**)), acetone (90 wt % (**28**), 70 wt % (**34**), 50 wt % (**37**), and 30 wt % (**44**)), ethanol (50 wt % (**38**), 40 wt % (**40**), 30 wt % (**43**), 20 wt % (**46**), and 10 wt % (**47**)), methanol (50 wt % (**45**)), HCl (EM, 36.5–38%) (0.1 M (**49**)), H<sub>2</sub>SO<sub>4</sub> (EM, 95–98%) (0.1 M (**50**)), oxalic acid (99+%) (0.1 M (**51**)), NaCl (EM, 99+%) (0.1 M (**52**)), and KClO<sub>4</sub> (99.9+%) (0.1 M (**53**)) using distilled water (**48**). The trace residues that remained in the KClO<sub>4</sub> solution after preparation were filtered before the solubility tests. Four cinchona alkaloids were studied in this work (molecular structures provided in Figure 1), namely, cinchonidine (96%) (CD), cinchonine (Alfa Aesar, 98%) (CN),

quinine (Acros, 99%) (QN), and quinidine (Acros, 95%) (QD). Those and the H<sub>2</sub> gas (Liquid Carbonic, 99.99+%) were used as received.

The solubilities of the cinchona were measured in the various solvents listed above using established reported methods.<sup>54</sup> Typically, 30–1000 mL of a given solvent was transferred into a transparent bottle and the solid solute was added in small increments and mixed using magnetic stirring until no additional solute could be dissolved. The total mass of the solute was then estimated by summing up the masses of the added aliquots before the end point and used to calculate the solubility in terms of grams of solute/liter of solvent. Alternatively, particularly in cases where the cinchona solubility was very low, batches of the liquid solvent were added to a measured amount of solute stepwise until a clear solution was just obtained.<sup>54</sup> All the solubility tests were carried out at room temperature (295  $\pm$  2 K).

In situ reflection–absorption infrared spectroscopy (RAIRS) was used to characterize the cinchona adsorbed on the platinum surface during treatments with the different solvents. These experiments were carried out using a setup described in detail elsewhere where the IR beam from a Mattson Sirius 100 Fourier transform infrared (FTIR) spectrometer is focused through a polarizer and a CaF<sub>2</sub> prism onto the Pt surface and refocused after reflection into a liquid-nitrogen-cooled mercury cadmium telluride (MCT) detector.<sup>52</sup> A polished Pt disk 10 mm in diameter and 1 mm in thickness was mounted onto a movable supporting rod inserted behind the prism. The liquid solvents and solutions were injected into the  $\sim$ 5-mL volume enclosed between the Pt sample and the CaF<sub>2</sub> prism using a syringe attached to a small tube in the side of the cell.<sup>52</sup>

The Pt surface was precleaned before each set of IR experiments by electrochemical oxidation–reduction cycles in a 0.1 M KClO<sub>4</sub> electrolyte solution for 1 h, after which the solution was replaced with CCl<sub>4</sub> (or another pure solvent), the Pt sample pressed tightly against the prism to form a thin liquid film above the surface, and two IR spectra recorded with p- and s-polarized light for reference. The Pt disk was then pulled back, the pure solvent replaced by a cinchona solution of specified concentration (a CCl<sub>4</sub> solution unless otherwise stated), and H<sub>2</sub> bubbled into the cell at a rate of  $\sim$ 0.85 cm<sup>3</sup>/min for 0.5 h to help with the adsorption.<sup>53</sup> The Pt disk was again pressed against the prism, and new p- and s-polarized spectra were recorded. The p-to-s spectra ratio from the experiments with the cinchona solution was ratioed against the equivalent background trace from the pure solvent. Afterward, the chirally modified Pt surface was treated in situ by flushing the cell (with the Pt disk retracted to allow for liquid exchange) with a given solvent, 20 mL at a time, and probed by RAIRS. All the reported spectra are averages of 512 scans, taken with a 4-cm<sup>−1</sup> resolution.

## 3. Results

**3.1. Correlation between Solvent Polarity and Cinchona Solubility.** The solubilities of the four cinchona alkaloids referred to above were measured in all 54 solvents listed in the Experimental Section. The data are provided in Table 1 together with the corresponding reported data for the empirical polarities ( $E_T^N$ ), dielectric constants ( $\epsilon_r$ ), and dipole moments ( $\mu$ ) of the solvents used.<sup>38,55–59</sup> To visualize possible correlations, the solubilities of cinchonidine (CD) are plotted against each of the three solvent parameters in Figure 2 (similar trends were obtained for the other alkaloids; see below). It was found that the solubility of the cinchona varies by as much as 5–6 orders

**TABLE 1: Solubility Data for Cinchonidine (CD), Cinchonine (CN), Quinine (QN), and Quinidine (QD) in 54 Different Solvents<sup>a</sup>**

