saturated $NaHCO_3$, drying over Na_2SO_4/K_2CO_3, and distillation). A gummy, insoluble oil present was best removed by stirring the mixture with Na_2SO_4 (the gummy residue seems to cling to the Na_2SO_4) while it was allowed to cool to room temperature. The drying agent was removed by filtration, the chloroform volume was reduced to about 300 mL, a few seed crystals were added, and the solution was chilled in the freezer (-20 °C). The first crop of crystalline acid (44 g) had a melting point of 70-72 °C. Evaporation of the chloroform produced a second crop (3 g) of acid of mp 70-73 °C producing a total yield of 47 g (72%). The specific rotation ($[\alpha]^{25}_D$ 16.02° (c 4.6, MeOH) (lit.[45] $[\alpha]^{25}_D$ 14.39° (c 4.7, MeOH))), and the melting point can be used as a measure of the enantiomeric purity of the acid, but a more reliable and precise method was used to prepare the amide with (S)-α-methylbenzylamine (Hexcel Corp., Zeeland, MI) that has been purified by threefold recrystallization of its tartrate salt[56] as follows. The acid was converted to the acid chloride,[45] and a small sample (0.100-0.250 g) in 10-20 mL of methylene chloride was treated with triethylamine (0.100-0.250 mL) and the (S)-α-methylbenzylamine (0.09-0.18 g). Workup by dilution with ether, washing with H_2O and $NaHCO_3$, and drying over Na_2SO_4 gives the amides. The *RS* amide had a melting point of 114-116 °C, while the *SS* amide was an oil that would not crystallize. Gas chromatographic analysis on the DB-1 capillary column gave *K'* values for the *SS* and *RS* amides of 5.07 and 5.38, respectively: IR (Nugol) 1775, 1660, 1390, 1240, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (3, d), 2.5-2.6 (4, m), 4.75-4.85 (1, t), 5.1-5.2 (1, m), 7.2-7.4 (5, m); MS (CI), *m/z* (relative abundance) 233 $(M)^+$ (*SS*, 20; *RS*, 50) 234 $(M + 1)^+$ (*SS* + *RS* 100).

The possibility of converting the crude acid directly to the acid chloride (after removal of the last traces of acetone under vacuum) was investigated by heating this crude acid with excess thionyl chloride[45] followed by distillation of the product. The acid chloride was obtained in 81% overall yield with an enantiomeric purity of 95.7%. The melting point of the acid is not a good measure of enantiomeric purity since samples of acid with a melting point of from 67 to 74 °C, produced acid chloride of high >99% enantiomeric purity.

Derivative Preparation. The acid chloride of the derivatizing acids were prepared by the following published methods: (S)-α-acetoxypropanoyl chloride (acid from Aldrich Chemical Co.),[57] (S)-tetrahydro-5-oxo-2-furancarboxyl chloride,[45] and (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[44] (the acid was purchased from Aldrich Chemical Co.). The diastereomeric esters were prepared as follows: (S)-α-acetoxypropanoates and (S)-tetrahydro-5-oxo-2-furancarboxylates; 100 μL of a 2 M solution of the acid chloride in methylene chloride was added to a cold mixture of 20 μL of the chiral alcohol and 80 μL of pyridine. The mixture was allowed to come to room temperature with stirring, two drops of 1 N hydrochloric acid and several milliliters of hexane were added, the layers were separated, and the organic layer was dried by passage through sodium sulfate. The (S)-α-methoxy-α-(trifluoromethyl)phenyl acetates were prepared similarly by using the neat acid chloride and no methylene chloride.

