Journal of Organometallic Chemistry, 307 (1986) 377–383
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

trans-CHLORO(*N*,*N*-DIMETHYL-D-PHENYLGLYCINE)-(3-METHYL-1-PHENYLPENT-1-ENE)PLATINUM(II) COMPLEXES. HPLC SEPARATION AND IDENTIFICATION OF ALL THE DIASTEREOMERS

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(Received December 30th, 1985)

Summary

The diastereomeric *trans*-chloro(*N*,*N*-dimethyl-D-phenylglycine)(3-methyl-1-phenylpent-1-ene)platinum(II) complexes, derived by coordination of the enantiomeric and geometric isomers of 3-methyl-1-phenylpent-1-ene (**2**), were separated by HPLC. Four *trans*- and two *cis*-olefin complexes were recognized in the chromatogram. The configuration of all chiral centers of the olefin in the six complexes were assigned. Under the conditions of preparation, the pairs of diastereomers *1R,2R,3S / 1S,2S,3S* and *1S,2S,3R / 1R,2R,3R* were formed in a ratio > 1 for the *trans*-isomer, whereas the *cis*-isomer gave the *1R,2S,3S* and *1S,2R,3R* epimers only. The complexes do not epimerize on standing at room temperature in solution; similar behaviour of the corresponding complexes of *trans*-stilbene (**4C**) indicates that the conjugated aromatic double bond is coordinated more strongly than those aliphatic and cycloaliphatic olefins.

The efficient HPLC separation of the diasteromeric complexes **2C**, permits the enantiomeric analysis of **2**, as well as the preparative resolution of the olefin.

Attempts to resolve enantiomeric olefinic hydrocarbons by chromatography have been successful only in isolated cases [1–3]. It was, however, demonstrated in our laboratory in 1981 [4] that diastereomeric olefin-platinum complexes, analogous to the title compound, can be separated by HPLC, and thus the coordinated olefins resolved. The complexes can be readily prepared by the reaction of olefins with *trans*-chloro(*N*,*N*,-dimethyl-D-phenylglycine)(ethylene)platinum(II) (**1C**) [5].

In our first paper on the topic [5], we described the application of this approach to a series of aliphatic, cyclopentenic, and cyclohexenic monoolefins. The usefulness

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0022-328X/86/$03.50

of the method was rapidly recognized, and other authors, such as Retzbach and Schurig [6], and, notably, Köhler and Schomburg [7], have produced many more examples of resolution of olefins through complexes of this type. They have further extended the procedure to the resolution of functionalized olefins, and to the chromatographic separation of achiral olefinic compounds.

In the present paper we report the results of a study on the title compound carried out several years ago [8], as well as some data on the corresponding complexes of *cis*- and *trans*-stilbene.

It is noteworthy that the procedure has not yet been tried on the important class of conjugated aromatic olefins. Search of the literature revealed the mention of only one achiral and one chiral non-conjugated aromatic olefin [9] complex formed from **1C**.

Experimental

Materials

3-Methyl-1-phenylpent-1-ene (2). This olefin was obtained by dehydration, with thionyl chloride in pyridine solution, of the alcohol formed by reaction of benzaldehyde with the Grignard reagent of (*S*)-2-methyl-1-butyl chloride, as described by Davis and Ansari [10]. The chloride was prepared from active amyl alcohol, one sample of which was optically pure and the other a mixture of 2/3 *S*- and 1/3 *R*-isomer. Whereas the alcohol derived from the first sample gave almost pure *trans*-olefin, $[\alpha]_D^{20}$ +47.5° (neat), in accordance with the literature [10], a product consisting of 85% *trans*- and 15% *cis*-olefin was obtained from the partially racemic alcohol, $[\alpha]_D^{20}$ +18.4° (*c* 11.63 in $CHCl_3$) (lit. [10] $[\alpha]_D^{20}$ + 50.5°, for optically pure *trans*-olefin). *Cis*-(**3**) and *trans*-(**4**)-stilbene were commercial products.

