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Chiral recognition of nitriles by ^{1}H NMR spectroscopy in the presence of a chiral dirhodium complex†

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ABSTRACT: The ^{1}H NMR spectra of a variety of chiral racemic nitriles were recorded in $CDCl_3$ in the absence and presence of dirhodium tetra-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate [$Rh_2(MTPA)_4$; MTPA ≡ Mosher's acid]. Moderate ^{1}H signal shifts but clear diastereomeric dispersions due to complexation were observed which allow the determination of the enantiomeric ratio of the nitriles. Tentative statements concerning the complexing mode of the cyano group at the rhodium atom (side-on *vs.* end-on) are presented. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR, ^{1}H NMR; chiral recognition; nitriles; dirhodium complexes; Mosher's acid

INTRODUCTION

Recently, we found that dirhodium tetra-(*R*)- and tetra-(*S*)-α-methoxy-α-(trifluormethyl)phenylacetate [$Rh_2(MTPA)_4$, **Rh***; MTPA = Mosher's acid[1]] are useful auxiliaries for the chiral recognition of olefins[2] and epoxides,[3] selenides and iodides.[4] Later, we tried to extend this technique to other compounds with functional groups which do not allow the application of chiral lanthanoid shift reagents (CLSR)[5] or, at least, where these classical reagents are difficult to apply. One of these functionalities is the cyano group, which is important in organic chemistry[6] and occurs in natural products.[7]

Our previous results[2,3] have suggested that there seems to be no straightforward connection between complexation shifts of ^{1}H signals (Δδ), their diastereoisomerism dispersions (Δν) and the distance of the protons involved from the complexation site (cyano group). Therefore, we synthesized a variety of chiral nitriles **1**–**22** as racemates (Scheme 1) in order to explore if there might be any systematic connection between those spectral and structural parameters.

EXPERIMENTAL

Syntheses of Rh* and 1–22

The synthesis of $Rh_2(MTPA)_4$ (**Rh***) has been described previously.[2]

The nitriles **1**–**22** were synthesized according to well established procedures from the corresponding alkyl bromides, iodides or toluenesulphonates with sodium cyanide. These precursors are either commercially available or readily prepared from the corresponding alcohols: $ROH + PBr_3$ or $ROH + CH_3C_6H_5SO_2Cl$. All compounds were purified by column chromatography and characterized by ^{1}H and ^{13}C NMR, IR and electron ionization mass spectrometry.

^{1}H NMR spectroscopy

The ^{1}H NMR spectra of most samples were recorded at 400 MHz (Bruker AM-400), except for **1**, **2**, **4**, **10** and **11**, where a spectrometer with a carrier frequency of 200 MHz (Bruker WP-200) was employed. $CDCl_3$ was used as a solvent. The concentrations of **Rh*** were *ca.* 0.003–0.005 mM, corresponding to 3–5 mg per ml of $CDCl_3$. The spectral widths were 4 (2 kHz, respectively), 32K (16K) data for FID acquisition with 32K (16K) zero-filling so that the digital resolution was 0.12 Hz. Pulse flip angles were *ca.* 30°.

RESULTS AND DISCUSSION

^{1}H signal shifts (Δδ) can be observed for many protons when their chemical shifts in free and in complexed nitriles are compared. Some of these signals display diastereotopism dispersions (Δν) since the two enantiomeric nitriles form diastereomeric complexes with the enantiomerically pure dirhodium complex **Rh***. Although the complexes are apparently weak and kinetically unstable, the spectral parameters mentioned are clear enough to identify the discrimination of the enantiomeric nitriles in many cases. A severe restriction in our examples (**1**–**22**) is the fact that sometimes the ^{1}H signals are very complex owing to homonuclear scalar

