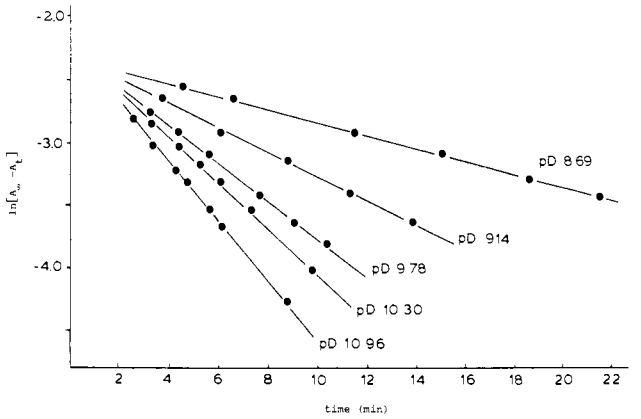

Figure 7. First-order plots (ln aldimine concentrations vs. time) for the pyridoxal and proton-catalyzed dealdolation of β-hydroxyvaline as a function of pD.

tribution from $k^{IV}[HSB][OH^-]$ to the observed rate. The values of k^I, k^{II}, and k^{IV} were obtained by regression analysis[19] of the sum of the squares of the errors, U, by minimizing U, defined as:

$$U = (k_{obsd}[SB_T] - k^I[H_2SB] - k^{II}[HSB] - k^{IV}[HSB][OH^-])^2 \quad (11)$$

The specific rate constants for the pyridoxal–β-hydroxyvaline Schiff base system were found to be: $k^I = 4.25 \times 10^{-4}$ s^{-1}; $k^{II} = 2.62 \times 10^{-4}$ s^{-1}; $k^{III} = 15.6$ M^{-1} s^{-1}. The protonation constants for the Schiff base species were determined spectrophotometrically and found to be $pK_1 = 6.65$; $pK_2 = 9.70$. The species distribution is shown in Figure 6. The specific rate constants were used with the concentrations of the individual species to determine calculated values of k_{obsd} as a function of pD. The small differences between the experimental and observed rate constants, illustrated in Figure 5, indicate that the model chosen to estimate the calculated rates is in accord with the experimental data.

Between pD values of 6 to about 9.5 the hydroxide ion concentration is low and thus the net contribution of k^{IV} on k_{obsd} is negligible. Thus in the pD range the value of k_{obsd} is due primarily to k^I and k^{II}. The diprotonated Schiff base, which is the most reactive species, is present in amounts less than 20% of the total Schiff base in this entire region of pD and its concentration decreases with increasing pD, thus explaining the slight initial drop in k_{obsd}. The major contributor to dealdolation in the pD range 7–10 is the monoprotonated species HSB. Between pD 9.5 and 11.0, the value of k_{obsd} increases rapidly with pD as illustrated in Figure 7, and then levels off, indicating a transfer of the main contribution to the reaction pathway from HSB^- to HSB^- and OH^-, and a corresponding shift of the reaction from mainly first-order to mainly second-order kinetics.

Registry No. Threonine, 72-19-5; β-hydroxyvaline, 2280-28-6; β-hydroxyleucine, 28908-11-4; pyridoxal, 66-72-8; Zn, 7440-66-6; Al, 7429-90-5; Ga, 7440-55-3.

(19) Brookes, C. J.; Bettely, I. G.; Loxston, S. M. "Mathematics and Statistics for Chemists"; Wiley & Sons: New York, 1966; Chapter 15.

Communications to the Editor

Resolution of Chiral Olefinic Hydrocarbons and Sulfoxides by High-Performance Liquid Chromatography via Diastereomeric Platinum Complexes

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Asymmetric olefinic hydrocarbons, unless found in nature, are not readily available in well-defined optical purity. Resolution of racemic olefins, e.g., by repeated crystallization of their diastereomeric Pt complexes,[1] does not guarantee that the final product is optically pure. Also, the determination of the optical purity of olefins of unknown specific rotation is not readily accomplished. An obvious approach is functionalization of the double bond and conversion to compounds of known $[\alpha]_D$ value. This method, except for being time-consuming, may involve racemization to an unknown extent, and the relevant information on the products formed may not be available.