Resolution of Racemic Dihydrobenzoin. Racemic dihydrobenzoin (prepared from the meso form by the published procedure[58]) (10.71 g, 0.05 mol) was placed in a 500-mL flask with 200 mL of dry methylene chloride and 9.7 mL (0.12 mol) of pyridine and chilled in an ice bath. (S)-Tetrahydro-5-oxo-2-furancarboxyl chloride dissolved in 50 mL of methylene chloride was added dropwise. The mixture was stirred at room temperature overnight and worked up by extraction with water, 5% HCl, saturated $NaHCO_3$ drying over Na_2SO_4, and recrystallized from benzene (100% yield). Typically 100 mL of benzene is used for each gram of bis-TOF derivative, and this yields from 7.2 to 10.6 g (65.6 to 96.7%) of >99% pure *RRSS* diastereomer from one recrystallization. If a small amount of *SSSS* diastereomer remains in the product, a second recrystallization from 50 mL of benzene produces product of >99% purity. Evaporation of the mother liquor from several recrystallizations leaves the *SSSS* diastereomer with from 23 to 14g *RRSS* diastereomer. This material can be purified by preparative HPLC or alternatively could be purified by saponification to the diol and resolution with the *R* enantiomer of TOF acid. The pure *RS* diastereomer was saponified by stirring 11 g (0.025 mol) with 10 g of NaOH in 250 mL of ethanol and 25 mL of water for 24 h. The mixture was diluted with two volumes of water and extracted several times with ether. The combined ether extracts were washed with water and dried over Na_2SO_4. Evaporation of the solvent after removal of the drying agent gave 5 g (93%) of pure (*R,R*)-dihydrobenzoin of 100% ee. Rederivatization of a small sample with (S)-TOF acid chloride and analysis by capillary GC on the DB-1 column showed no racemization had occurred. The resolved *RR* enantiomer had a specific rotation $[\alpha]^{25}_D$ 96.8° (c 1.3, ethanol) (lit.[52] $[\alpha]^{25}_D$ 96.5° (c 1.6, ethanol)).

Preparative High-Performance Liquid Chromatography. In a preparative separation of entry VIII with $3 < K' < 5$ a resolution of 3 was obtained with a 50-mg injection and a resolution of 0.9 with 250-mg injection of the racemic TOF ester. This was done on a 2.54 × 25 cm column packed[55] with Bio-Sil A, 2-10 M, operated at a flow of 9.9 mL/min of 20% ethyl acetate/hexane.

Acknowledgment. We gratefully acknowledge the diligence and conscientious efforts of Elizabeth Adamek and Barbara Dueben. Mention of a commercial or proprietary product does not constitute an endorsement by the USDA.

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Circular Dichroic Detection in the HPLC of Chiral Molecules: Direct Determination of Elution Orders

Piero Salvadori,* Carlo Rosini, and Carlo Bertucci

Centro di Studio del CNR per le Macromolecole Stereoordinate ed Otticamente Attive, Istituto di Chimica Organica, Facoltà di Scienze M.F.N., Via Risorgimento, 35, 56100 Pisa, Italy

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The use of a dichrograph as a detector in the HPLC of chiral molecules is presented; the sign of the CD at a suitable wavelength is used to determine the absolute configuration of the fractions eluted, i.e., the elution order, by means of sector rules or nonempirical models. A general procedure for selecting the wavelength for the CD detection is presented. The advantages of such a method are discussed.

Polarimetric[1] and circular dichroic[2] (CD) detectors for HPLC instruments have been recently described: the usefulness of these devices is due to their selectivity (the detector will "observe" only chiral molecules) and to the

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fact that positive and negative signals can be obtained. Actually there is an important advantage of the CD detection which has not yet been utilized. The knowledge of the sign of the CD at a suitable wavelength can allow the determination of absolute configuration by means of empirical rules,[3] like the sector rules, or nonempirical methods such as the exciton model.[4] Recently the application of the above model has been extended to diols,[5] allylic alcohols,[6,7] etc. by means of transforming the above compounds in the corresponding benzoates, i.e., suitable systems to give rise to exciton coupling. Moreover, direct calculations of CD features, both by using molecular wavefunctions[8] or independent system techniques,[9] can afford additional nonempirical relationships between the sign of the CD and absolute configuration. Owing to the developments of nonempirical methods, it is today possible to assign the absolute configurations to several classes of compounds from CD measurements, including molecules constituted by a simple chromophore chirally perturbed by nonabsorbing groups.[8,9] On the contrary, analogous relationships between rotatory power and configuration cannot be easily established and, at the same time, direct evaluation of rotatory power is well beyond present calculation capability. This fact makes the polarimetric detector useful, in practice, only when the relationship between sign of the rotatory power and absolute configuration is already known.