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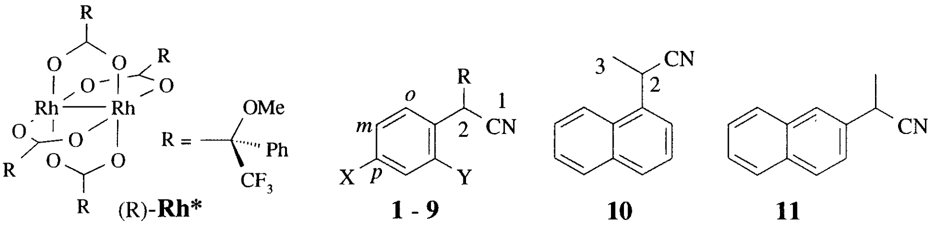
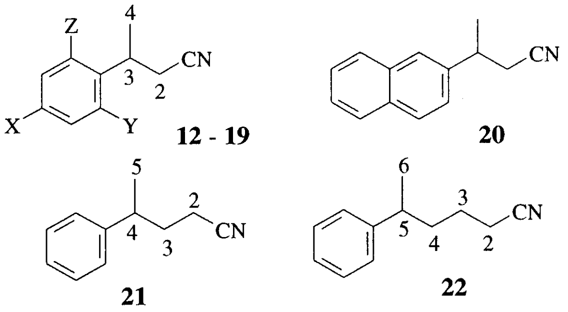


	1	2	3	4	5	6
R =	CH_3	C_2H_5	n-C_3H_7	i-C_3H_7	n-C_4H_9	n-C_5H_{11}
X/Y =	H	H	H	H	H	H

	7	8	9
R =	CH_3	CH_3	CH_3
X =	OCH_3	NO_2	H
Y =	H	H	OCH_3



	12	13	14	15	16	17	18	19
X =	H	CH_3	OCH_3	NO_2	H	H	CH_3	OCH_3
Y =	H	H	H	H	OCH_3	NO_2	CH_3	OCH_3
Z =	H	H	H	H	H	H	CH_3	OCH_3

Scheme 1. Structures of $Rh_2(MTPA)_4$ and the nitriles **1–22**.

coupling and high-order effects. This becomes particularly effective in cases with extended hydrocarbon chains (e.g. **5**, **6** and **22**). Moreover, the ^1H signals of all unsubstituted phenyl groups (C_6H_5) are nearly isochronous so that no evaluation was possible. Therefore, we introduced substituents (**7–9** and **13–19**) resulting in a larger range of aromatic ^1H chemical shifts so that it was possible to determine their $\Delta\delta$ and $\Delta\nu$ values, at least for the *para*-substituted species. Since these display the strongest $\Delta\nu$ values, we have no doubt that diastereomeric interaction is also active on the protons of the unsubstituted phenyl groups but that their observation is not possible owing to the isochrony mentioned.

In several cases we investigated what the optimum ratio of **Rh*** relative to the nitrile might be, and found that the $\Delta\delta$ and $\Delta\nu$ values increase up to a ratio of approximately 2:1. Further addition of **Rh*** does not significantly enhance these parameters further. This ratio is clearly higher that those necessary for olefins and epoxides,[2,3] indicating a weak interaction between rhodium and the cyano group. The same ratio of 2:1 had to be used for selenides and iodides.[4]

All pertinent data for compounds **1–22** that could be determined safely from the spectra are compiled in Table 1. They are given for an **Rh*** to nitrile ratio of 2:1. Entries marked × denote signals shifts ($\Delta\delta$) and dispersions ($\Delta\nu$) not observable as discussed above. The dashes indicate that no significant dispersions could be detected. It should be noted that no configurational assignment of diastereotopic protons was made. Some ^1H NMR experiments (**1**, **2**, **4**, **10** and **11**) were recorded at 200 MHz at an early stage of this study; later 400 MHz was employed exclusively. Since the dispersions $\Delta\nu$ are given in hertz, i.e. they are field-dependent, those of **1**, **2**, **4**, **10** and **11** have been recalculated (doubled in value) in Table 1 for better comparability with the others.

Signal shifts ($\Delta\delta$)

The $\Delta\delta$ data in Table 1 clearly show that they adopt only moderate or low values and that they decay uniformly with the distance of the protons (in terms of

Table 1. ^{1}H signal shifts (Δδ, ppm) and diastereomerism dispersions (Δν, Hz) in compounds **1–22**[a,b]