It is, therefore, not surprising that the data in the literature on the chirooptical properties and the magnitude of inductive effects in olefin synthesis and conversion reactions may be seriously in error.[2] In the present communication we wish to report on the resolution of this class of chiral compounds[3] by HPLC of

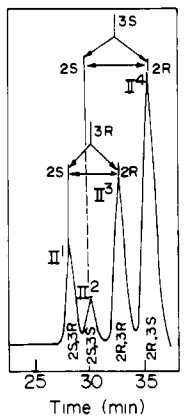

Figure 1. Chromatogram of the platinum complexes of 3-methylpent-1-ene (II); mobile phase: *n*-hexane/CH_2Cl_2/2-butanol, 60/40/1.

diastereomeric Pt complexes as well as on the extension of this approach to sulfoxides.

Diastereomeric *trans*-dichloro((*R*)-α-phenlyethylamine)(olefin)platinum (II) complexes, used for the resolution of olefins by crystallization,[1] could not be separated by HPLC under all con-

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(1) Cope, A. C.; Ganellin, C. R.; Johnson, H. W., Jr.; van Auken, R. V.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1963**, *85*, 3276.

(2) Schurig, V.; Gil-Av, E. *Isr. J. Chem.* **1976/77**, *15*, 96.

(3) Resolution by GC on dicarbonylrhodium(I) 3-(trifluoroacetyl)-1-(*R*)-camphorate [Schurig, V. *Angew. Chem.* **1977**, *89*, 113, see also ref 2] was found to be limited to 3-methyl- and 3-ethylcyclopentene. Sporadic reports on the separation of enantiomeric olefins by LC include the resolution of *cis*- and *trans*-1,1′,2,2′,3,3′-hexahydro-4,4′-biphenanthrylidene through charge-transfer complexation on a support coated with a chiral acceptor [Ferringa, B.; Wynberg, H. J. Am. Chem. Soc. **1977**, *99*, 602] and resolution of 3-methylcyclohexene, 3- and 5-phenylnorbornene on triacetylcellulose [Hesse, G.; Hagel, R. *Liebigs Ann. Chem.* **1976**, 996].

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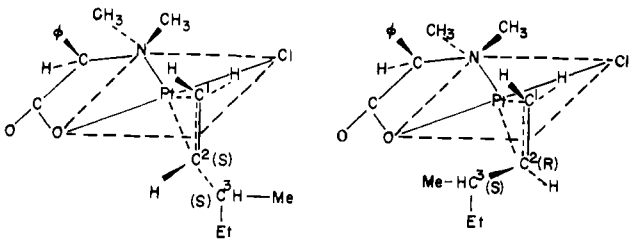
ditions tried by us;[4] neither was a complex with the bidentate ligand D-phenylglycine effective. But eventually it was found that *trans*-chloro(*N*,*N*-dimethyl-D-phenylglycine)(olefin)platinum(II) compounds[5] were suitable for our purpose (Figure 1). Introduction of the *N*-dimethyl groups into the coordination sphere leads to very crowded structures[6,7] in which differences in the molecular shapes of the diastereomers, formed on complexation of platinum with the chiral olefins, become apparently more pronounced, resulting in the differences in partitioning coefficients observed.

For preparing the desired complexes, *trans*-chloro(*N*,*N*-dimethyl-D-phenylglycine)(ethylene)platinum(II) (I) was first synthesized[5] by reacting Zeise's salt (1.2 g) with *N*,*N*-dimethyl-D-phenylglycine[8] (0.6 g) in 10 mL of 0.25 N HCl under argon and then KOH was added until the resulting solution had a pH 6–7 (yield 66%). In a typical experiment, ethylene in I (1–5 mg in 0.1–0.5 mL of CH_2Cl_2) was displaced by adding 3–5 equiv of the olefin to be resolved and leaving the solution at room temperature for 4–24 h.

For chromatography, a 25-cm × 0.46-cm i.d. column was employed, slurry packed with 5μ Lichrosorb Si 60. The eluent (rate, 1.0–1.2 mL/min) was a CH_2Cl_2/*n*-hexane with small amounts of alcohol (e.g., 1–2% of *i*-PrOH). About 20 μL of solution was injected into the column and detection made at 254 nm.

trans-Chloro(*N*,*N*-dimethyl-D-phenylglycine)(3-methylpent-1-ene)platinum(II) (II) was prepared, as described above. Anal. Calcd for $PtC_{16}H_{24}NO_2Cl$: C, 38.97; H, 4.91. Found: C, 38.79; H, 4.90. The NMR data are in agreement with structure II.