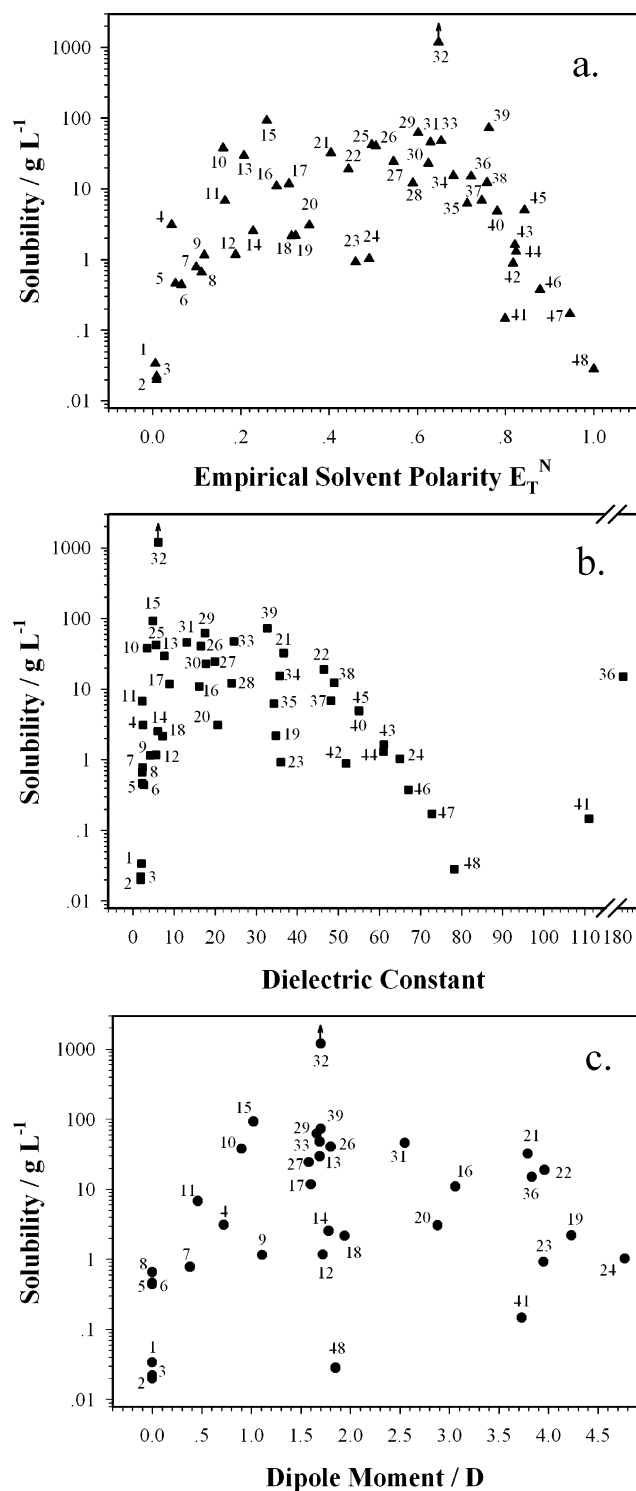
no.	name	solvent			solubility/g L <sup>-1</sup>			
		$E_T^{N38}$	$\epsilon_r^{38}$	$\mu/D^{55}$	CD	CN	QN	QD
1	cyclohexane	0.006	2.02	0.00	$3.4 \times 10^{-2}$	$7.2 \times 10^{-3}$	$7.6 \times 10^{-2}$	$9.8 \times 10^{-2}$
2	<i>n</i> -pentane	0.009	1.84	0.00	$2.0 \times 10^{-2}$	$2.1 \times 10^{-3}$	$2.8 \times 10^{-2}$	$2.9 \times 10^{-2}$
3	<i>n</i> -hexane	0.009	1.88	0.00	$2.2 \times 10^{-2}$	$3.2 \times 10^{-3}$	$4.2 \times 10^{-2}$	$4.7 \times 10^{-2}$
4	triethylamine	0.043	2.42	0.72	$3.1 \times 10^0$	$5.2 \times 10^{-1}$	$1.0 \times 10^1$	$9.2 \times 10^0$
5	carbon tetrachloride	0.052	2.23	0.00	$4.6 \times 10^{-1}$	$9.0 \times 10^{-2}$	$2.8 \times 10^0$	$5.3 \times 10^0$
6	carbon disulfide	0.065	2.64	0.00	$4.4 \times 10^{-1}$	$8.0 \times 10^{-2}$	$7.3 \times 10^0$	$4.6 \times 10^0$
7	toluene	0.099	2.38	0.38	$7.9 \times 10^{-1}$	$1.3 \times 10^{-1}$	$3.6 \times 10^0$	$4.1 \times 10^0$
8	benzene	0.111	2.27	0.00	$6.6 \times 10^{-1}$	$1.7 \times 10^{-1}$	$6.5 \times 10^0$	$8.5 \times 10^0$
9	ethyl ether	0.117	4.20	1.11	$1.2 \times 10^0$	$1.8 \times 10^{-1}$	$3.6 \times 10^0$	$2.9 \times 10^0$
10	trichloroethylene	0.160	3.42	0.90	$3.8 \times 10^1$	$1.0 \times 10^1$	$2.6 \times 10^1$	$9.9 \times 10^1$
11	1,4-dioxane	0.164	2.21	0.46	$6.8 \times 10^0$	$1.5 \times 10^0$	$6.4 \times 10^0$	$1.2 \times 10^1$
12	chlorobenzene	0.188	5.62	1.72	$1.2 \times 10^0$	$1.7 \times 10^{-1}$	$9.1 \times 10^0$	$9.7 \times 10^0$
13	tetrahydrofuran	0.207	7.58	1.69	$3.0 \times 10^1$	$3.6 \times 10^0$	$2.0 \times 10^2$	$1.5 \times 10^2$
14	ethyl acetate	0.228	6.02	1.78	$2.6 \times 10^0$	$3.0 \times 10^{-1}$	$1.6 \times 10^1$	$6.1 \times 10^0$
15	chloroform	0.259	4.81	1.02	$9.3 \times 10^1$	$4.4 \times 10^0$	$7.3 \times 10^2$	$6.2 \times 10^2$
16	cyclohexanone	0.281	16.10	3.06	$1.1 \times 10^1$	$1.7 \times 10^0$	$3.4 \times 10^1$	$5.3 \times 10^1$
17	dichloromethane	0.309	8.93	1.60	$1.2 \times 10^1$	$1.0 \times 10^0$	$4.2 \times 10^2$	$3.0 \times 10^2$
18	ethyl formate	0.315 <sup>55</sup>	7.16 <sup>55</sup>	1.94	$2.2 \times 10^0$	$6.0 \times 10^{-1}$	$1.5 \times 10^1$	$6.6 \times 10^0$
19	nitrobenzene	0.324	34.78	4.23	$2.2 \times 10^0$	$3.5 \times 10^{-1}$	$2.5 \times 10^1$	$1.3 \times 10^1$
20	acetone	0.355	20.56	2.88	$4.3 \times 10^0$	$5.1 \times 10^{-1}$	$5.3 \times 10^0$	$1.9 \times 10^1$
21	<i>N,N</i> -dimethyl formamide	0.404	36.71	3.79	$3.2 \times 10^1$	$4.5 \times 10^0$	$3.0 \times 10^1$	$8.0 \times 10^1$
22	dimethyl sulfoxide	0.444	46.45	3.96	$1.9 \times 10^1$	$2.1 \times 10^0$	$3.2 \times 10^1$	$9.3 \times 10^1$
23	acetonitrile	0.460	35.94	3.95	$9.3 \times 10^{-1}$	$1.6 \times 10^{-1}$	$4.3 \times 10^0$	$6.1 \times 10^0$
24	propylene carbonate	0.491	64.92	4.77	$1.0 \times 10^0$	$1.5 \times 10^{-1}$	$2.4 \times 10^0$	$3.1 \times 10^0$
25	dioxane (90 wt %)-water	0.497 <sup>56</sup>	5.61 <sup>57</sup>	n.a.	$4.2 \times 10^1$	$4.9 \times 10^0$	$2.3 \times 10^2$	$2.4 \times 10^2$
26	2-butanol	0.506	16.56	1.8 <sup>59</sup>	$4.1 \times 10^1$	$5.2 \times 10^0$	$3.9 \times 10^2$	$2.0 \times 10^2$
27	2-propanol	0.546	19.92	1.58	$2.5 \times 10^1$	$3.1 \times 10^0$	$2.1 \times 10^2$	$1.4 \times 10^2$
28	acetone (90 wt %)-water	0.590 <sup>56</sup>	24.0 <sup>58</sup>	n.a.	$1.2 \times 10^1$	$1.5 \times 10^0$	$1.7 \times 10^2$	$9.8 \times 10^1$