Compound	H	Δδ	Δν	Compound	H	Δδ	Δν
1	2	0.33	–	**14**	2a	0.59	1.8
	3	0.26	1.0[c]		2b	0.52	–
2	2	0.46	–		3	0.24	2.3
	3	0.24	×		4	0.12	4.4
	4	0.11	6.0[c]		*m*	−0.06	1.3
3	2	0.53	–		*p*-OCH$_3$	−0.05	1.1
	3	0.21	×	**15**	2a	×	×
	4	0.11	×		2b	×	×
	5	−0.05	2.0		3	0.20	0.5
4	2	0.55	–		4	0.10	4.7
	3	0.18	~1[c]		*o*	0.05	6.8
	4a	0.16	6.0[c]		*m*	−0.11	2.7
	4b	0.07	~1[c]	**16**	2a	0.53	–
5	2	0.52	–		2b	0.44	–
	3	0.22	×		3	0.25	–
	4	0.10	×		4	0.12	1.4
	5	−0.03	×	**17**	2a	0.62	3.0 or 5.0
	6	−0.12	–		2b	0.58	3.0 or 4.5
6	2	0.52	–		3	0.17	2.1
	3	0.11	×		4	0.09	2.2
	4	0.14	×		arom. H	0.02	×
	5/6	−0.06	×	**18**	2a	×	×
	7	−0.08	0.7		2b	×	×
7	2	0.47	–		3	0.24	2.0
	3	0.19	0.5		4	0.10	3.0
	o	−0.01/0.00	8.5		*m*	−0.02	5.7
	m	−0.17/−0.20	13.5		*o*-CH$_3$	−0.13	2.2
	OCH$_3$	−0.04	7.0		*p*-CH$_3$	−0.02	–
8	2	0.47	2.2	**19**	2a	0.63	0.5
	3	0.20	0.5		2b	0.36	–
	o	0.02/0.00	12.6		3	0.24	2.0
	m	−0.22/−0.25	21.5		4	0.09	2.5
9	2	0.46	0.5		*m*	0.02	0.5
	3	0.21	–		*o*-OCH$_3$	−0.03	–
	OCH$_3$	−0.01	1.8		*p*-OCH$_3$	−0.01	–
10	2	0.53	~1[c]	**20**	2a	0.58	2.6
	3	0.22	–		2b	×	×
11	2	0.54	~1[c]		3	0.24	–
	3	0.26	2		4	0.12	5.7
12	2a	0.55	1.5	**21**	2a	0.63	×
	2b	0.48	–		2b	0.40	×
	3	0.21	2.5		3a	0.29	10.0
	4	0.09	2.5		3b	0.12	1.5
13	2a	0.59	–		4	0.20	×
	2b	0.54	–		5	−0.03	8.4
	3	0.24	×	**22**	2a/b	0.40	×
	4	0.12	3.3		3a/b	0.04	×
	p-CH$_3$	−0.05	1.4		4a/b	−0.04	×
					5	0.00	20.0
					6	−0.06	–

[a] Recorded at 400 MHz in CDCl$_3$; the ratio of **Rh*** to ligand was 2 : 1; ×, not observable owing to signal overlap and/or signal complexity; –, no splitting observable.

[b] Atom numbering is along the aliphatic chain with respect to the CN group (C-1); compare Scheme 2.

[c] Recorded at 200 MHz but converted to 400 MHz by doubling their magnitudes.

intervening bonds) relative to the cyano group which is considered to be the complexation site. When the hydrogen atom observed is in an α-position, deshieldings of 0.46 and 0.63 ppm are found in general; only in two cases (**1**, 0.33 ppm; **19**, 0.36 ppm) are they smaller. Corresponding values in the β-position are clearly smaller (0.11–0.29 ppm); there seems to be no overlap of these two shift ranges so that α-hydrogen signals can easily be recognized. γ-Hydrogen atoms experience an even smaller deshielding (0.07–0.20 ppm), and those even further away are hardly affected; slight shieldings (negative $\Delta\delta$ values) were observed for some far remote protons.

The uniform decay of the signal shift values, which is more or less independent of the nitrile structures, suggests that they originate in a through-bond inductive effect from the cyano group, the group electronegativity of which is modified (slightly enhanced) by the complexation at the rhodium atom.

The small magnitudes of the $\Delta\delta$ values can be regarded as advantageous because it is not necessary to perform a series of experiments with increasing content of the auxiliary, as is often necessary when using CLSR. The high amount of **Rh***, however, can lead to severe overlap of nitrile signals by those of the four MTPA residues in **Rh*** (OCH_3 and phenyl), since the molar ratio of MTPA to nitrile is 8 : 1!

Signal dispersions ($\Delta\nu$)

As mentioned above, it is unfortunate that a number of ^1H signals could not be evaluated owing to signal complexity and/or overlap. Nevertheless, the $\Delta\nu$ data allow some interpretation as far as the relationship between the hydrogen atoms from the complexing site and the distance between the cyano group and the chirality centres is concerned.

