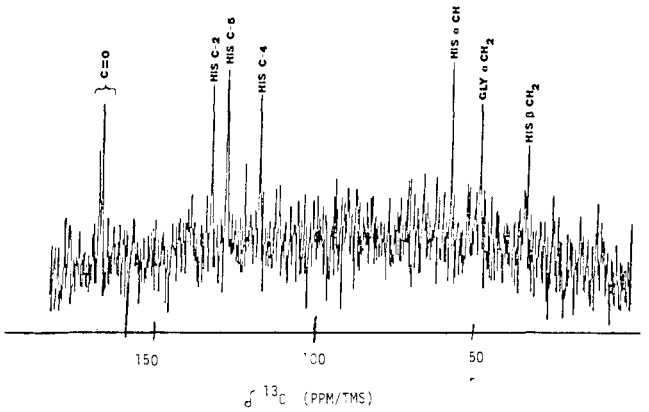

Figure 1. ^{13}C NMR spectrum of *cyclo*-(Gly-His)$_3$ in D_2O

in 2% HOAc and extracted with ethyl acetate to remove the free dinitrophenyl derivatives. The aqueous layer was then concentrated, and the yellowish residual Dnp peptides (incompletely deprotected) were separated from the colorless free peptide by using reverse-phase chromatography (μ-Bondapak C_{18}, Waters) and eluting with 2% aqueous HOAc. The yield of crude hexapeptide after chromatography was 42% (as determined by amino acid analysis of several samples and calculated based on the loading of the (aminomethyl)polystyrene resin). The crude peptide was further purified by ion-exchange chromatography (Chelex 100, 200–400 mesh). The cyclic hexapeptide was eluted with 0.1 M trifluoroacetic acid and precipitated as a white hydrochloride salt (or a trifluoroacetate salt).

The purified cyclic peptide showed a negative ninhydrin test, indicating the absence of free amino groups, and therefore contained no linear structures. It also gave a positive Pauli test,[21b] indicating the presence of unsubstituted histidine side chains. Amino acid analysis of the purified peptide showed a ratio of 1.02:1.00 of Gly to His. Field desorption mass spectral analysis of *cyclo*-(Gly-His)$_3$ showed peaks at $(MH)^+$ 583, $(MH - H_2O)^+$ 565, and $(M + Na)^+$ 605, as expected for a molecular ion of 582. There was no indication of higher molecular weight cyclic or linear peptides. High-pressure liquid chromatographic analysis of the purified peptide on an amino column (Altex Ultrasphere amino, 4.6 mm × 25 cm) using 65% aqueous acetonitrile containing 4×10^{-3} M KH_2PO_4 buffer showed a single peak (with a retention time of 25 min at a flow rate of 1.5 mL/min). The ^{13}C NMR spectrum[23] of the cyclic hexapeptide (as a trifluoroacetate salt) in D_2O shows signals from eight different carbons, which have been assigned as shown in Figure 1.[24] This simple carbon-13 pattern is consistent with the C_3-type symmetry expected for the symmetrical cyclic hexapeptide. The proton NMR spectrum in D_2O at 100 and 360 MHz also showed a simple pattern consistent with the cyclic structure, with the carbon protons assigned as follows: His CH-2, 905 ppm (s, 1 H); His CH-4, 7.74 ppm (s, 1 H); His α-CH, 5.22 ppm (s, 1 H); Gly α-CH_2, 4.37 ppm (m, br, 2 H); His β-CH_2, 3.67 (m, br, 2 H). The UV spectrum of the cyclic hexapeptide (in water) showed a shoulder at 214 nm followed by strong end absorption.

The solid-phase cyclization method used here (with a resin loading of 0.2 mmol NH_2/g of resin) resulted in a high yield of ring closure with no measurable amount of linear peptides remaining. Neither the crude product obtained directly after thiolytic cleavage nor the purified cyclic hexapeptide contained detectable amounts of linear or oligomeric cyclic peptides. This was checked by several techiques, including gel filtration, high-voltage electrophoresis, high-pressure liquid chromatography, and mass spectral analysis of both the unpurified and the final purified peptide products.

(23) The ^{13}C NMR spectrum was obtained on a Varian XL-100-Nicholet TT-100 system (100 MHz) with a ^{13}C microprobe (Varian).