In the present note it is shown how the above considerations can be applied to the determination of the absolute configuration of fractions eluted from a HPLC column, using the data coming from a CD detector. Therefore a series of compounds for which the relationship between sign of the CD and absolute configuration was known was first examined to test the reliability of the method. Finally, the elution order for a compound which has not been resolved so far is proposed, making use only of the present approach.

Results and Discussion

A Jouan II dichrograph or a Jasco J500C spectrometer equipped with a micro HPLC flow cell was connected to a Jasco Twincle HPLC system possessing an UV detector UVIDEC-100V in order to obtain a UV and CD detection. Separations of racemic mixtures were carried out by means of Pirkle[11] ionic and the Yuki–Okamoto poly(trityl methacrylate)[12] chiral columns.

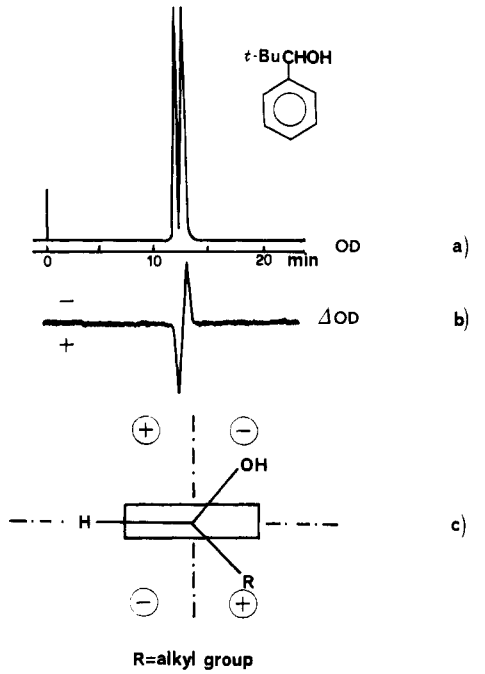
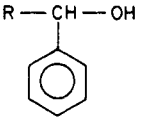


Figure 1. The chromatographic resolution of Ic on the Pirkle ionic column: (a) absorption and (b) CD detection at λ 270 nm; mobil phase hexane/isopropyl alcohol 99/1. (c) The Brewster–Buta sector rule for the ^1L_b electronic transition of chiral benzylic derivatives I.

The series of arylalkylcarbinols having the general formula shown below has been prepared by reduction of the corresponding ketones. The racemic alcohols have been



Ia, R = Me;
Ib, R = *i*-Pr;
Ic, R = *t*-Bu

resolved by the Pirkle ionic column. In Figure 1 parts a and b the separation of racemic Ic, representative for all the series, is shown: two peaks of the same area are observable both in the absorption and CD detection; in the latter case they are oppositely signed. For all the compounds I, the less retained enantiomer shows a positive CD peak and the most retained shows a negative peak at 270 nm, i.e., a wavelength which is within the region of the ^1L_b electronic transition of the benzene chromophore. Knowledge of the sign of the CD associated with such a transition allows one to assign, by the Brewster–Buta sector rule for chiral benzylic derivatives,[13] the absolute configuration of the eluates. Figure 1 part C depicts the most stable conformation of (*R*)-I, where the benzylic hydrogen eclipses the edge of the benzene ring.[13,14] Considering the sign–sector relationship and that the hydroxyl group is assumed to determine the sign of the CD,[13,14] the *R* absolute configuration is related to a negative CD. The elution order is then determined: the less retained enantiomer has the *S* absolute configuration and the most retained one has the *R* absolute configuration. This result is in agreement with the elution order deter-

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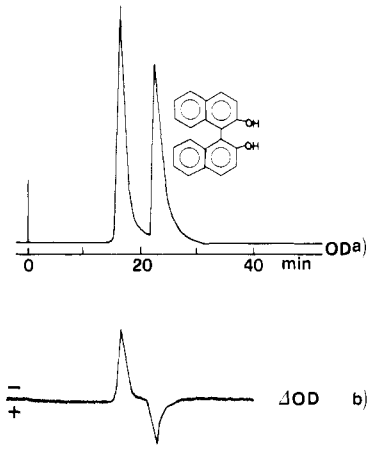

Figure 2. The chromatographic resolution of II on the Pirkle ionic column: (a) absorption and (b) CD detection at 220 nm; mobil phase hexane/isopropyl alcohol 95/5.

mined by Pirkle and Finn[11] on the basis of elution mechanisms.