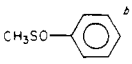
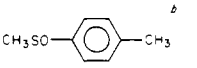
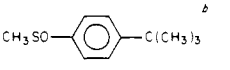
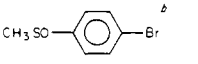
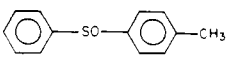


II

Rotation of the olefin in the complex around the axis passing through the double bond is restricted, leading[9] to the generation of new chiral centers at the unsaturated carbon atoms which carry two different groups. For an olefin with a given configuration, two diastereomers can form with I (see below), and four peaks may, therefore, appear in the chromatogram of a complexed racemic isomer.

The chromatogram of II (Figure 1) shows, as expected, four peaks. The injected sample of II had been enriched optically by recrystallization from CH_2Cl_2:MeOH (1:1); indeed, the area of $II^2 + II^4$ is larger than $II^1 + II^3$. Peak assignment was made as follows: (1) Isomers II^1, II^3, and II^4 were each isolated by HPLC and left in $CHCl_3$ at room temperature for 1–3 days. Partial interconversion of II^1 and II^3 into each other and of II^4 into II^2 takes place. As racemization of the olefin (at C_3) cannot occur under the experimental conditions, it is clear that the isomers making up each of the above two pairs differ in their configuration at C_2 but not at C_3. Though rotation around the Pt-π-electron bond (at C_2) is restricted, the barrier is not high enough to stop epimerization at room temperature. (2) The olefin liberated with KCN from the mixture, enriched in II^2 and II^4, was dextrorotatory [α_D +0.02° ($CHCl_3$)]; i.e., these two peaks correspond to isomers with the 3*S* configuration;[10] by inference II^1 and II^3 must be the 3*R* compounds. (3) With the configuration of C_3 assigned, that at C_2 can be determined by NMR spectroscopy. Data on the chemical shifts of the methyl protons (a) $-CHCH_3$ and (b) $-CH_2CH_3$ for diastereoisomers of known structure of the analogous *trans*-dichloro(benzylamine)(3-methylpent-1-ene)platinum(II) are available[11] and permitted to establish that both II^3 and II^4 belong to the 2*R* series (Figure 2).

Table I. HPLC Resolution of Sulfoxides via Diastereomeric Platinum Complexes

sulfoxide	capacity factor (k') of diastereomers[a]		resolution factor
	k'_1	k'_2	k'_2/k'_1
	2.91	3.14	1.10
	2.81 (*R*)[c]	3.14 (*S*)[c]	1.12
	1.86 (*R*)[c]	2.27 (*S*)[c]	1.22
	2.38 (*R*)[c]	2.62 (*S*)[c]	1.10
	4.94	5.56	1.13

[a] Capacity factor = (retention time of peak – retention time of solvent)/(retention time of solvent); retention time of solvent = 4.5 min; capacity factor of complex *I* = 2.0 with mobile phase b. [b] Eluent: *n*-hexane/CH_2Cl_2/2-propanol, 60:40:2. [c] Configuration assigned with optically pure (*R*)-sulphoxide. [d] Eluent: *n*-hexane/CH_2Cl_2/2-propanol, 80:20:1.5.

Similarly, 2,3-dimethylhex-1-ene, 3-ethylcyclopentene, 3-*n*-propylcyclopentene, 3-isopropylcyclopentene, 3-phenylcyclopentene, and 3,5,5-trimethylcyclohexene could be resolved, each giving four peaks. By interconversions it was established which pair of peaks correspond to olefins with the same configuration.

Once the peak interrelationships are known, it is possible to determine the optical purity of the olefin, e.g., for II (Figure 1), the ratio to be measured is that of II^1+II^3/II^2+II^4. In any method of resolution utilizing diastereomer formation, asymmetric induction may occur on derivatization. Therefore, for accurate analysis, an excess (3–5 equiv) of the chiral Pt reagent (I) has to be used to avoid distortion of the original enantiomeric composition of the olefin examined.

The potential of this approach for resolution of compounds other than olefins has been demonstrated on sulfoxides.[12] The corresponding diastereomeric compounds were prepared and chromatographed essentially under the same conditions as for the olefins. Results for five aromatic compounds are given in Table I. In contrast to the olefins, sulfoxides coordinate with Pt^{II} not through the S=O bond but rather through the S atom[13] so that only two diastereomers are formed by reaction with I. Whenever optically enriched samples were available, it could be shown that the (*R*)-sulfoxide complex emerged first. It is also seen in Table I that with increase in the size of the alkyl para substituent in $CH_3SOC_6H_4X$, the resolution factors increase. The nonaromatic cyclohexyl methyl sulfoxide could not, however, be resolved.