(24) (a) C., George Levy, Ed. "Topics in Carbon-13 NMR Spectroscopy"; Wiley: New York, 1978; Vol. 2. (b) Smith, I.; Jennings, H.; Deslauriers, R. *Acc. Chem. Res.* **1975**, *8*, 306.

The synthetic scheme described here has provided convenient access to *cyclo*-(Gly-His)$_3$, making use of the bidirectional peptide synthesis method.[14c] By variation of the amino acids, this scheme can lead to cyclic hexapeptides with different coordination environments. Such cyclic peptides can be designed to incorporate amino acid side chains that are important for the function of various enzymes.

The cyclic hexapeptide, *cyclo*-(Gly-His)$_3$, described here provides only three coordination positions around the metal ion and the fourth coordination position to the metal ion can be varied to include oxygen-, nitrogen-, or sulfur-donor ligands such as water, imidazole, dimethyl sulfide, or mercaptoethanol. The 1:1 complexes of *cyclo*-(Gly-His)$_3$ with Cu(II) and Zn(II) have been formed in solution and their spectral, physical, and electrochemical properties are currently under study in our laboratory.

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Registry No. VI, 80954-37-6; Boc-His, 17791-52-5; Gly-OBzl, 1738-68-7; Boc-Gly, 4530-20-5; Boc-His(Dnp), 25024-53-7.

Liquid Crystalline Catalysis. 1. Reactivity Induced by Smectic Solvents

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Reported results of catalytic and stereochemical effects of liquid crystalline solvents in thermal[1-3] and photochemical reactions[4] seem to discourage expectations of notable developments; the use of thermotropic liquid crystalline solvents as a tool in the elucidation of reaction mechanisms, as well emphasized by Nerbonne and Weiss,[3] might seem to be the only really encouraging development to be expected in this field.

However, apart from one exception[4] (where the rate of a photochemical reaction is enhanced only by a cholesteric and not a smectic or a nematic solvent) these results have been all obtained by using only nematic or cholesteric liquid crystalline solvents whose "microscopic matrix effect", determined by the short-range orientational order, is very similar to that of isotropic solvents.[5,6] By use of more tightly ordered smectic solvents and selection of a reaction whose energy of activation is expected to be mainly determined by the entropy term (i.e., with severe orientational demands in the transition state), relevant catalytic effects due to solvent ordering have been displayed and are presented in this paper.

The guest–host intermolecular interactions resulting from dissolving an organic substance in a liquid crystal induce modifications in the orientational correlation of the molecules of the mesomorphic solvent and anisotropy in both the diffusion and

(1) Bacon, W. E.; Jun-Ling, K.; Brown, G. H. *Mol. Cryst. Liq. Cryst.* **1979**, *56*, 13-17.

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(5) Gottarelli, G.; Samori, B. In "Liquid Crystals"; Chandrasekhar, S., Ed.; Heyden & Sons: London, Philadelphia, and Rheine, 1980; pp 505-514.

(6) Croucher, M. D.; Patterson, D. *J. Chem. Soc., Faraday Trans. 1* **1981**, *77*, 1237-1248.

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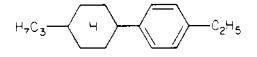
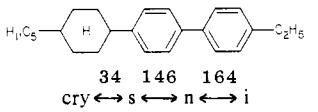
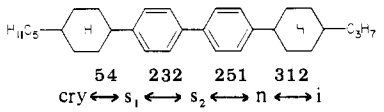
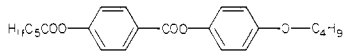
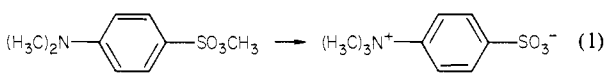
Table I. Mesomorphic Solvents

 extrapolated clearing point −70 °C	S-1484 (E. Merck)
 34 146 164 cry ⟷ s ⟷ n ⟷ i	ZLI-1409 (E. Merck)
 54 232 251 312 cry ⟷ s_1 ⟷ s_2 ⟷ n ⟷ i	ZLI-1544 (E. Merck)
 58 87 cry ⟷ n ⟷ i	CBPB (Hoechst)