The resolution of 2,2′-dihydroxy-1,1′-binaphthyl, II, shows how the exciton model[4] for optical activity can be usefully exploited to determine the elution order. As it has been recently pointed out[15] this method provides the basis for the determination of either the absolute configuration or conformation of molecules in a nonempirical manner. In this model, electrically allowed transitions which are present in (at least) two chromophoric moieties chirally disposed each other in the same molecule (see, for instance, dissymmetric structures having a dimeric nature, such as diphenylallene,[16] calycanthine,[17] etc.) are coupled together. This fact, due to the electrostatic interaction between the transitional charge distributions, gives rise to a high-energy and a low-energy coupling mode with respect to the same transition in the uncoupled chromophore. These modes show opposite sign in the CD spectrum giving rise to the characteristic "couplet".[18] Whether the low energy mode carries a positive or a negative CD band depends only on the absolute configuration of the molecular aggregate, for a chosen, known electrically allowed transition. Therefore the succession of signs of the CD bands corresponding to an intense UV absorption can be used for configurational assignments. In particular, to this end, it will be sufficient to establish which of the coupling modes will carry the positive or the negative CD band. In the case of II, the 210–250-nm region of the CD spectrum can be considered as dominated by the coupling of the long axis polarized ^1B_b transition of the β-naphthol chromophore (absorption maximum at ca. 224 nm). Of course, at longer wavelengths (for instance 235 nm) the low energy coupling can be found, whilst at shorter wavelengths (for instance 220 nm) the high energy coupling is present. In other words, from all the above discussion, it is possible to set criteria for choosing the wavelength at which to monitor the elution of the two fractions from the chiral column: for instance, a wavelength corresponding to the high energy coupling mode (220 nm) can be selected for the CD detection. In Figure 2 the resolution of II is reported. The two enantiomers are well separated and give rise to distinct peaks, having comparable areas both in absorption and in CD detection. Coming back to the general discussion for configurational assignments using

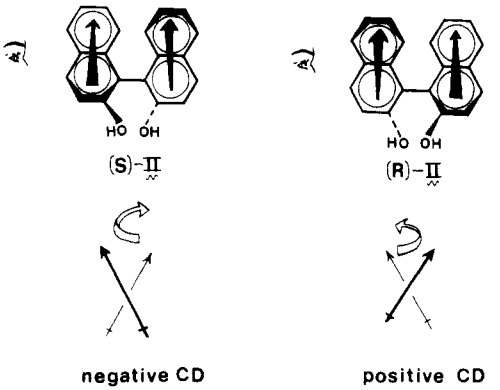

Figure 3. Relationship of the in-phase coupling mode of the long axis polarized ^1B_b transition of the β-naphthol chromophore and CD in the two enantiomers.

the exciton model, a negative CD is related to the high energy region (in-phase mode) for the *S* absolute configuration, whilst a positive CD will be found in the low energy region (out-of-phase mode) for the same absolute configuration. The high energy coupling mode is depicted in Figure 3 as well as the signs of the CD expected for either absolute configurations. Therefore the sign of the CD detected at 220 nm for the fractions eluted (Figure 3) points out that the enantiomer having the *S* absolute configuration is the less retained one. This elution order is in agreement with that determined by Pirkle and Schreiner.[19]