trans-Chloro(N,N-dimethyl-D-phenylglycine)(ethylene)platinum(II) (1C) * was prepared as described by Panunzi et al. [11] by mixing Zeise's salt (1.2 g) with a solution of *N*,*N*-dimethylphenylglycine [12] (0.6 g) in 10 ml 0.25 *N* HCl and adding aqueous KOH to pH 6–7; yield 66%.

trans-Chloro(N,N-dimethyl-D-phenylglycine)(ethylene)(3-methyl-1-phenylpent-1-ene)-platinum(II) (2C) was formed by mixing reagent **1C** (5–10 mg) with an excess of up to five times the equivalent amount of 3-methyl-1-phenylpent-1-ene (**2**), and leaving the solution at room temperature for 4–5 h; only traces of **1C** remained in solution at the end of the reaction. Elemental analysis: Found: C, 46.50; H, 4.94. Pt $C_{22}H_{28}NO_2Cl$ calcd.: C, 46.44; H, 4.96%.

The structure assigned to the products was confirmed by the NMR spectra of the various diastereomers isolated (see text).

The analogous complexes **3C** and **4C** of *cis*-(**3**) and *trans*-(**4**)-stilbene were prepared by the same procedure.

Chromatographic conditions

HPLC of the Pt complexes was carried out on a stainless steel column (25 × 0.46 cm I.D.) slurry packed with 5μ Lichrosorb Si 60. The mobile phase consisted of a mixture of CH_2Cl_2/n-hexane to which 1% of isopropanol had been added. About 20

* Complexes are designated by an arabic numeral standing for the coordinated olefin and the letter C.

μl of solution (about 1%) was injected into the column and the detection made at 254 nm on a Laboratory Data Control Monitor. The rate of flow was 1–1.5 ml/min.

For the NMR measurements, samples of 10–20 mg of the individual diastereomers were isolated by repeated injections of about 2 mg of the mixture of the complexes and operating, as above for the analytical mode. The *cis*-olefin complexes were not separated from the *trans*-compounds under these conditions.

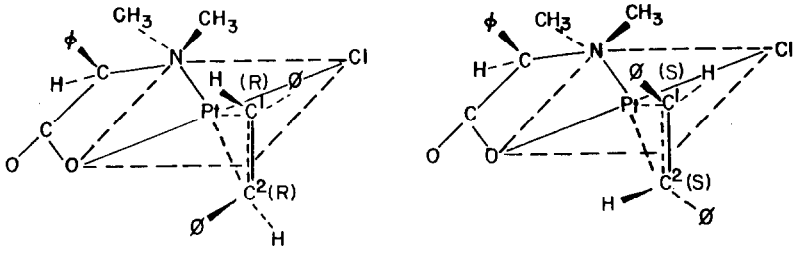
The ratio of *cis*- to *trans*-isomers of 3-methyl-1-phenylpent-1-ene was determined by GC on a stainless steel capillary column (30 m × 0.5 mm I.D.) coated with *O*-lauroyl-L-lactate of lauroyl alcohol.

Results and discussion

In complexes of the type considered here platinum can coordinate with either of the faces of the double bond of an ethylenic ligand. As the rotation around the axis passing through the double bond and perpendicular to the plane of coordination of the metal is restricted, new asymmetric centers can be generated at the unsaturated carbons [13]. This in turn may lead to two isolable isomers for an achiral olefin if the latter does not possess C_2 symmetry with respect to an axis passing through the double bond and perpendicular to it. *trans*-Stilbene (**4**) presents such a case. (Scheme 1), and complex **4C** does, indeed, give a chromatogram with two peaks (Fig. 4), whereas *cis*-stilbene (**3**), which has C_2 symmetry, gives only one peak in HPLC (Fig. 4). On the other hand, for the chiral *cis*- and *trans*-3-methyl-1-phenylpent-1-ene formation of four diastereomeric complexes would be expected for each geometric isomer (see Scheme 2).