As detection by UV spectroscopy is very sensitive, analysis can be carried out on $\sim 10^{-5}$ g or less and requires only minute amounts of reagent I. The method also permits to prepare small amounts

(4) Another chiral ligand tried unsuccessfully for resolution was (*S*)-α-(1-naphthyl)ethylamine.

(5) Panunzi, A.; Palumbo, R.; Pedoni, C.; Paiaro, G. *J. Organomet. Chem.* **1966**, *5*, 586. On the basis of the method of synthesis, the olefin was assigned trans geometry with respect to the amino function of the chiral ligand.

(6) See Nash and Schaefer (Nash, C. P.; Schaefer, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 1319) for structure of analogous square-planar Cu^{II} complexes.

(7) Weinstein, S. *Angew. Chem.*, in press.

(8) Bowman, R. E. *J. Chem. Soc.* **1950**, 1346.

(9) Paiaro, G.; Panunzi, A. *J. Am. Chem. Soc.* **1964**, *86*, 5148.

(10) Pino, P.; Lardicci, L.; Centoni, L. *J. Org. Chem.* **1959**, 1399.

(11) Lazzaroni, R.; Salvadori, P.; Pino, P. *Chem. Commun.* **1970**, 1164 and references therein.

(12) For other methods of resolution of sulfoxides by LC through hydrogen bonding and CT complexation, see: Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

(13) Price, J. H.; Williamson, A. N.; Schramm, R. F.; Wayland, B. *Inorg. Chem.* **1972**, *11*, 1280.

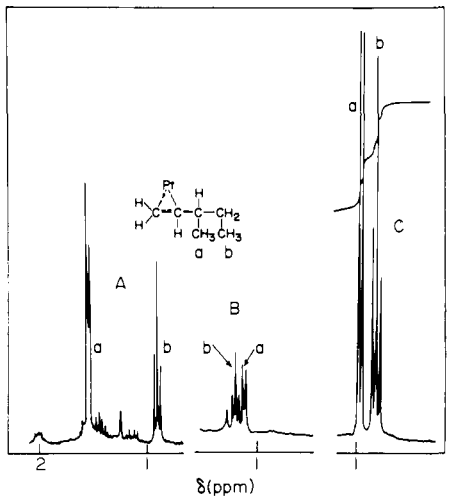


Figure 2. NMR spectra of complexed and uncomplexed 3-methylpent-1-ene. (A) 2*R*,3*S* diastereomer of the Pt complex II. The signal of the doublet at about 1.5 ppm contains a peak emanating from an impurity of the solvent. (B) 2*R*,3*R* diastereomer of the Pt complex II. (C) Uncomplexed 3-methylpent-1-ene.

of optically pure olefins and sulfoxides. Since in olefin resolution via Pt complexes one deals with a mixture of four diastereomers (olefins with one asymmetric center), the use of HPLC is obviously superior to that of crystallization.

Other important applications of the approach are in the field of metal-coordination chemistry, as manifest from the procedures used for the peak assignment of II. Even small amounts of the various stereoisomers, formed on complexation, can be detected. For unstable diastereomers, the purification of which by crystallization may not be possible,[14] HPLC offers an attractive route for the preparation of pure samples for NMR and chirooptical studies. Also, the relative stability of interconvertible isomers can be easily determined and the rate of epimerization measured.

Changes in the nature of the chiral *N*,*N*-dialkyl-α-amino acid coordinated to Pt makes available a variety of reagents with different stereoselective properties.[7] Such compounds could permit to widen the scope of the method to difficult problems of olefin and sulfoxide resolutions as well as extend it to additional classes of substances.

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Registry No. I, 80376-23-4; II[1], 80376-08-5; II[2], 80408-93-1; II[3], 80408-94-2; II[4], 80408-95-3; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*R*-methylphenyl sulfoxide)Pt[II], 80376-41-6; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylgycine)(*S*-methylphenyl sulfoxide)Pt[II], 80409-00-3; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*R*-methyl(4-methylphenyl) sulfoxide)Pt[II], 80376-38-1; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*S*-methyl(4-methylphenyl) sulfoxide)Pt[II], 80408-99-7; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*R*-methyl(4-*tert*-butylphenyl) sulfoxide)Pt[II], 80376-39-2; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*S*-methyl(4-*tert*-butylphenyl) sulfoxide)Pt[II], 80408-98-6; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*R*-methyl(4-bromophenyl) sulfoxide)Pt[II], 80433-06-3; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*S*-methyl(4-bromophenyl) sulfoxide)Pt[II], 80376-42-7; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*R*-phenyl(4-methylphenyl) sulfoxide)Pt[II], 80376-40-5; *trans*-chloro(*N*,*N*-dimethyl-*D*-phenylglycine)(*S*-phenyl(4-methylphenyl) sulfoxide)Pt[II], 80408-97-5; 3-methylhex-1-ene, 3404-61-3; 2,3-dimethylhex-1-ene, 16746-86-4; 4-methylcyclohexene, 591-47-9; 3,5,5-trimethylcyclohexene, 933-12-0.