First, we investigated the dependence of the $\Delta\nu$ values for compounds **1**–**6** where the chirality centre is next (α) to the cyano group and the alkyl residue is extended stepwise [Scheme 2(a)]. Although the diastereotopic CH_2 protons were generally not evaluable, a certain trend can be observed. There is apparently a range of medium distance with respect to the binding site, namely hydrogen atoms on carbons two bonds away, where noticeable effects can be seen, whereas effects on closer hydrogens and those beyond the δ-position with respect to CN are zero or close to zero. This finding, which is in contrast to the general experience with CLSR, is understandable if one considers the shape of the molecule. The dirhodium complex has roughly the shape of a wheel with the rhodium–rhodium moiety forming the axle and the cyano group of the substrate attached (Fig. 1). The chirality information, however, resides mainly in the periphery of the molecule. Consequently, signal dispersions will be better if the proton is not too close to the cyano group because the through-space anisotropy interaction with the chiral MTPA moieties is most efficient. Hence signals of protons more remote from both the cyano group and the chirality centre respond better to complexation by dispersion.

The situation is not improved by enlarging the aromatic residue of the nitrile. Both the 1- and 2-naphthyl derivatives of **1** (**10** and **11**) do not display significantly higher $\Delta\nu$ values for aliphatic protons. The aromatic protons, however, are strongly affected, as can be seen from the data for the *ortho*- and *meta*-protons in **7** and **8** (Fig. 2). (There are unfortunate signal overlaps again in the spectrum of **9**). These effects are the largest so far observed by us in any spectrum using **Rh*** as an auxiliary. This is in line with our above rationalization that again the more remote proton in both cases (*meta*) show the larger $\Delta\nu$ values.

The situation is reversed in compounds where the chirality centre is in a β-position with respect to the cyano group [**12**–**20**, Scheme 2(b)]. Now the $\Delta\nu$ values are significant for β-(CH) and γ-protons (CH_3), whereas those of the α-protons are again small or even negligible. On the other hand, the effects observed for the aromatic protons are clearly smaller compared with those in **7** and **8**, although they are still considerable. It is interesting that there seems to be a clear difference between systems carrying methoxy groups (**14** and **19**) and those methyl (**18**) and nitro groups (**15**). Since there seems to be no dependence on the steric demand of such substituents, we assume that the effects of electron density exerted by the attached groups (mesomeric and inductive) are responsible. Apparently, electron-rich aromatic systems are able to reflect the diastereoisomerism in the dirhodium complex to a much lesser extent.

Our molecular systems were not good enough to investigate $\Delta\nu$ dispersion effects for systems with larger distances between the cyano group and the chirality centre on a reliable basis. Because of too severe overlap and/or signal complexity (high-order effects), it was not possible to extract this parameter for the protons along the alkyl chain in **21** and **22**. The few data (Scheme 2) which we were able to identify are in part of remarkable

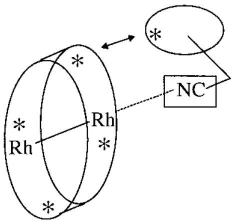


Figure 1. Schematic representation of the steric interaction between those parts of the molecules in the complex where their chiral shapes (indicated by asterisks) are most effective.