29	1-butanol	0.602	17.51	1.66	$6.3 \times 10^1$	$8.4 \times 10^0$	$5.7 \times 10^2$	$3.8 \times 10^2$
30	dioxane (70 wt %)-water	0.625 <sup>56</sup>	17.69 <sup>57</sup>	n.a.	$2.3 \times 10^1$	$2.6 \times 10^0$	$1.1 \times 10^2$	$9.0 \times 10^1$
31	ethyl lactate	0.630 <sup>55</sup>	13.1 <sup>55</sup>	2.55	$4.6 \times 10^1$	$1.1 \times 10^1$	$6.1 \times 10^2$	$4.3 \times 10^2$
32	acetic acid	0.648	6.17	1.70	$> 1.2 \times 10^3$	$> 1.1 \times 10^3$	$> 1.3 \times 10^3$	$> 1.3 \times 10^3$
33	ethanol	0.654	24.55	1.69	$4.8 \times 10^1$	$6.0 \times 10^0$	$6.3 \times 10^2$	$2.2 \times 10^1$
34	acetone (70 wt %)-water	0.682 <sup>56</sup>	35.7 <sup>58</sup>	n.a.	$1.5 \times 10^1$	$2.0 \times 10^0$	$2.4 \times 10^2$	$7.0 \times 10^1$
35	dioxane (50 wt %)-water	0.713 <sup>56</sup>	34.26 <sup>57</sup>	n.a.	$6.2 \times 10^0$	$6.2 \times 10^{-1}$	$2.3 \times 10^1$	$1.4 \times 10^1$
36	<i>N</i> -methylformamide	0.722	182.4	3.83 <sup>59</sup>	$1.5 \times 10^1$	$1.7 \times 10^0$	$8.2 \times 10^1$	$5.2 \times 10^1$
37	acetone (50 wt %)-water	0.746 <sup>56</sup>	48.2 <sup>58</sup>	n.a.	$6.9 \times 10^0$	$6.6 \times 10^{-1}$	$7.7 \times 10^1$	$2.0 \times 10^1$
38	ethanol (50 wt %)-water	0.758 <sup>56</sup>	49.0 <sup>58</sup>	n.a.	$1.2 \times 10^1$	$1.3 \times 10^0$	$2.2 \times 10^2$	$8.7 \times 10^0$
39	methanol	0.762	32.66	1.70	$7.3 \times 10^1$	$8.7 \times 10^0$	$1.6 \times 10^3$	$9.5 \times 10^0$
40	ethanol (40 wt %)-water	0.781 <sup>56</sup>	55.0 <sup>58</sup>	n.a.	$4.9 \times 10^0$	$4.2 \times 10^{-1}$	$2.2 \times 10^1$	$3.2 \times 10^0$
41	formamide	0.799	111.0	3.73 <sup>59</sup>	$1.5 \times 10^{-1}$	$3.5 \times 10^{-2}$	$1.7 \times 10^{-1}$	$4.5 \times 10^{-1}$
42	dioxane (30 wt %)-water	0.817 <sup>56</sup>	51.90 <sup>57</sup>	n.a.	$8.9 \times 10^{-1}$	$1.2 \times 10^{-1}$	$1.0 \times 10^0$	$1.3 \times 10^0$
43	ethanol (30 wt %)-water	0.821 <sup>56</sup>	61.1 <sup>58</sup>	n.a.	$1.6 \times 10^0$	$1.4 \times 10^{-1}$	$7.8 \times 10^0$	$9.0 \times 10^{-1}$
44	acetone (30 wt %)-water	0.824 <sup>56</sup>	61.0 <sup>58</sup>	n.a.	$1.3 \times 10^0$	$1.6 \times 10^{-1}$	$7.1 \times 10^0$	$2.4 \times 10^0$
45	methanol (50 wt %)-water	0.843 <sup>56</sup>	54.9 <sup>58</sup>	n.a.	$5.0 \times 10^0$	$3.7 \times 10^{-1}$	$1.9 \times 10^1$	$6.0 \times 10^{-1}$
46	ethanol (20 wt %)-water	0.878 <sup>56</sup>	67.0 <sup>58</sup>	n.a.	$3.8 \times 10^{-1}$	$3.7 \times 10^{-2}$	$5.6 \times 10^{-1}$	$2.7 \times 10^{-1}$
47	ethanol (10 wt %)-water	0.946 <sup>56</sup>	72.8 <sup>58</sup>	n.a.	$1.7 \times 10^{-1}$	$1.9 \times 10^{-2}$	$2.1 \times 10^{-1}$	$1.4 \times 10^{-1}$
48	water	1.000	78.30	1.85	$2.8 \times 10^{-2}$	$7.0 \times 10^{-3}$	$3.1 \times 10^{-2}$	$3.6 \times 10^{-2}$
49	HCl (0.1 M)	n.a.	n.a.	n.a.	$2.8 \times 10^1$	$2.8 \times 10^1$	$2.5 \times 10^1$	$1.8 \times 10^1$
50	H <sub>2</sub> SO <sub>4</sub> (0.1 M)	n.a.	n.a.	n.a.	$3.5 \times 10^1$	$3.5 \times 10^1$	$3.2 \times 10^1$	$3.5 \times 10^1$
51	oxalic acid (0.1 M)	n.a.	n.a.	n.a.	$2.1 \times 10^1$	$2.6 \times 10^1$	$1.7 \times 10^1$	$2.2 \times 10^1$
52	NaCl (0.1 M)	n.a.	n.a.	n.a.	$2.2 \times 10^{-2}$	$6.2 \times 10^{-3}$	$2.7 \times 10^{-2}$	$3.2 \times 10^{-2}$
53	KClO <sub>4</sub> (0.1 M)	n.a.	n.a.	n.a.	$2.2 \times 10^{-2}$	$6.1 \times 10^{-3}$	$2.5 \times 10^{-2}$	$3.2 \times 10^{-2}$
54	ethyl pyruvate	n.a.	n.a.	n.a.	$> 2.1 \times 10^2$	$> 2.2 \times 10^2$	$> 3.1 \times 10^2$	$> 3.7 \times 10^2$