Complex **2C** was first prepared from a sample of **2** consisting of 2/3 of the *S*(+) and 1/3 of the *R*(−) olefin, accompanied by 15% of the *cis*-isomer. Under the best conditions of separation (see Fig. 1) six components were observed in the chromatogram. Two shoulders of the main peaks II and IV and were recognized as due to the *cis*-isomer, and only the products corresponding to these two peaks gave, on decomplexation, olefins which contained *cis*-compound. Furthermore, the relative areas of the shoulders were in agreement with the respective proportions of the geometric isomers listed in Table 1.

The assignment of the configuration of the coordinated olefin was made as follows. Comparison of the chromatograms in Fig. 1 and 2, for the complexes derived, respectively, from *R,S*-**2** and the optically pure olefin showed that peaks II and III corresponded to the *S*-isomer, and that, consequently, I and IV relate to the *R*-enantiomer. The chromatogram of Fig. 2 further proves that the shoulder of peak



SCHEME 1. The *1R,2R*- and *1S,2S*-Pt^{II} complexes (**4C**) of *trans*-stilbene.

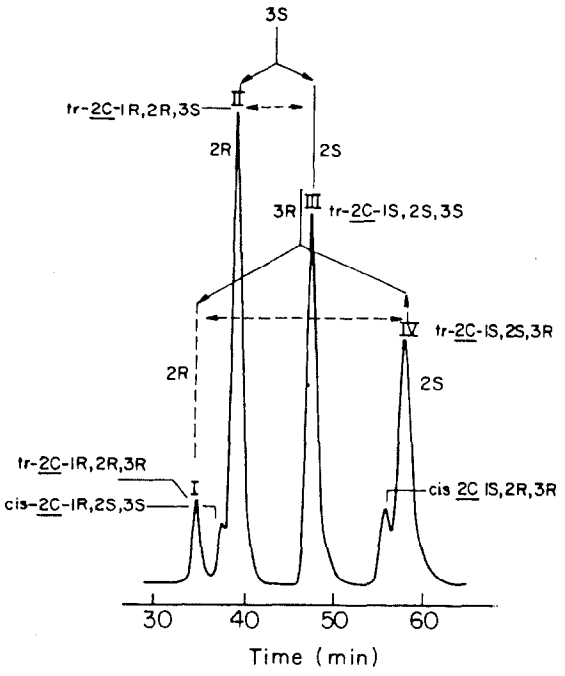


Fig. 1. Chromatogram of the *trans*-chloro(*N*,*N*-dimethyl-D-phenylglycine)platinum(II) olefin complexes derived from 3-methyl-1-phenylpent-1-ene, containing 85% *trans*- and 15% *cis*-isomer and having an *S*/*R* enantiomer ratio of ~ 2/1.

II must be due to the *S*-olefin; in keeping with the smaller proportion of *cis*-isomer in the olefin derived from the optically pure alcohol, the shoulder is less apparent than in the chromatogram of Fig. 1.

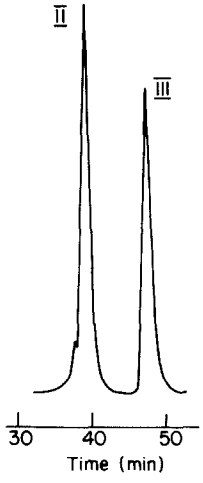


Fig. 2. Chromatogram of the *trans*-chloro(*N*,*N*-dimethyl-D-phenylglycine)platinum(II) olefin complexes derived from *trans*-(*S*)-3-methyl-1-phenylpent-1-ene containing a small amount of the *cis*-isomer.

TABLE 1

GEOMETRICAL ISOMERS IN THE OLEFINS LIBERATED FROM THE DIASTEREOMERS OF COMPLEXES **2C** [a]

Olefin isolated from the product corresponding to peak number (see Fig. 2)	I	II	III	IV
cis-Isomer (%)	–	10	–	20
trans-Isomer (%)	100	90	100	80

[a] The isomer concentration was determined by GC (see Experimental).