molecular orientation of the solute. If the solute molecules are able to react, the tendency of the solvent to maintain its lowest energy, undistorted state can exert constraints on the conformations[7] and encounters of the reactant molecules so as to decrease or increase the free energy of activation of the reaction. Rate acceleration is expected when a favorable reactant orientation or rotamer distribution, which prefigures the transition state, is driven by the anisotropically ordered solvent. As these driving forces are obviously linked to the rigidity of the molecular packing of the mesomorphic solvent, tightly ordered smectic mesophases (whose heat and entropy of transition to the isotropic state may be comparable to those of crystalline phases[8]) will certainly be much more effective to this end than nematic and cholesteric solvents. The amount of mesomorphic solvent rigidity required to provide a desired catalytic effect must, in any case, be considered dependent on the activation parameters of the investigated reaction. As orientational effects are expected to act mainly on the entropic part of the free energy of activation, reactions with low enthalpy of activation and high entropic demand to reach the transition state are expected to be influenced by a mesomorphic solvent.

The rearrangement of methyl *p*-(dimethylamino)benzenesulfonate (methyl sulfonate ester (MSE)) to its zwitterion (ZWI) is reported to occur, even at room temperature, in crystals of MSE. Solutions of MSE in various isotropic organic solvents are indefinitely stable. This rearrangement, due to an intermolecular methyl migration (eq 1) that is controlled not by the normal

 (1)

reactivity of the functional groups but by stacking of the reactant molecules of MSE,[9] has been selected as a probe of the occurrence of liquid crystalline catalysis.

The ZLI-1409 and ZLI-1544 liquid crystals (see Table I) recently synthesized at E. Merck (Darmstadt, West Germany) are, owing to their hydrocarbonic structure and very wide smectic phases, particularly suitable as reaction solvents.

The transition temperatures between the crystal (cry), the smectic (s), the nematic (n), and the isotropic (i) phases are reported in Table I. A very recent X-ray analysis[10] of the ZLI-1490 smectic phase has demonstrated its very highly ordered B structure, whose layered arrangement has the periodicity and rigidity of a two-dimensional solid. The ZLI-1409 liquid crystal, by addition of the homologous S-1484 (isotropic down to −70 °C) up to about a 3:1 (wt/wt) ratio, is so disturbed in its s_B layer structure that from about 80 to 110 °C it becomes an s_B-n two-phase system.

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Table II. Conversion Yields of MSE in ZWI

temp, °C	solvent	phase	reaction time, h	% product
81	ZLI-1409	s_B	4	7
81	ZLI-1409	s_B	16	50
81	ZLI-1544	s	16	50
100	ZLI-1409	s_B	4	15
100	ZLI-1409	s_B	16	65
100	ZLI-1409	s_B	24	70
100	ZLI-1409/S-1484	s_B-n	24	
100	S-1484	i	24	
81	CBFC	n	24	
50	ethyl acetate	i	65	

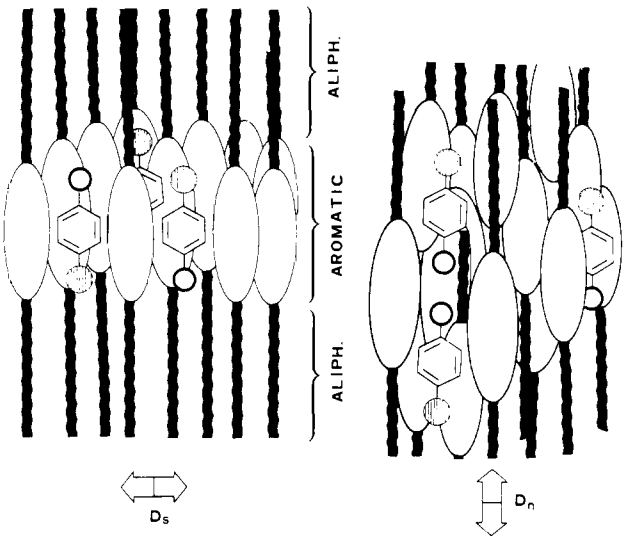

Figure 1. Orientation and D_s and D_n directions of the preferred translational diffusion of the MSE molecules inside smectic and nematic solvents, respectively.