Another example of determination of elution orders by means of CD detection and application of rules correlating circular dichroism and structure is provided by the resolution of the dibenzoate of *trans*-1,2-cyclohexandiol, III, using the Yuki–Okamoto poly(trityl methacrylate) (PTMA) chiral column,[12] and by applying the "dibenzoate chirality rule", proposed[5] by Harada and Nakanishi. To this end, the knowledge of the sign of the CD band corresponding to the low energy coupling mode of the benzoate 230-nm transition is necessary. Therefore 235 nm can be considered as a suitable wavelength to represent this mode. The resolution of III is reported in Figure 4 parts a and b; the first eluted peak shows a positive CD at 235 nm.[20] The above mentioned dibenzoate chirality rule points out that a "positive chirality", i.e., the *S,S* absolute configuration, reported in Figure 4 part c, is to be assigned to the less retained peak. Even in this case the elution order is so easily determined. This compound has been previously resolved on this column, a polarimetric detector having shown that the +-isomer is the first eluted.[12] Although it is not possible to compare directly this result with the elution order proposed in the present work, the intense positive CD band at lower energies in III should give rise to a positive rotatory power.

All the above results strongly indicate the simplicity, rapidity, and reliability of the present method in assigning elution orders; therefore this technique will be applied in the final part of the paper to determine the elution order of a molecule which, to the best of our knowledge, has not been resolved earlier. Therefore the resolution of the benzoate of racemic 1-acenaphthenol, IV, has been attempted on the PTMA column with the aim of determining the absolute configuration of the eluates by means of the "aromatic chirality rule", a method which has been

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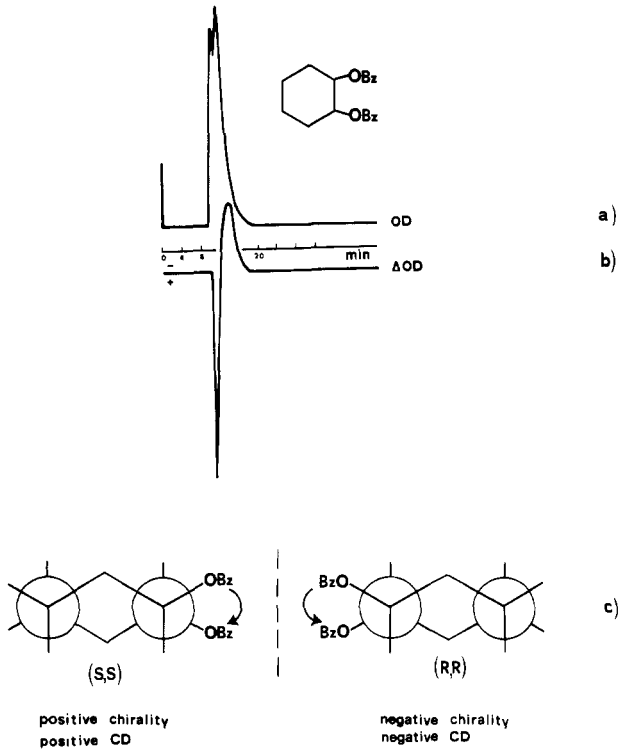

Figure 4. The chromatographic resolution of III on the chiral PTMA column. Eluent: methanol, flux 0.5 mL/min. (a) UV detection at 230 nm. (b) CD detection at 235 nm. (c) The application of the dibenzoate chirality rule.

largely employed in determining the absolute configuration of chiral aromatic alcohols.[5] This rule requires the knowledge of the sign of the CD corresponding to the low energy coupling mode deriving from the interaction of the benzoate 230-nm transition and the naphthalene long axis polarized excitation at about 220 nm. The absorption spectrum recorded on the racemate can help in choosing the wavelength to be used in CD detection: an intense band is observed at about 225 nm; therefore at longer wavelengths (say, 230–235 nm) the low energy coupling mode can be found whilst at shorter wavelengths (say, 215–220 nm) the high energy coupling mode is present. Therefore the first region has to be chosen to carry out the CD detection. In Figure 5 parts a and b the resolution of IV is reported; the first eluted peak shows a negative CD at 230 nm (i.e., in the region of the low energy coupling mode). This information is sufficient to apply the aromatic chirality rule: a negative CD for the first fraction eluted means a negative couplet for this enantiomer; thus the two interacting chromophores describe a "negative chirality", pointing out the *S* absolute configuration (Figure 5 part c). In this way the elution order is simply and safely determined. To further support this result, the CD monitoring can be repeated also for the high energy coupling mode, for which 220 nm could be a representative wavelength. As expected, an inversion of the sign sequence in the CD detection is observed confirming the elution order proposed above.