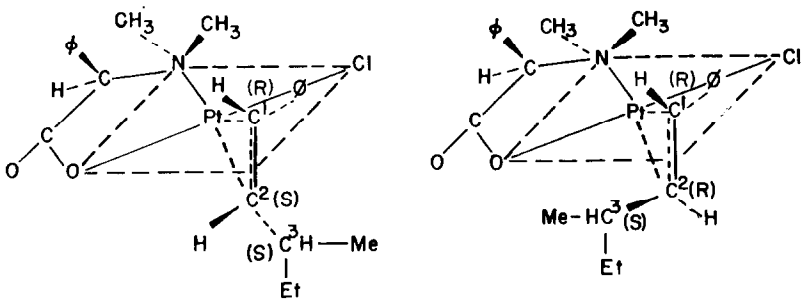
By elimination, *cis*-**R-2**, which must be present to the same extent in the *R,S*-**2** sample, must be contained in the complex corresponding to the shoulder of peak IV. This conclusion is further supported by the NMR data, quoted below.

At room temperature, complexes **2C** do not epimerize, even on standing for days in CH_2Cl_2 solution. The same observation was made for the derivative of *trans*-stilbene (Fig. 4). Thus, coordination of aromatic conjugated olefins appears to be kinetically more stable than that of aliphatic and cycloaliphatic olefins [5].

The configuration at carbon 2, bonded to the platinum (and by extension that of C(1) was made by NMR. Studies with the analogous *trans*-dichloro-(benzylamine)-(3-methylpent-1-ene)platinum(II) [14] and *trans*-chloro(*N,N*-dimethyl-D-phenylglycine)(3-methylpent-1-ene)platinum(II) [5] have shown that the doublet and the triplet due, respectively, to the methyl groups a and b (see structure in Fig. 3) are close to each other when C(2) and C(3) have the same configuration (*2S,3S; 2R,3R*). However, the triplet is shifted upfield and the doublet downfield for the diastereomers *2R,3S* and *2S,3R*. The spectra given in Fig. 3 for the compounds corresponding to peaks III and IV accordingly confirm that the configurations of *tr*-$\mathbf{2C}^{III}$ and *tr*-$\mathbf{2C}^{IV}$ are respectively, *2S,3S* and *2R,3S*. It follows from these results that *tr*-$\mathbf{2C}^{I}$ and *tr*-$\mathbf{2C}^{II}$ must be the *2R,3R* and *2R,3S* compounds.

Signals of a relatively small area appear in the NMR spectra of the compounds corresponding to the second and fourth peaks at about 1.2 ppm (see, e.g., Fig. 3A). The stereochemistries at the pertinent centers are consequently assigned as *cis-2S,3S* and *cis-2R,3R*, respectively.

The configuration at C(2) fixes that at C(1). For the two carbons, the stereochem-



SCHEME 2. Example of two complexes derived from **2** with configuration of coordinated olefin: *cis*-**2**-*1R,2S,3S* and *trans*-**2**-*1R,2S,3S*.

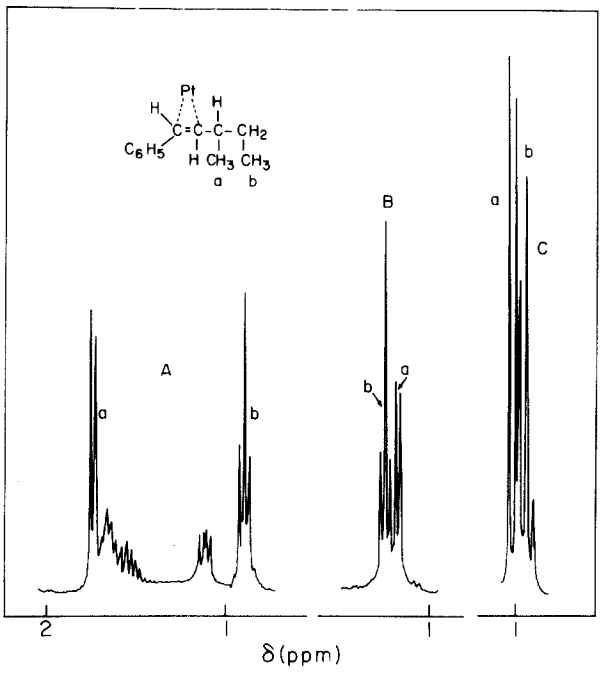


Fig. 3. NMR of the *cis,trans*[chloro-*N*,*N*-dimethyl-D-phenylglycine)(3-methyl-1-phenylpent-1-ene)platinum(II) complexes: (A) isolated from peak IV (Fig. 1) (*tr*-**2C**-*1S, 2S,3R* plus *cis*-**2C**-*1S,2R,3R*); (B) isolated from peak III (*tr*-**2C**-*1S,2S,3S*); (C) NMR spectrum of the uncomplexed olefin **2**.