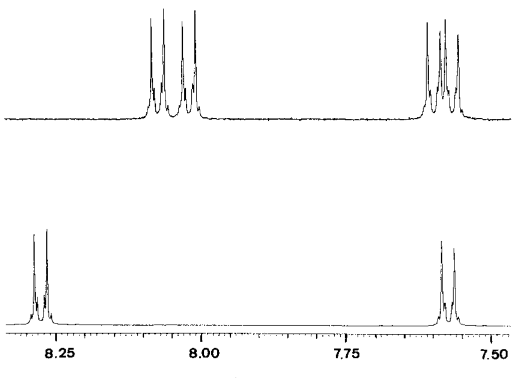
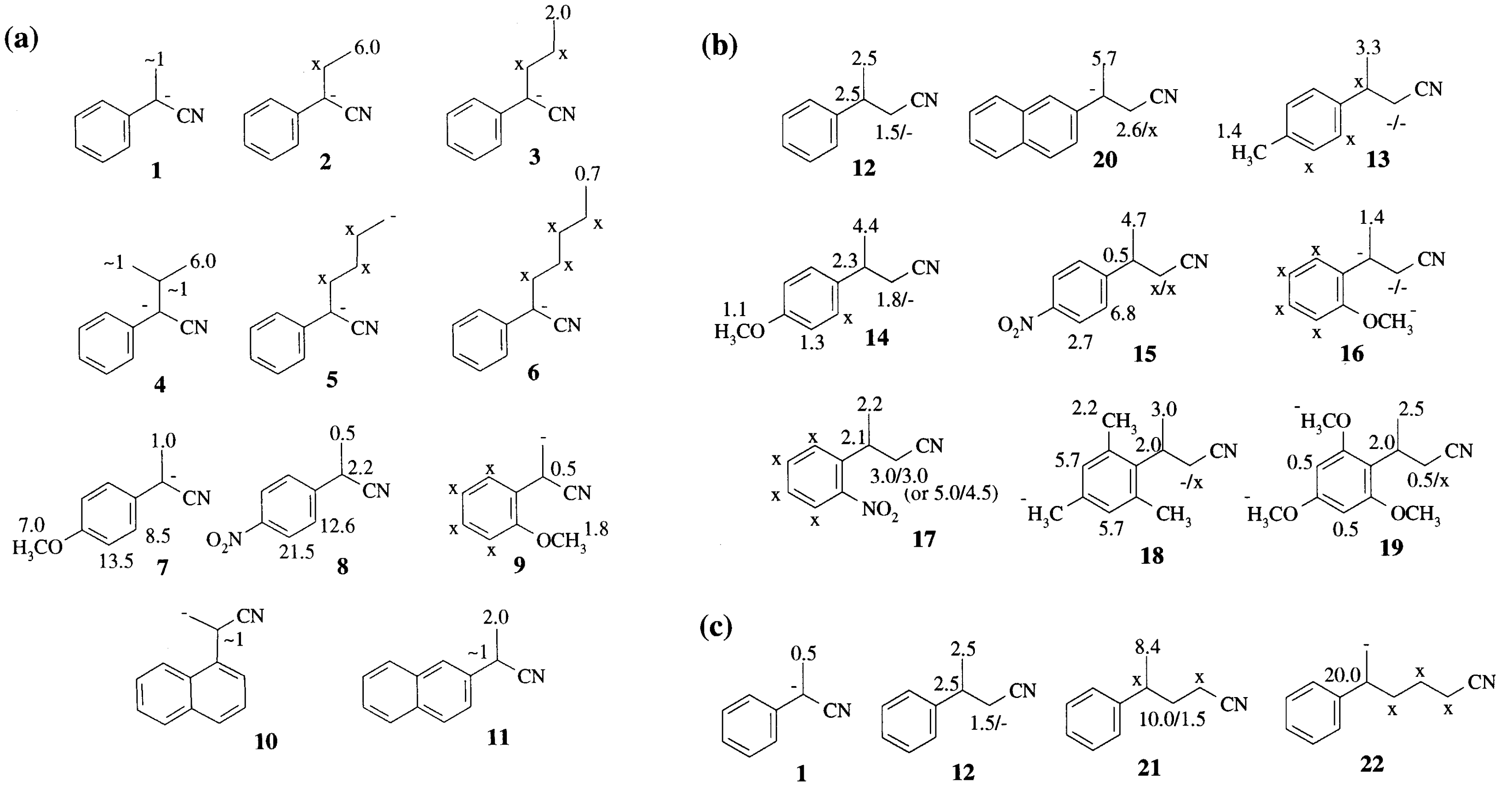


Figure 2. Aromatic ^1H signals of **8** in the absence (lower trace) and presence (upper trace) of a twofold molar amount of **Rh***.



Scheme 2. Structures of the nitriles investigated; numbers indicate diastereomerism dispersions $\Delta\nu$. –, $\Delta\nu \approx 0$; ×, not observed owing to signal overlap or complexity; aromatic signals of all naphthyl and phenyl (C_6H_5) rings without further substituents are nearly isochronous and therefore not amenable to evaluation.

size, but no safe trend could be ascertained. Nevertheless, we are confident that chiral recognition is possible, and may be even better, in molecular systems (C*—C_n—CN; $n = 1$–4) compared with those represented by the model compounds **1**–**20** (C*—CN; $n = 0$).