The rearrangement of MSE has been carried out at both 81 and 100 °C (i.e., at temperatures below and above the melting point of MSE) and at the same concentration (1.5% wt/wt) both in the s_B mesophase of ZLI-1409 and in the mixture of ZLI-1409/S-1484. Conversion of MSE was determined by a UV spectrophotometric analysis of the ZWI, extracted by water from an organic solution of the reaction mixture. An X-ray diffraction analysis has demonstrated the constancy of the s_B structure of the solution in the course of a reaction performed at 81 °C. The increase in rate between 81 and 100 °C rules out the occurrence of crystallization effects.

The conversion yield reported in Table II clearly emphasizes how *the reaction is promoted by the ZLI-1409 solvent only when its smectic structure is completely preserved.* The observation that the ordering of a nematic or isotropic solvent is inadequate to this end is further supported by the yields of ZWI in CBPB, S-1484, and ethyl acetate.

Besides the differences in the tightness of the constraints given to the reaction by the various mesomorphic solvents, different encounters of the reactants can be expected to be promoted by the layer and nonlayer structures of the smectic and nematic matrices, respectively. In fact, in a smectic solvent, an MSE molecule, which is assumed to be preferentially dissolved in the aromatic part of the smectic layers (Figure 1), is rigidly orientated and constrained to higher translational diffusion along a direction (D_s) parallel to the layers.[11,12] The face-to-face encounters with the other molecules of MSE, required by the transition-state configuration, can thus be induced by the smectic solvent. On

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(12) Franklin, W. *Phys. Rev. A* **1975**, *11*, 2156–64.

the contrary, the absence of aromatic "layers" in a nematic medium allows higher translational diffusion along the director (D_n),[12] so one expects head-to-tail encounters to be promoted by the nematic solvent, as actually seems to result in the polymerization of phenylacetylene.[2]

Acknowledgment. We are grateful to Dr. Eerdmann and Dr. Eidenschink (E. Merck, Darmstad) for supplying the ZLI and S-1484 liquid crystals, Professor Rustichelli, Dr. Albertini, and Dr. Torquati (Ancona) for the X-ray measurements, and Dr. P. De Maria (Bologna) for a stimulating discussion. We also thank CNR (Rome) for financial support.

Registry No. MSE, 57270-54-9; ZWI, 19329-61-4; ZL1-1409, 77702-36-4; ZL1-1544, 81204-41-3.

Phosphine Functionalized Macrocycles. A New Type of Bridging Ligand for the Synthesis of Heterometallic Complexes

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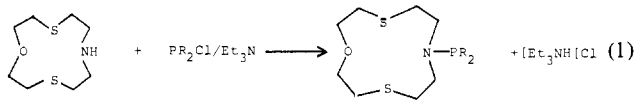
Hybrid ligands in which a cyclopentadienyl and a phosphorus donor or a Schiff base and a phosphorus donor are combined have been recently described.[1] Interest in such ligands stems from their potential for the synthesis of new bimetallic complexes containing different metal centers in close proximity. We report the synthesis of a mono-P-donor ligand in which an aminophosphine function and a macrocycle are combined. Several complexes of this unusual bridging ligand are described.

The 1-aza-4,10-dithia-7-oxacyclododecane ring, **1**,[2] may be derivatized by reaction with chlorodiphenylphosphine or chlorodimethylphosphine in the presence of 1 equiv of a tertiary amine, to give aminophosphine ligands **2a,b** (reaction 1). **2a,b** ($\subset$NPR$_2$),



(1)

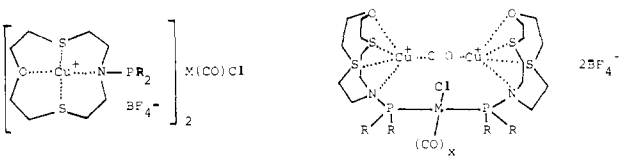
1

2a, R = Ph
2b, R = Me

obtained as colorless, air-sensitive oils on workup and characterized spectroscopically,[3] have the potential to coordinate to two metal atoms, through the phosphine center and via the heteroatom donors of the ring.