The results of the present work show that the absolute configuration of chiral eluates coming from a HPLC column can be determined by means of a detector which provides the sign of the CD at a suitable wavelength. The choice of the wavelength for the CD detection is carried out after the transition to be used for the correlation structure–spectrum has been selected; so, for instance, any wavelength within the ^1L_b transition of the benzene chromophore will be suitable for compounds I. For compounds II and III the choice is determined by the fact that

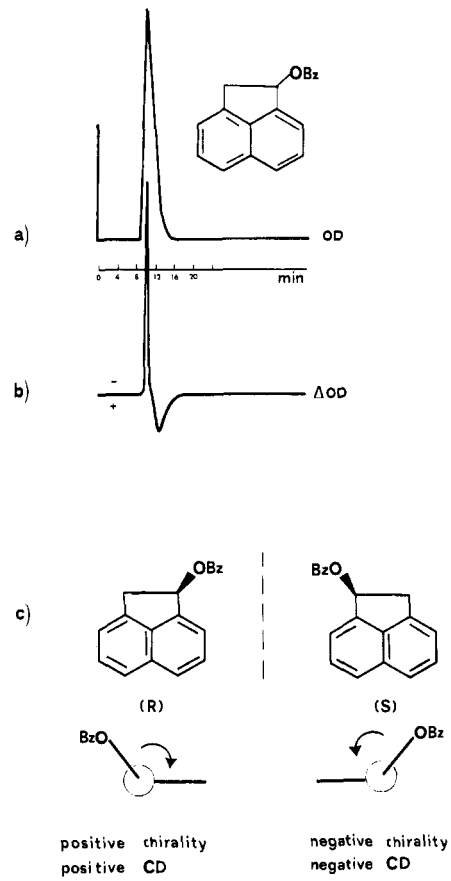

Figure 5. The chromatographic resolution of IV on the chiral PTMA column. Eluent: methanol, flux 0.5 mL/min. (a) UV detection at 225 nm. (b) CD detection at 230 nm. (c) The application of the aromatic chirality rule.

the elution order can be determined by means of the exciton model or its derivative, i.e., the exciton chirality rule. Then, a suitable wavelength, corresponding to one of the coupling modes has to be selected. This can be done by referring to the known absorption spectra of the isolated chromophores, i.e., the β-naphthol and the benzoate moieties. In the case of IV, the same choice can be made recording at first the absorption spectrum on the racemate to find the spectral range suitable for the application of the aromatic chirality rule. The absorption maximum observed provides a guide for selecting a coupling mode and the wavelength for the CD detection. It is to be noticed that some other method can be applied to the calculations of CD features, so as to obtain a spectrum–structure correlation, such as general independent system techniques[9] or rotatory strength calculations from molecular wavefunctions.[8] All these methods allow, at least in principle, one to also treat molecules which are constituted by a chromophore and alkyl perturbers only. Examples of this last kind of approach to molecular absolute stereochemistry have not been reported here because columns able to resolve such simple molecules are not yet available.

All the above discussion should clearly show that this approach does not require an a priori knowledge of the CD spectrum of the sample under examination; this fact could have constituted a strong limitation of the method. A possible difficulty in applying the present method is that one has to establish which transition is the most suitable for correlation with the structure. This may be difficult particularly in complex molecules where overlapping contributions from several chromophores are present. With the present method elution orders can be determined not only for molecules for which the relationship between

optical activity and structure is known, as in the case of polarimetric detectors, but indeed this limitation is overcome by using empirical or nonempirical rules, which directly relate the sign of the CD to the absolute configuration. Even if the above correlations have to be used carefully (in particular those which require the use of sector rules), it is to be expected that current progress in theoretical interpretation of CD data will make the present approach increasingly reliable and applicable.