It should be noted that the aryl groups and the nitro substituents are not involved in the interaction process because related alkylbenzene and nitro derivatives lacking the cyano group did not show any $\Delta\delta$ or $\Delta\nu$ effect.

Complexation mode

The diverging trends in the $\Delta\nu$ values of the aliphatic *vs.* aromatic proton signals in the two series of compounds, cyano group and chirality centre in α- [Scheme 2(a)] and β-positions [Scheme 2(b)], seem to indicate a principal difference in the structures of the two types of complexes. If we assume that larger dispersions are associated with a more intimate contact with the chiral MTPA residues, we are led to the conclusion that in the α-series of compounds such contact is basically confined to the aromatic part of the nitriles, whereas the aliphatic chains (or at least the α-methine and β-positioned methyl groups in **1**–**11**) are directed away. This suggests some rigidity and conformational preference in the orientation of the nitrile molecules **1**–**11** (α-series) when complexed with the rhodium atom. On the other hand, this differentiation of the molecular parts is much less pronounced in the β-series of compounds so that, on the basis of the same arguments, the nitrile is much more flexible here. The question arises of what the reason for such significant difference might be.

Figure 3 shows the two possible complexation modes, either via the multiple bond π system (η^2, side-on, formula **A**) or the nitrogen lone pair (n, end-on, formula **B**). A qualitative evaluation of the spatial arrangements of the two types of complexes (**A** and **B**) gives the following tentative interpretation: if the nitriles are bound via the nitrogen lone pair (**B**), all parts of the molecules of both structure types are at moderate distances with respect to the dirhodium complex and the differences discussed above are difficult to understand. If, however, the η^2-complexation (**A**) is effective, at least in part, the phenyl group of the α-series of nitriles can approach the MTPA residues and/or eventually their CF_3 groups very closely, so that a certain degree of rigidity is achieved and charge-transfer interactions between aromatic moieties become conceivable (Fig. 4). This is consistent with the above-mentioned observation of a dependence of $\Delta\nu$ values on the π-charge density of the aromatic rings in the nitriles. In the β-series of nitriles, it is different: the complex is expected to be much more flexible, and less effective charge-transfer interactions allow an easier approach of the aliphatic part of the nitriles towards the MTPA residues. Unfortunately, all attempts to grow crystals suitable for x-ray analysis of our complexes have failed, possibly owing to the weak intermolecular interaction.

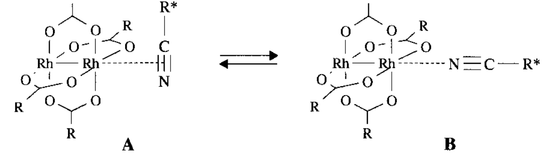


Figure 3. Conceivable complexation equilibrium.

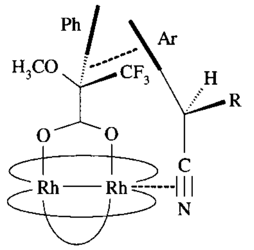


Figure 4. Tentative complex structure stabilized by π–CF_3 charge-transfer interaction.

Although this is only a crude and tentative interpretation, we believe that it may indicate a significant contribution of complexation mode **A** in an equilibrium between **A** and **B** (Fig. 3). However, this interpretation has to be seen in view of x-ray studies, e.g. that of a related chiral dirhodium tetrakiscarboxamide complex having two acetonitrile molecules in axial positions[8] and that of a dirhodium–nitrile complex with a known crystal structure which is a $[Rh_2(CH_3CN)_{10}]^{4+}$ cation.[9] In both cases, the nitrogen atoms are the binding sites although considerable deviations from Rh—N—C linearity (e.g. 166^0 in $[Rh_2(CH_3CN)_{10}]^{4+}$) have been noted for the axial positions supporting the idea of **A** and **B** in Fig. 3 being mesomeric forms. Further support comes from the ESEEM (electron spin echo envelope modulation) lines of the complex $[Rh(CN)_6]^{4-}$ in the KCl host lattice which suggest that the axial CN groups are bent, probably in more than one orientation.[10]

Further investigations of these complexes observing ^{13}C and ^{19}F and also NOE experiments are in progress. Owing to the low solubility of **Rh***, such measurements are time consuming.

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