istry is the same for the *trans*-olefin, but opposite for the *cis*-isomer. The full assignment for all chiral centers of the olefin in the various diastereomers of **2C** is given in Fig. 1.

From Fig. 1, it can be seen that under the conditions of preparation, the *trans*-olefin leads to a higher ratio of *2R,3S / 2S,3S* and *2S,3R / 2R,3R*, whereas the

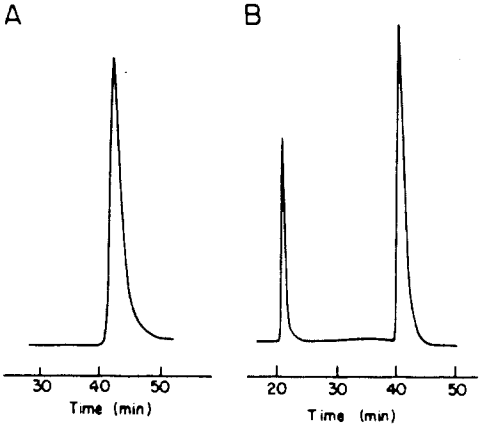


Fig. 4. Chromatogram of the *trans*-chloro-(*N*,*N*-dimethyl-D-phenylglycine)platinum(II) olefin complexes of: (A) *cis*-stilbene (**3**), and (B) *trans*-stilbene (**4**).

cis-isomer forms exclusively the *2S,3S* and *2R,3R* epimers. As no epimerization occurs at room temperature, these results appear to be due to kinetic control, although, judging by previous experience [5], they may be indicative of thermodynamic factors. Obviously, further experiments are required to determine unambiguously the relative stabilities of the various diastereomers differing in the configuration at the unsaturated carbon bonded to platinum.

Figure 1 also shows that, under the conditions of preparation (with excess of **2** and complete disappearance of **1C** at the end of the reaction), the consumption of the olefin is such that the proportion of *S/R* in **2** is almost preserved in the product, but more *trans*- than *cis*-isomer is coordinated. The ratio of the sum of the *trans-S* to that of the *trans-R* diasteromeric complexes [peaks of $(tr\text{-}2R,3S + tr\text{-}2S,3S)/(tr\text{-}2R,3R + tr\text{-}2S,3R)$], is indeed equal to 2.2/1, compared with a ratio of *S/R* of 2/1 in the starting olefin. The *cis*-olefin complexes, on the other hand, represent about 10% of the total diastereomers, whereas the starting material contains 15% of the *cis*-compound, i.e. 50% more of the latter isomer (see Experimental).

Resolution of 3-methyl-1-phenylpent-1-ene

As the chromatographic peaks are well separated it is easy to isolate diastereomeric complexes coordinated to only one of the antipodal olefins. Liberation of the ligand (for instance, with KCN [5]) leads to the optically pure compound. In the present work (10–20 mg were resolved (see Experimental), but it should be easy to increase the scale of operation. The method can, of course, also be applied to quantitative enantiomeric olefin analysis. For this purpose, an excess of reagent **1C** would have to be used in order to avoid distortion of the results by kinetic effects. If the sample contains both *cis*- and *trans*-**2** use of a silver nitrate coated silica column [15] for the preparative separation of the geometric isomer is recommended. For precise analysis of the concentration of *cis*-isomers, representative fractions of liberated olefins must be submitted to gas chromatography (see, e.g. Experimental) for the determination of *cis/trans* ratios.

Acknowledgement

D.S. is indebted to the Minerva Foundation for the grant of a Fellowship.

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