<sup>a</sup> The reported empirical solvent polarity ( $E_T^N$ ),<sup>38</sup> dielectric constant ( $\epsilon_r$ ),<sup>38</sup> and dipole moment ( $\mu$ )<sup>55</sup> of each solvent are also provided for reference.

of magnitude depending on the nature of the solvent. The solubility is low in nonpolar solvents such as cyclohexane (**1**), *n*-pentane (**2**), and *n*-hexane (**3**), and in general increases with solvent polarity up to  $E_T^N$  values of  $\sim 0.6$ . This behavior agrees with the empirical observation that nonpolar solvents tend to dissolve nonpolar solutes, whereas polar solvents tend to dissolve polar solutes (note that the cinchona alkaloids are polar).<sup>38</sup> However, the solubility of the cinchona then decreases gradually for  $E_T^N$  values above 0.6: an overall volcano-type correlation between solubility and solvent  $E_T^N$  is clear in Figure 2a. A similar, although less well characterized, behavior was

previously reported for benzoic acid, the solubility of which follows the sequence carbon tetrachloride < benzene < ethanol  $\gg$  water.<sup>60</sup>

It is interesting to note that low solubilities were observed here for all four cinchona in either water (**48**) or aqueous solutions of dioxane, acetone, ethanol, and methanol with large proportions ( $> 50$  wt %) of water (**40** and **42–47**), even though the  $E_T^N$  values of all those solvents are above 0.6. It could be argued that this is justified given that most organic compounds, especially those with long hydrocarbon chains, mix poorly with water,<sup>61</sup> but decreases in solubility were also seen with highly



**Figure 2.** Correlations between the solubility of CD and the reported empirical polarities ( $E_T^N$ ) (a), dielectric constants ( $\epsilon_r$ ) (b), and dipole moments ( $\mu$ ) (c) of the 54 solvents used in these studies.<sup>38,55–59</sup> Those solvents are identified by the numbers assigned in the Experimental Section. Nice volcano-like correlations are seen in the first two cases but not with dipole moment.

polar solvents such as *N*-methylformamide (**36**) and formamide (**41**). In addition, the solubility of the cinchona in 70–90 wt % dioxane (**30** and **25**) or acetone (**34** and **28**) aqueous solutions was found to be higher than that in pure dioxane (**11**) or acetone (**20**). Nevertheless, all those solubility data points fit well into the volcano-type curve in Figure 2a. It has been empirically determined that, at least when working with two liquid solvents,

homogeneous mixing requires a small difference in  $E_T^N$  values.<sup>38</sup>  $E_T^N$  refers only to solvents and therefore is not applicable to solid cinchona, but the  $E_T^N$  value of quinoline is 0.269,<sup>38</sup> and cinchona alkaloids are apparently more polar than quinoline. It could be argued that the intermediate polarities of these alkaloids justify the maximization of their solubility in solvents of medium to high polarities.

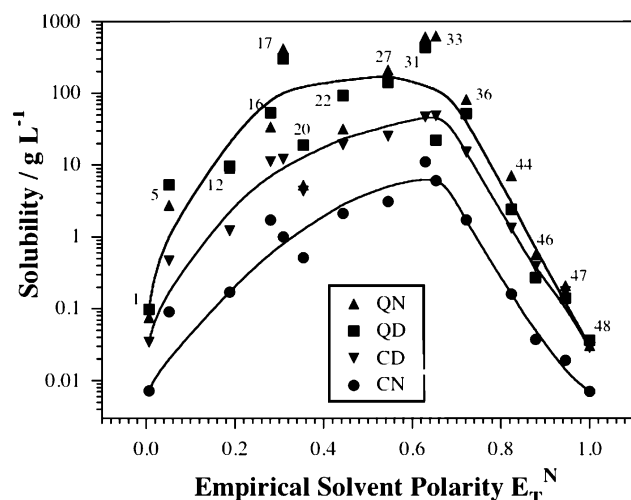
Some unique cases deviate significantly from the general volcano shape of the data in Figure 2a. In particular, the solubilities of all cinchona in acetic acid (**32**) are much higher than expected. This behavior may be ascribed to an acid–base interaction,<sup>62</sup> namely, a protonation of the basic nitrogen in the quinuclidine ring of the cinchona.<sup>63</sup> To test the effect of solvent acidity on cinchona solubility directly, additional solubility experiments were carried out with 0.1 M aqueous solutions of HCl, H<sub>2</sub>SO<sub>4</sub>, and oxalic acid as solvents. It was seen that the solubility in water is significantly enhanced by small amounts of the added acid. In contrast, neutral additives such as NaCl or KClO<sub>4</sub> lead to virtually no changes in solubility (Table 1, entries **48**–**53**). Another less extreme deviation from the general shape of the data in Figure 2a (also seen with the other three cinchona alkaloids) is that with chloroform (**15**), which also shows a higher-than-expected dissolving power, perhaps because of its ability to form C–H···N hydrogen bonds with the cinchona molecules.<sup>62</sup> Clearly, the solvent polarity is not the only factor determining the solute solubility; other parameters such as the degree of similarity between functional groups and the potential interaction between solvent and solute also play a role in this.<sup>62</sup>

Volcano-shaped trends were also identified in the plots of cinchona solubility versus dielectric constant ( $\epsilon_r$ ) (Figure 2b). In this case, the distributions are more skewed and peak for dielectric constant values between 10 and 40. The solubility data for 70–90 wt % dioxane (**30** and **25**) and acetone (**34** and **28**) still fit well into the volcano curves, but the solubilities of CD in formamide (**41**) and *N*-methylformamide (**36**), both solvents with large dielectric constants, seem to fall out of that trend even though those data fit well in the plot versus  $E_T^N$  shown in Figure 1a. Last, the case of acetic acid (**32**) is unique here as well, again because of possible acid–base interactions.

Interestingly, even though dipole moment is often used to express polarity in physics,<sup>38,55</sup> it is not a good parameter for predicting solubility in the cinchona system (Figure 2c). The solubilities of the cinchona in zero-dipole-moment solvents such as cyclohexane (**1**), *n*-pentane (**2**), *n*-hexane (**3**), carbon tetrachloride (**5**), carbon disulfide (**6**), and benzene (**8**) are low, but aside from that, there is no clear-cut correlation between dipole moment and solubility, in the sense that similar solubilities are observed for solvents within a wide range of dipole moments and, conversely, a range of solubility values is also seen for solvents with similar dipole moments, in particular around  $\mu = 1.7$ . In fact, no good linear correlations are observed between dipole moment and either empirical solvent polarity or dielectric constant; a better correlation is seen between empirical solvent polarity and dielectric constant, although the reported dielectric constants for formamide (**41**) and *N*-methylformamide (**36**) are quite a bit higher than those expected on the basis of their  $E_T^N$  values.