2a (R = Ph) and **2b** (R = Me) react with $[Rh(CO)_2Cl]_2$ and $[(CyO)_2Ir(CO)Cl]_2$ (CyO = cyclooctene) (2 equiv of ligands/metal atom), to give the Vaska-type complexes *trans*-[Rh(CO)Cl($\subset$NPPh$_2$)$_2$], **3** (ν_{CO} 1947 cm^{-1}), *trans*-[Ir(CO)Cl($\subset$NPPh$_2$)$_2$], **4** (ν_{CO} 1947 cm^{-1}), and *trans*-[Rh(CO)Cl($\subset$NPMe$_2$)$_2$], **5** (ν_{CO} 1949 cm^{-1}) as fully characterized yellow-orange solids.[4-6]

When an acetonitrile solution containing 2 equiv of Cu(MeCN)$_4$BF$_4$ is added to a solution of **3** under argon, an orange precipitate, **6** (ν_{CO} 2005 cm^{-1}), is isolated on addition of methanol. Spectroscopic and analytical data are consistent with the complexation of one Cu(I) ion by each ring chelate in the complex.[7] (i.e., structure I). Significantly, the addition of a single equivalent



I R = Ph, M = Rh; 6
R = Ph, M = Ir; 8
R = Me, M = Rh; 9

III R = Ph, M = Rh x = 1; 13
R = Ph, M = Ir, x = 2; 11
R = Me, M = Rh, x = 1; 10

of Cu(MeCN)$_4$BF$_4$ to complex **3** gives an orange solid, **7**, whose infrared spectrum contains a single ν_{CO} absorption at 1980 cm^{-1}. These results indicate that a single Cu(I) is complexed by only one ring in each Rh compound before a second copper ion is coordinated to the remaining chelate ring and that complexation of Cu(I) decreases the donor properties of the Ph$_2$P group (increases ν_{CO}).

Similar treatment of [($\subset$NPPh$_2$)$_2$Ir(CO)Cl], **4**, and [($\subset$NPMe$_2$)$_2$Rh(CO)Cl], **5**, with 2 equiv of Cu(MeCN)$_4$BF$_4$ gives the corresponding bis(Cu(I)) adducts [(Cu$\subset$NPPh$_2$)$_2$Ir(CO)Cl](BF$_4$)$_2$, **8**, and [(Cu$\subset$NPMe$_2$)$_2$Rh(CO)Cl](BF$_4$)$_2$, **9**.[7-9]

The dications **6**, **8**, and **9**, containing two ring-chelated copper(I) ions, exhibit some properties typical of Vaska-type compounds and others of a more unusual nature. Thus, for example, the iridium complex **8** oxidatively adds H_2 to give the expected dihydride [(Cu$\subset$NPPh$_2$)$_2$Ir(CO)ClH$_2$](BF$_4$)$_2$,[10] which can also be obtained from **4** via oxidative addition of H_2 followed by reaction with 2 equiv of Cu(MeCN)$_4$BF$_4$. Infrared studies (acetonitrile solution) indicate that both **8** and **9** react reversibly with CO. On exposure to CO **9** gives the acetonitrile solution species **10**, stable only under CO, with two ν_{CO} bands, at 2065 and 1989 cm^{-1}. **8** reacts reversibly with CO to give the acetonitrile solution species **11**, stable only under CO, with three ν_{CO} bands, at 2068, 2013, and 1963 cm^{-1}. It is well known that Vaska-type complexes form reversible CO adducts of formula [Ir(CO)$_2$Cl(PR$_3$)$_2$],[11] and complex **4**, containing no Cu(I), does indeed react reversibly with CO to form [($\subset$NPPh$_2$)$_2$Ir(CO)$_2$Cl], **12**, as shown by the presence of two strong bands, at 1983 and 1930 cm^{-1}, in its solution IR spectrum. By analogy with **12**, the ν_{CO} bands at 1963 and 2013 cm^{-1} in the spectrum of **11** are likely associated with the Ir center. The ν_{CO} absorptions in the region of 2070 cm^{-1} found in **10** and **11** are possibly associated with a Cu(I)-CO-Cu(I) species. Osborn has reported that a bis(copper(I)) "earmuff" complex forms a CO adduct (of possible structure II) with ν_{CO} at 2070 cm^{-1}.[12] Analogy and molecular models suggest III as a possible structure for the CO adducts **10** and **11**. In contrast to the reversible reaction of **8** and **9** with CO, the dication **6** reacts with