(14) Lazzaroni, R.; Bertozzi, S.; Bertucci, C.; Salvadori, P.; Pino, P. *Isr. J. Chem.* **1976/77**, *15*, 63.

A New Role for Hydrogen-Bond Acceptors in Influencing Packing Patterns of Carboxylic Acids and Amides

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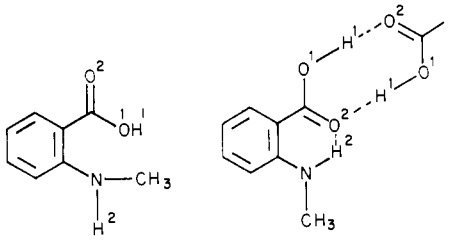
Received September 8, 1981

Several criteria for predicting the hydrogen-bonding patterns in carboxylic acids and amides previously have been proposed on the basis of lattice energy calculations[1] and analysis of the structures of many kinds of amides and acids.[2-4] Two of these criteria have proven particularly useful: (1) The crystal structure of an acid or amide will form in such a way that the maximum number of hydrogens which could possibly form H bonds will in fact form such bonds. (2) Certain H-bonding patterns have special significance because they are observed to occur so frequently. Among these are the cyclic H-bonded dimer pattern, the doubly H-bonded carbonyl groups, and the intramolecular H bond which occurs between ortho substituents on aromatic rings. In our studies of solid-state rearrangements of derivatives of anthranilic acid and related compounds[5] we have found that an additional principle appears to be operating: (3) The crystal structure of an acid or amide will form in such a way that the maximum number of hydrogen acceptor sites will be involved in H bonding.

This concept is best illustrated by considering the structures of acids or amides in which there are more hydrogen acceptor sites than hydrogens available for forming H bonds. In these cases the hydrogen atoms have a choice about both how many and which acceptor sites to use in forming hydrogen bonds. A clear example of this is seen by comparing the structures of *N*-methylanthranilic acid (I)[6] and *N*-acetylanthranilic acid (II).[7] Compound II has more acceptor sites than hydrogens (3:2), while I has an equal number. In the structure of I, shown below, its two hydrogens



I

are involved in the usual intramolecular and cyclic dimer H-bond arrangements referred to above. There are no other acceptor sites present. Addition of an extra acceptor at the methyl position of I need not interfere with the H-bonding scheme of I, but a significant change in the packing pattern is observed. The cyclic dimer pattern has been replaced by a polymeric-like pattern incorporating the acetyl group (O3–H1), resulting in a structure which satisfies criterion 3. Another indication that this structure represents the maximum use of its hydrogen acceptor sites is that

(1) A. T. Hagler and S. Lifson, *J. Am. Chem. Soc.*, **96**, 5327 (1974).
(2) L. Leiserowitz, *Acta Crystallogr., Sect. B*, **B32**, 775 (1976).
(3) L. Leiserowitz and G. M. J. Schmidt, *J. Chem. Soc. A*, 2372 (1969).
(4) J. Donahue, *J. Phys. Chem.*, **56** 502 (1952).
(5) L. A. Errede, M. C. Etter, R. C. Williams, and S. M. Darnauer, *J. Chem. Soc., Perkin Trans. 2*, 233 (1980).
(6) N. N. Dhaneshwar and L. M. Pant, *Acta Crystallogr., Sect. B*, **B28**, 647 (1972).
(7) We solved the structure of this compound inadvertently when we collected data on crystals of acetylanthranyl recrystallized from water. We thought we had grown the hydrated form of acetylanthranyl but the water had actually reacted with this compound to form I. We discovered the error when we used the CIS crystallography data base to retrieve all known structures with space group *Fdd*2 and found that compound I was in this space group and had the same unit cell parameters as our crystal. The structure of I can be found in Y. P. Mascarenhas, V. N. deAlmeida, J. R. Lachat, and N. Barelli, *Acta Crystallogr. Sect. B*, **B36**, 502 (1980).
(8) L. Leiserowitz and F. Nader, *Acta Crystallogr., Sect. B*, **B33**, 2719 (1977).

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