Comparative studies with all four cinchona alkaloids indicated that, with the same solvent, their solubility generally follows the order CN  $\ll$  CD < QN, QD. Figure 3 illustrates this trend in a plot of solubilities versus  $E_T^N$  for selected solvents (the complete data set is provided in Table 1). This solubility ordering, in particular the large difference between CD and CN,



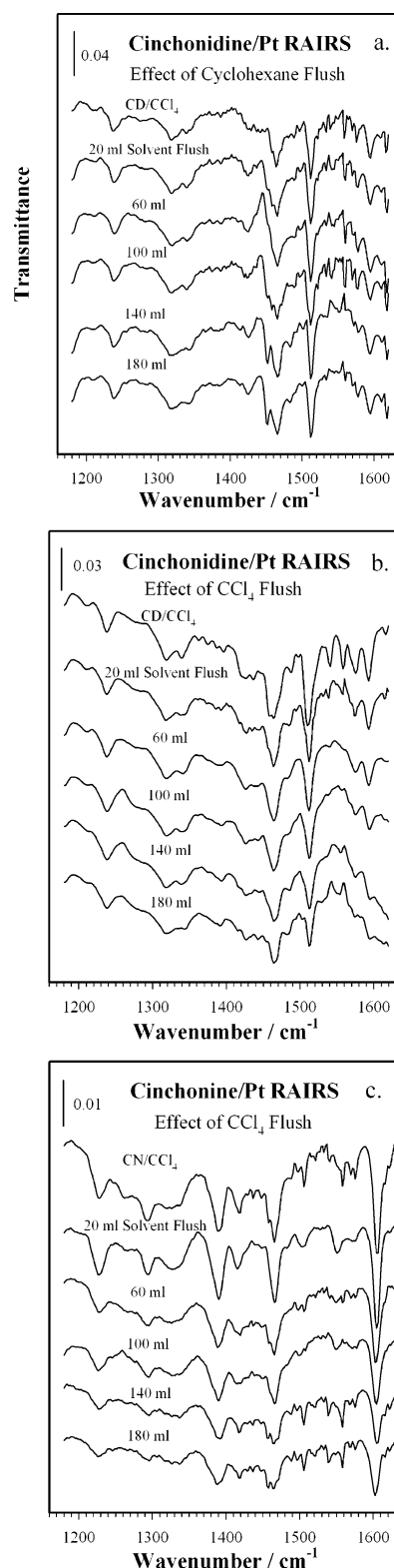


**Figure 3.** Correlation between the solubilities of CD, CN, QN, and QD and empirical polarities ( $E_T^N$ ) of selected solvents (the full set of data is provided in Table 1). This graph highlights the differences in solubilities of the different modifiers in each solvent, which in general follow a  $CN < CD < QN, QD$  sequence.

is quite surprising given that CN and CD, as well as QN and QD, are near enantiomers with the same molecular formulas and similar structures (Figure 1). Nevertheless, the differences in solubility observed here are in agreement with reported differences in catalytic performance (more on this later).

To the best of our knowledge, detailed volcano plots between solubility and solvent properties such as those presented in Figures 2 and 3 have not been reported before. We are only aware of an attempt to introduce a parameter, dielectric requirement, to define the dielectric constant range in which the solubility of a solute such as benzoic acid is maximized.<sup>54</sup> On the other hand, previous attempts have been made to identify correlations between the empirical polarity or dielectric constant of solvents and the enantioselective excess (ee) obtained in chiral hydrogenations using cinchona-modified metal catalysts, with mixed success.<sup>5,6,15,17,39,40,42,43</sup> It is our contention that the solubility behavior reported here and explained by a matching of polarities between solvent and solute may be quite general.

**3.2. Correlation between Cinchona Solubility and Its Ease of Desorption from Pt Surfaces.** Next, the stability of preadsorbed cinchona on Pt surfaces under different solvents was investigated. In these studies, a chiral modifier was first adsorbed from a  $CCl_4$  solution onto the Pt surface and then flushed by a pure solvent in a stepwise manner while monitoring the fate of the adsorbed modifier in situ by IR spectroscopy. The extent of desorption of cinchonidine (CD) adsorbed on Pt was probed systematically with all 54 solvents used in this work. It was found that, in general, the ease of desorption is largely determined by the power of the solvent to dissolve the cinchona: the higher the solubility, the larger the extent of desorption of the modifier. Specifically, among the common organic solvents, only cyclohexane, *n*-pentane, and *n*-hexane cannot flush away the adsorbed CD at all. Figure 4a shows typical data for the case of cyclohexane: no detectable changes in the RAIRS traces are seen even after flushing with 180 mL of that solvent. On the other hand, when solvents with enhanced dissolving power are used, the amount of CD desorption increases. For instance, with pure  $CCl_4$ , the intensities of the CD RAIRS features that identify the adsorbed species decrease gradually, losing ~40% of the initial values after nine 20-mL  $CCl_4$  flushes (Figure 4b). With  $CS_2$ , toluene, benzene, ethyl



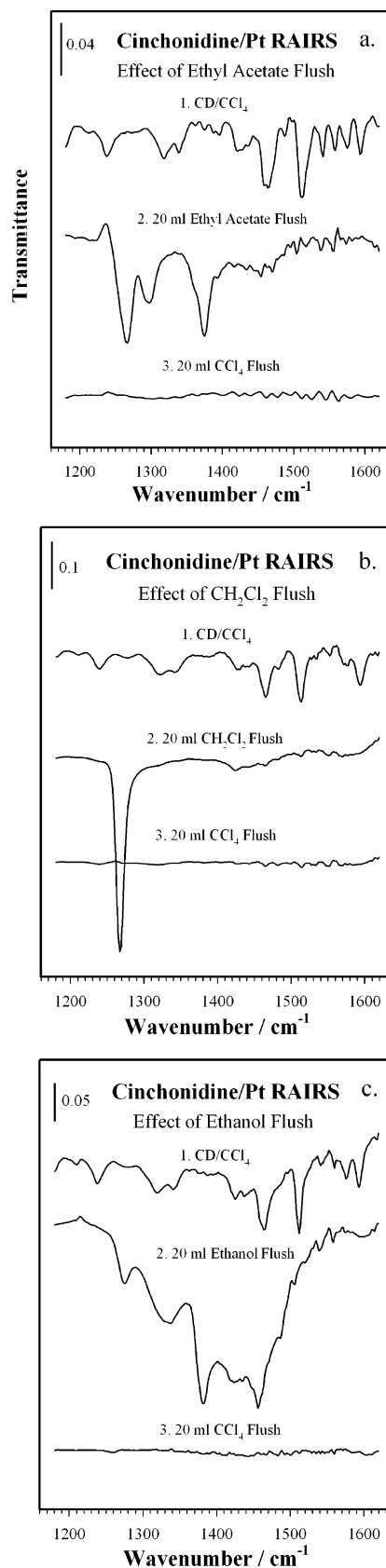
**Figure 4.** Reflection-absorption infrared spectroscopy (RAIRS) results from experiments designed to test the effect of solvent flushing on cinchona adsorbed on a Pt surface. The surface was first exposed to either 3.4 mM  $CD/CCl_4$  (Figure 4a and b) or 0.3 mM  $CN/CCl_4$  (Figure 4c) solution in the presence of  $H_2$  and then flushed with sequential 20-mL aliquots of a pure solvent, cyclohexane in Figure 4a and  $CCl_4$  in Figure 4b and c. While cyclohexane can hardly remove any preadsorbed CD from the surface, flushing with 180 mL of  $CCl_4$  does remove a small fraction of the adsorbate over time. Notice that the CD peak at  $1465\text{ cm}^{-1}$  overlaps with a growing signal at  $1452\text{ cm}^{-1}$  in Figure 4a due to the  $-CH_2-$  scissoring vibrational mode of cyclohexane.

ether, chlorobenzene, and formamide, in which the CD solubility is  $<1.2$  g/L, the adsorbed CD still displays some stability, although less than when flushing with  $\text{CCl}_4$ .