In summary, the possibility of determining elution order constitutes a basis for investigation of chiral discrimination mechanisms and helps to clarify at least the most important interactions in the chiral recognition. In addition, when preparative HPLC systems are used for the separation of enantiomers it is possible to assign at the same time absolute configuration and optical purity to the fractions eluted from the absorption and CD detection. This will be of great practical importance because it will allow one to test immediately important molecular properties, like biological ones, which are often strongly dependent on absolute stereochemistry.[4]

Experimental Section

Materials. Compounds Ia and II were commercial samples from Fluka and were used without further purification. Compounds Ib and Ic were prepared by Al-*i*-Bu_3 and $LiAlH_4$ reduction of the corresponding ketones, respectively. Compounds III and IV were prepared from the corresponding alcohols (Jansen) by using standard procedures.

Chromatographic Resolutions. The separations were carried out by means of a Jasco Twinckle apparatus. The absorption was obtained by means of a UVIDEC-100V detection, whilst the CD detection was provided by Jouan II dichrograph or a JASCO J500C spectrometer equipped with a micro HPLC cell. The Pirkle column (i.e., (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine ionically bonded to a commercial 5 μm γ-aminopropylsilanized silica column from Merk, Darmstadt, West Germany) was prepared in situ, following the procedure reported.[11] The mobile phase was hexane containing up to 5% isopropyl alcohol. The poly(trityl methacrylate) was prepared and coated on phenylsilanized silica as reported by Yuki, Okamoto, et al.[12] In this case the eluent was methanol.

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Registry No. Ia, 98-85-1; Ib, 611-69-8; Ic, 3835-64-1; II, 602-09-5; III, 1460-57-7; IV, 92720-77-9.

Kinetics and Mechanism of the Oxidation of Aromatic Aldehydes by Hexachloroiridate(IV)

Kalyan Kali Sen Gupta,* Sanghamitra Dey, Shipra Sen Gupta, and Amalendu Banerjee

Department of Chemistry, Jadavpur University, Calcutta - 700 032, India

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The kinetics of oxidation of benzaldehyde and some substituted benzaldehydes by hexachloroiridate(IV) have been studied spectrophotometrically in the visible region. The reaction is first order in benzaldehyde and in iridium(IV). The influence of acidity on the reaction is small. The activation parameters of the reaction have been calculated. The oxidation reaction is found to have a deuterium isotope effect, k_H/k_D, of 7.0, indicating that the cleavage of the C-H bond of the aldehyde is the rate-determining step. The reaction appears to be of outer-sphere type and occurs through the intermediate formation of free radicals.

Introduction

The oxidation of some organic compounds such as phenols,[1] quinols,[2] alcohols,[3,4] and neutralized α-keto[5] and α-hydroxy acids[6] by hexachloroiridate(IV) has been studied. The kinetics and mechanism of the oxidation of some aliphatic and aromatic aldehydes by some other oxidants have been studied.[7,8] In some cases the mechanistic approach has been based on intermediate ester formation[8] between the substrate and the oxidant followed by the decomposition of the ester to give products; in other cases the results have been interpreted by the intermediate formation of free radicals[7c] followed by the reaction of the free radical with the oxidant to give products. The present investigation on the oxidations of aromatic aldehydes by hexachloroiridate(IV) was carried out in view of the results reported earlier with other oxidants.[7,8]

Experimental Section

Reagents. Glacial acetic acid of BDH (AnlaR) was heated under reflux for 6 h with excess of $K_2Cr_2O_7$ and distilled just before use. The solution of benzaldehyde in water was made by delivering a known volume of freshly distilled (under inert atmosphere) benzaldehyde from a calibrated pipette. The aldehydes were purified by distillation under reduced pressure just before use. Benzaldehyde exhibited an absence of peroxide by starch iodide test and no red coloration with $FeSO_4$-NH_4SCN reagent. A solution of benzaldehyde in sodium acetate–acetic acid buffer was worked up for benzoic acid in the same manner as shown in product analysis. It indicated that the amount of benzoic acid was less than 0.5% in a freshly prepared solution and remained

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