(1) (a) Shore, N. E.; Hope, H. *J. Am. Chem. Soc.* **1980**, *102*, 4251. (b) Kraihanzel, C. S.; Sinn, E.; Gray M. G. *J. Am. Chem. Soc.* **1981**, *103*, 960.
(2) Black, C. St. C.; McLean, I. A.; *Aust. J. Chem.* **1971**, *24*, 1401.
(3) **2a**: mass spectrum, parent ion 391 m/e^+; ^{1}H NMR ($CDCl_3$) δ 7.2-7.5 (m, 10 H), 2.4-3.5 (m, 16 H). 2b: mass spectrum, parent ion 267 m/e^+; ^{1}H NMR ($CDCl_3$) 2.6-3.9 (m, 16 H), 1.10 (d, J_{P-H} = 6 Hz, 6 H). Both compounds show strong absorptions at ~730 cm^{-1}, attributable to the P-N stretching mode.
(4) Anal. Calcd for $C_{41}H_{52}ClN_2O_3P_2RhS_4$ (**3**): C, 50.87; H, 5.52; N, 2.95; Cl, 3.73; mol wt, 949. Found: C, 50.78; H, 5.21; N, 2.96; Cl, 3.50; mol wt, 927. Calcd for $C_{41}H_{52}ClIrN_2O_3P_2S_4$ (**4**): C, 47.47; H, 5.05; N, 2.70; Cl, 3.41; mol wt, 1039. Found: C, 48.66; H, 5.03; N, 2.77; Cl, 3.66; mol wt, 992. Calcd for $C_{21}H_{44}ClN_2O_3P_2RhS_4$ (**5**): C, 35.97; H, 6.33; N, 4.00; Cl, 5.06; mol wt, 691. Found: C, 36.73; H, 6.88; N, 4.03; Cl, 5.14; mol wt, 723. Molecular weights (±5%) were determined osmometrically in $CHCl_3$.
(5) The phosphorus methyl resonances of **5** appear as a 1:2:1 triplet at δ 1.60 (J_{P-H} = 3 Hz) in the ^{1}H NMR spectrum, implying a trans disposition of the **2b** ligands about the rhodium atom.
(6) Reaction of **2b** with $[(C_8H_{14})_2Ir(CO)Cl]_2$ gave only viscous yellow oils of indeterminate stoichiometry, on attempted workup.
(7) Anal. Calcd for $C_{41}H_{52}B_2ClCu_2F_8N_2O_3P_2RhS_4$ (**6**): C, 39.39; H, 4.19; N, 2.24; Cl, 2.84. Found: C, 40.06; H, 4.25; N, 2.80; Cl, 2.87. Calcd for $C_{41}H_{52}B_2ClCu_2F_8IrN_2O_3P_2S_4$ (**8**): C, 36.77; H, 3.91; N, 2.09; Cl, 2.64. Found: C, 37.14; H, 3.74; N, 2.19; Cl, 2.98. Calcd for $C_{21}H_{44}B_2ClCu_2F_8N_2O_3P_2RhS_4$ (**9**): C, 25.28; H, 4.44; N, 2.81; Cl, 3.55. Found: C, 25.93; H, 4.08; N, 2.84; Cl, 3.79.
(8) The symbol Cu$\subset$NPR$_2$ in used to indicate complexation of the Cu(1) ion by the aminophosphine ring.
(9) ^{1}H NMR for **9** (CD_3CN) δ 1.60 (1:2:1 br tr, 12 H, CH_3), 2.8-3.9 (m, 32 H, ring).
(10) Anal. Calcd for $C_{41}H_{54}B_2ClCu_2F_8IrN_2O_3P_2S_4$: C, 36.71; H, 4.06; N, 2.09; Cl, 2.64. Found: C, 36.18; H, 3.97; N, 2.11; Cl, 2.50. High-field ^{1}H NMR (CD_3CN) δ -9.41, -14.09 (each a 1:1 d of 1:2:1 tr, J_{P-H} = 14 Hz, J_{H-H} = 3 Hz). This dihydrido complex is very O_2 sensitive.
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