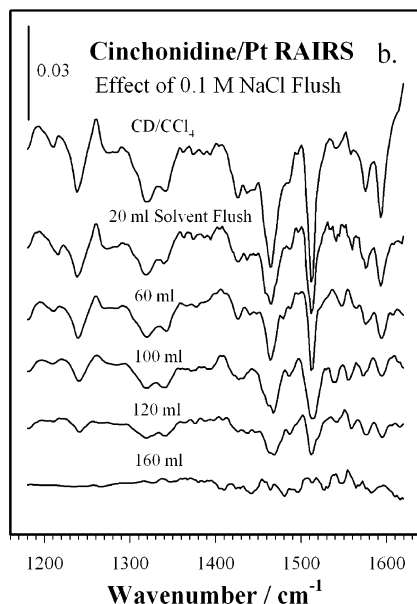
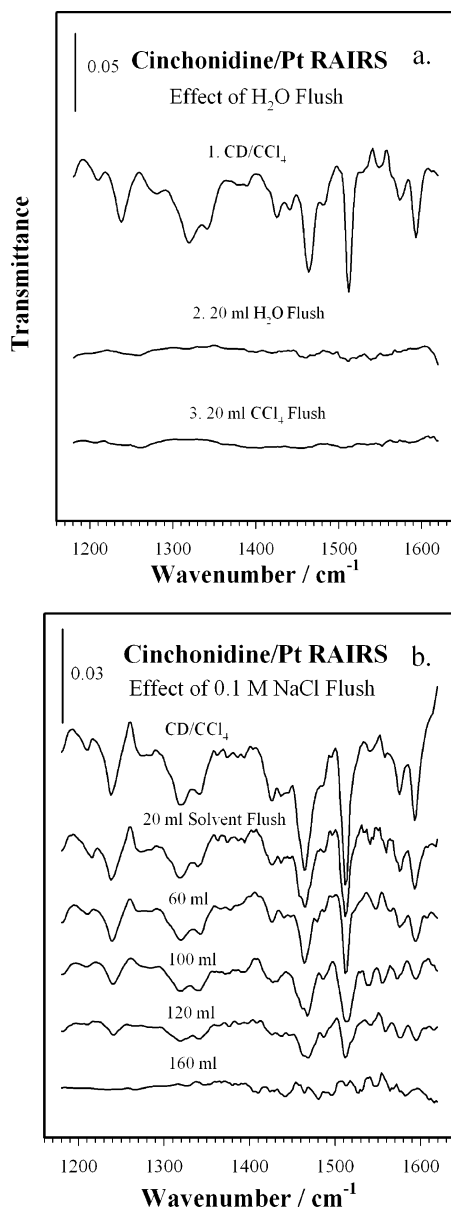
The adsorbed CD is more easily removed from the surface with solvents in which its solubility is higher than  $\sim 1.2$  g/L. Figure 5 shows typical results to illustrate this behavior, for the cases of ethyl acetate, dichloromethane, and ethanol. Due to the high solubility of CD in these solvents, the majority of the preadsorbed CD is removed after the first 20-mL flush, as indicated by the absence of the corresponding RAIRS features in the middle traces of Figure 5. To check that the CD RAIRS signal is not masked by the solvent, the Pt surface was subsequently flushed by  $\text{CCl}_4$  (bottom traces); note that no significant CD RAIRS peaks are evident in those spectra either. In general, since solutes hold on to solid surfaces more strongly from solutions with poor rather than good solvent,<sup>60,64</sup> adsorbates are expected to desorb more easily into solvents with high dissolving power. This is what was observed in our studies on the adsorption of cinchona on platinum.

The behavior discussed above is in general followed by the other solvents used in this study (data not shown). Surprisingly, though, the stability of adsorbed CD in water is rather low even though the solubility of CD in water is low (Figure 6a), and similar low stabilities are also seen with the mixed organic–water solvents, including aqueous dioxane, acetone, ethanol, and methanol, irrespective of the solubility of CD in them. The underlying reason for this behavior is not obvious, but reports of analogous phenomena with octadecanol and benzoic acid adsorbates can be found in previous publications.<sup>60,64</sup> In addition, it was determined that the stability of adsorbed CD is enhanced when a small amount of an inorganic salt such as NaCl or  $\text{KClO}_4$  is added to water. As an example, Figure 6b shows how the presence of NaCl in water retards the removal of CD from the Pt surface. On the other hand, this is not the case with aqueous HCl,  $\text{H}_2\text{SO}_4$ , or oxalic acid, all of which display a much higher dissolving power toward CD. The addition of NaCl has been previously reported to increase the adsorption of butanoic acid from water onto active carbon, allegedly because of an increase in the activity coefficient of the solute caused by the addition of the salt.<sup>60</sup> However, it is worth remembering that the addition of NaCl or  $\text{KClO}_4$  to water does not alter the solubility of the cinchona in any significant way.

The experiments discussed above were all done by adsorbing CD from  $\text{CD}/\text{CCl}_4$  solutions and then flushing the premodified Pt surface with a second solvent. To test the generality of the correlations from our work, further studies were carried out by generating the preadsorbed CD layer at a  $\text{CH}_2\text{Cl}_2$ –Pt interface. Those experiments showed that the solubility–desorption correlation discussed above holds regardless of the solvent from which the CD is adsorbed. Figure 7 shows the data for the case of CD deposited from  $\text{CD}/\text{CH}_2\text{Cl}_2$  solutions followed by flushing with either  $\text{CH}_2\text{Cl}_2$  (Figure 7a) or cyclohexane (Figure 7b). It should be pointed out that since  $\text{CH}_2\text{Cl}_2$  is a much better solvent for CD than  $\text{CCl}_4$ , a higher CD concentration was required for the initial deposition of the CD in this case. Despite the interference in the RAIRS data by the  $\text{CH}_2\text{Cl}_2$  peak at  $1267\text{ cm}^{-1}$ , it is clear that pure  $\text{CH}_2\text{Cl}_2$  is able to easily flush away the majority of adsorbed CD (Figure 7a). On the other hand, cyclohexane, with its much lower dissolving power, cannot remove the adsorbed alkaloid (Figure 7b). Also evident from the data in Figure 7a is the fact that re-exposure of the surface to the  $\text{CD}/\text{CH}_2\text{Cl}_2$  solution reinstates the CD adsorbate layer. This attests to the reversibility of the adsorption–desorption process.



**Figure 5.** RAIRS on the effect of flushing CD-premodified Pt surfaces with ethyl acetate (a),  $\text{CH}_2\text{Cl}_2$  (b), or ethanol (c). Because of the high dissolving power of those solvents, the majority of preadsorbed CD is flushed away by as little as 20 mL in all three cases. The removal of the surface CD, manifested by the disappearance of the IR peaks in the middle traces, was corroborated by further flushing with pure  $\text{CCl}_4$  (bottom data). Similar trends were found for many other polar organic solvents.

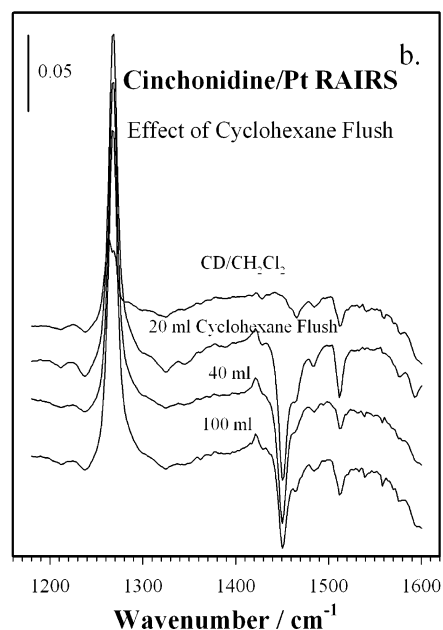
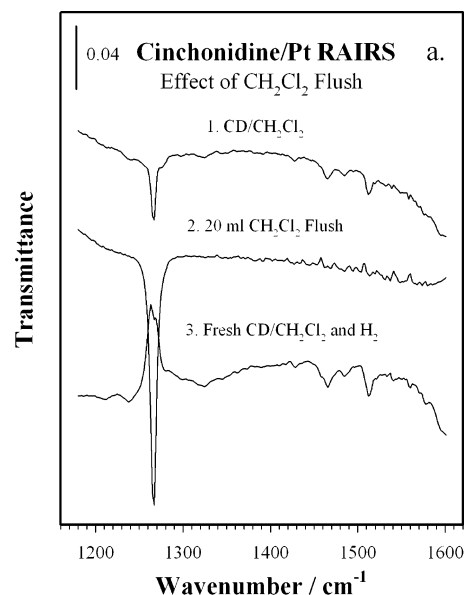


**Figure 6.** RAIRS on the effect of flushing CD-preadsorbed Pt surfaces with either water (a) or a 0.1 M NaCl solution (b). Water is quite efficient at removing the surface CD, but the addition of a neutral inorganic salt to the liquid phase retards the desorption.

Additional experiments with the other (CN, QN, and QD) chiral modifiers confirmed the generality of the solubility–desorption correlation reported above. Figure 4c shows an example for the case of a CN adlayer generated at the  $\text{CCl}_4$ –Pt interface and subsequently flushed by sequential aliquots of pure  $\text{CCl}_4$ . In this case, as with CD (Figure 4b), the removal of the adsorbed molecule is slow. Solvents with high dissolving power such as 1-butanol and methanol were shown to be more efficient at this removal (data not shown).

#### 4. Discussion

As mentioned in the Introduction, solvents may heavily influence both reaction rates and enantioselectivity in heterogeneous chiral catalysis in complex ways.<sup>5,6,10</sup> A number of studies have reported on the effect of solvents in these systems, but, to date, no universal explanation has been developed to explain all the experimental findings. Perhaps the most general and convincing proposal so far is that the decrease in hydro-



**Figure 7.** RAIRS on the effect of flushing CD adsorbed on Pt surfaces with  $\text{CH}_2\text{Cl}_2$  or cyclohexane. In contrast with the experiments reported in Figures 4–6 where the CD was pre-deposited using a 3.4 mM CD/ $\text{CCl}_4$  solution, here the Pt surface was pre-exposed to a 40 mM CD/ $\text{CH}_2\text{Cl}_2$  solution instead. While as little as 20 mL of  $\text{CH}_2\text{Cl}_2$  is sufficient to flush the majority of the adsorbed CD away, flushing with as much as 100 mL of cyclohexane still leaves the adsorbed CD virtually intact. Note that since pure  $\text{CH}_2\text{Cl}_2$  (rather than  $\text{CCl}_4$ ) was used in these experiments, an interference is seen in the RAIRS traces at  $1267\text{ cm}^{-1}$ .

genation ee as a function of solvent polarity may correlate with a decrease in population of the so-called Open(3) conformer of cinchona, since both properties appear to decrease with the dielectric constant of the solvent in experiments with 1-phenyl-1,2-propanedione,<sup>15</sup> ketopantolactone,<sup>48</sup> or butane-2,3-dione.<sup>49</sup> However, poorer-than-predicted ee's have been observed with solvents with dielectric constants lower than 2,<sup>5,39,48</sup> and no similar correlations have been found with other reactants.<sup>14,17,65</sup> Also, this model only deals with the behavior of the cinchona in solution, and does not address the issue of adsorption on the surface of the platinum catalyst. All these caveats limit the generality of the explanation of catalytic performance in terms of cinchona molecular configuration, and demand a more

comprehensive study of the role of the solvent in chiral catalysis. Because of the complexity of these systems, it is advisable to assess the individual contributions of the different pairwise interactions among the reactants, products, chiral modifier, catalyst surface, and solvent using simpler models. With this in mind, the present study was designed to isolate and characterize the interactions between the solvent and the modifier both in solution and on Pt surfaces.

A general finding deriving from our work is that the solubility of cinchona follows volcano-type correlations with either the empirical polarity ( $E_T^N$ ) or the dielectric constant of the solvent, and that solubility also correlates with the ease of desorption of the cinchona from a solid surface. It has been often stated that polar solutes dissolve in polar solvents and nonpolar solutes in nonpolar solvents, but, to the best of our knowledge, detailed solubility–polarity–adsorption correlations such as this have never been reported. We propose that optimal solubility is obtained when the polarity of the solvent matches the polarity of the solute. Since  $E_T^N$  is a parameter devised for liquid solvents only, its value is not available for solid solutes such as the cinchona studied here, but related electrical properties such as the dielectric constant may be used in those cases as close substitutes. It should be noted, however, that other chemical interactions also play a role in determining solubilities. In the case of the cinchona, for instance, acid–base and hydrogen-bonding interactions appear to facilitate dissolution. Nevertheless, solvent polarity may be the dominant determinant of solubility, and can be used for first-order screening of solvents for a given system.

Our findings on the solubility of cinchona as a function of the nature of the solvent have direct implications for the performance of cinchona-modified catalytic systems. Specifically, it was determined that the solubilities of the cinchona in a given solvent correlate well with the extent of their adsorption–desorption equilibrium, and since this is a central step in the mechanism of chiral modification in heterogeneous catalysis, they are expected to also directly affect the performance of those systems in terms of both total activity and enantioselectivity (ee). Earlier references have in fact been made already to interrelations between the physical chemistry properties of solvent and the catalytic behavior of cinchona-modified platinum catalysts,<sup>5–10</sup> but the solubility data from our work can perhaps better justify previous reported adsorption and catalytic results. For instance, Blaser et al. found that the coverage of CD adsorbed from a methanol solution onto a Pt/Al<sub>2</sub>O<sub>3</sub> catalyst amounted to only one-eighth of that obtained with toluene as a solvent, even though the initial CD concentration in methanol was twice that in toluene.<sup>66</sup> This can be explained by our solubility data, which show that the solubility of CD in methanol (**39**) is almost 1 order of magnitude larger than that in toluene (**7**), together with the general trend that a higher solubility leads to a higher degree of desorption. In another example, Baiker et al. reported that when a pair of modifiers is used simultaneously for the chiral modification of hydrogenation catalysts, the ee is to a large extent determined by the one that adsorbs more strongly on the surface. They reported that with 2-propanol as the solvent this adsorption preference follows a CN > CD > QD > QN sequence,<sup>67</sup> a trend that again agrees nicely with the solubility order (CN < CD < QD < QN) obtained in our work (Table 1, entry **27**).

Another important aspect to be considered when discussing the effect of solvents in this catalysis is the potential loss of the modifier from the surface. Traditionally, chiral hydrogenation on cinchona-modified Pt catalysts has been carried out in

batch reactors, by either in situ modification in the reactor during reaction<sup>6</sup> or ex situ modification in another vessel before transferring to the reactor.<sup>3,4,8</sup> Some of the modifier is lost to the reaction mixture in the latter case, but that can be minimized by using low solubility solvents. For instance, Bartók et al. reported that the loss of CD preimmobilized on clay-supported Pt catalysts could be reduced by switching from acetic acid to toluene as the solvent.<sup>18</sup> This is in agreement with both the order of solubility and the spectroscopic results reported in the present work. Modifier losses over time have also been seen in fixed-bed reactor processes,<sup>20,44</sup> and again minimized by choosing an appropriate solvent. For instance, slower temporal decreases in ee have been observed on CD-premodified Pt/Al<sub>2</sub>O<sub>3</sub> with ethanol compared to acetic acid and with toluene instead of ethanol.<sup>44</sup> These trends can be easily justified by the solubility and spectroscopy data from our work.

To remedy the loss of adsorbed modifier to the solvent, trace amounts of modifier are sometimes added continuously in both batch<sup>9,19</sup> and fixed-bed<sup>20</sup> reactors. However, in such cases, the use of poor solvents for the alkaloid modifier may lead to the buildup of an excess of cinchona on the surface of the catalyst. This could have adverse effects, because too much adsorbed modifier can reduce the ee of the catalytic process.<sup>9,33</sup> This is what was reported by Reschetilowski et al., who found that, with Pt/zeolite in a batch reactor, supplementing CD after each reaction cycle leads to a decrease in activity if cyclohexane is used as the solvent, and that better long-term activity is obtained with acetic acid, a better solvent for CD.<sup>19</sup> Again, their observations are in agreement with the fundamental information derived from our study.

Finally, it needs to be reiterated that the current research is to be placed within the general frame of the isolation of individual interactions between the reactants, products, catalyst, chiral modifier, and solvent in heterogeneously catalyzed enantioselective hydrogenation.<sup>26</sup> From the above experimental results and discussion on the interactions between the chiral modifier and the solvent, it can be concluded that the solubility of chiral modifiers varies considerably depending on the nature of the solvent, and that such variations influence the extent of the adsorption–desorption equilibrium of cinchona modifiers on the surface of Pt catalysts, thus profoundly influencing their catalytic behavior. The correlations between cinchona adsorption and their solubility in different solvents and between that solubility and solvent polarity provide a basic guideline for choosing the appropriate solvent to fine-tune a specific catalytic system. In addition, considering the fact that cinchona alkaloids are also frequently used homogeneous chiral catalysts in organic synthesis,<sup>68</sup> the solubility data reported here may also help with the understanding and design of new homogeneous catalytic processes.

## 5. Conclusions

Our studies have indicated that cinchonidine, cinchonine, quinine, and quinidine, being polar molecules, tend to be dissolved more easily into solvents with suitable polarity. Specifically, their solubility first increases with the empirical polarity of the solvent ( $E_T^N$ ), reaches a maximum at a value of  $\sim 0.6$ , and then decreases again with further increases in polarity. A similar volcano-type trend is evident versus dielectric constant, where the best solubilities are observed in solvents with dielectric constants between 10 and 40. On the other hand, correlations between cinchona solubility and the dipole moment of the solvent are not evident. Although other factors such as similarities in local molecular structures and specific interactions



between modifier and solvent may also influence the solubility of the former in the latter, solvent polarity has proven to be the major factor determining such solubility in these systems.

It was also determined that the extent of the adsorption–desorption equilibrium of cinchona on Pt surfaces is largely related to the solubility of the solvent used. Nonpolar organic solvents, which often display poor dissolving power, can hardly remove the adsorbed modifiers, at least under our experimental conditions. On the other hand, the extent of the removal can be increased by using polar solvents, in which the solubility is higher. Water and some aqueous solutions proved to be an exception to this rule, since they facilitate the removal of the modifier from the Pt surface even though they are poor solvents for the cinchona. However, the addition of neutral salts such as NaCl and KClO<sub>4</sub> into water retards that desorption. The reversibility of the adsorption was demonstrated in experiments with dichloromethane.

The solubility data and desorption behavior reported in this work are in agreement with the catalytic data for the case of the enantioselective hydrogenation of  $\alpha$ -ketoesters by cinchona-modified Pt catalysts. In the case of continuous flow reactors, this behavior can be directly correlated with the ease of removal of the adsorbed chiral modifier by the solvent. The relative solubilities of the different cinchona alkaloids, which follow a CN < CD < QD, QN sequence, also seem to correlate well with the nonlinear effects observed with mixtures of those modifiers.

**Acknowledgment.** Financial support for this work was provided by the U.S. Department of Energy.

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