

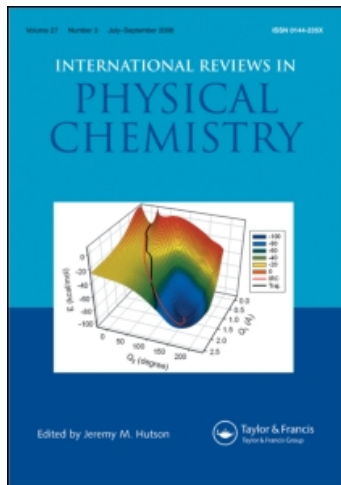
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Origins of the Pfeiffer effect

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The Pfeiffer effect concerns the change in optical activity of a solution containing a chiral substance, the environment compound, when a racemic mixture of another substance, classically a coordination complex of diimine ligands, is added to it. Several mechanisms have been proposed to account for the effect and these are discussed with respect to specific interactions leading to the observed chiral discriminations. Some new related systems involving Ru(II) complexes are reported.

1. Introduction

The interaction of chiral molecules is a major theme in modern stereochemistry and is of the greatest importance in studies of molecules of biological origin. Discriminatory interactions are found to occur between molecules of the same or of opposite hand. Large chiral discriminations are evident in biological systems, whether they be of kinetic or thermodynamic origin, but significant effects are also found with small molecules *in vitro*. This fact has several important chemical consequences, not the least of which concerns the resultant ability to resolve enantiomers.

The origin of the discriminating forces in these cases attracted the attention of two great Australian chemists, the late F. P. Dwyer and D. P. Mellor, who in turn stimulated D. P. Craig to address the problem of how molecules could distinguish between each other, their enantiomers and diastereomers. Over the last few decades, Professor Craig has been the leading worker in attempts to understand what might be called the chemical physics basis of chiral discriminations and his enquiries have resulted in a number of key publications (Craig 1979, 1980, Craig and Mellor 1976).

One particular manifestation of chiral discrimination that has intrigued Craig, his students and colleagues, is known as the Pfeiffer effect. Pfeiffer, a student of Alfred Werner, noticed a change in the rotation of polarized light passing through an aqueous solution of cinchonine hydrochloride and zinc (II) sulphate, upon the addition of 1,10-phenanthroline (phen) (Pfeiffer and Quehl 1931). In general, the term has been applied to changes in chiroptical properties of solutions containing an optically active solute (the environment substance) and a racemic coordination complex (originally *tris*-chelated complexes of diimines but now extended to other classes of compounds).

Several recent reviews have summarized work in this area (Gillard 1979, Kirschner *et al.* 1979, Kirschner and Bakker 1982). Here we review some of the highlights of the Pfeiffer effect and consider in turn the chemical interactions resulting in the chiral discriminations found in Pfeiffer-active systems.

2. Discussions

Classically, studies of the Pfeiffer effect have involved kinetically labile complexes of the diimines phen or 2,2'-bipyridyl (bipy) with Zn(II), Ni(II), Co(II), Fe(II) and the like. The racemic Pfeiffer compound may have the same or opposite sign of charge as that of the environment compound. Commonly the latter is an alkaloidium cation, although

inert optically active coordination complexes have themselves been used in this role and special cases involving the development of the effect by dissolution of the Pfeiffer compound in chiral solvents have been reported (Gillard 1979, Kirschner *et al.* 1979).

The effect is only known to occur in polar solvents (almost always water) and no effect is found in non-polar solvents such as benzene (Kirschner *et al.* 1979, Kirschner and Ahmad 1971, Brasted *et al.* 1969). We could therefore anticipate a variety of mechanisms and interactions which could account for the observations.

However, in the class of complexes mentioned above, and in nearly all cases which have been categorized as being Pfeiffer-active, the measured changes of chiroptical properties accompany the antiracemization of the Pfeiffer compound. This fact was quickly recognized by early workers in the field. Ni(II) complexes of diimines have been recovered optically active from Pfeiffer solutions (Dwyer *et al.* 1951, 1955, Dwyer and Davies 1954). The latter workers also studied the rates of racemization of Δ - and Λ -[Ni(phen)₃]²⁺ (0.012 M) in aqueous solutions containing (+)-bromocamphorsulphonate or (+)-cinchoninium ion (0.054 M). By observing that the rates of racemization were different over a range of temperatures, it is possible to calculate the chiral discrimination energies between the propellor molecules as 0.30 and 0.34 kJ mol⁻¹, respectively, for the two environment substances. These numbers were among the first to be provided and are important in that they permit an evaluation of some of the mechanisms which contribute to the Pfeiffer effect. An excess of from 0 to 3% is typically found for coordination complexes in Pfeiffer systems (Miyoshi *et al.* 1980), although larger discriminations are known and these are mentioned below.

As data have accumulated on the Pfeiffer effect, several mechanisms have been proposed to account for it. These are summarized in (1) to (4) where Δ and Λ refer to the absolute configuration of the Pfeiffer compound and E is the environment substance. The various mechanisms have been the subject of an excellent review by Schipper (1975 a), elaborated at a latter date (Schipper 1978).



The non-associative or equilibrium shift mechanism neglects steps (1) to (3), assuming that no association occurs. This notion was first advanced in terms of configurational activity (in the thermodynamic sense) by Dwyer *et al.* (1951). It relies on the simple, and undoubtedly true, idea that the activities of optical antipodes in a chiral medium are not equal. Several lines of evidence have been advanced in support of the mechanism. The first is that large effects have been noted in cation-cation Pfeiffer systems even when the highly charged [Co(en)₃]³⁺ ion (en = 1,2-diaminoethane) is used as the environment substance (Barnes *et al.* 1955). Furthermore it was found (Davies and Dwyer 1953) that (+)-bromocamphorsulphonate association with Δ , Λ -[Ni(phen)₃]²⁺ is not important except at high concentrations—much higher, indeed, than those necessary for the observation of a Pfeiffer effect. Secondly it has been reported in systems where the Pfeiffer complex is resolvable by classical means that O.R.D. and C.D. spectra of the Pfeiffer-active mixture are the same as the pure antipode (Kirschner *et al.* 1979, Kirschner and Bakker 1982).

It is pleasing to note that the theoretical framework developed by Craig and co-workers (Craig 1979, 1980, and references therein) can explain the magnitudes of the chiral discrimination energies usually observed in such Pfeiffer systems. This has been further elaborated by Schipper (1975 a, b, 1978) who points out that the induced optical activity as a result of differences of configurational activity is probably due to electrostatic interactions (Craig and Schipper 1974). The magnitude of discrimination energies due to induction and dispersion energies is too low (about 4 J mol^{-1}) to be of any great significance (Craig *et al.* 1971).

However, even for the non-associative mechanism, contacts of a special kind might be envisaged, especially in polar solvents such as water. It has been pointed out that the solvent sheath around a chiral molecule will itself be chiral and that preferential contact between selected solvated chiral species may provide a mechanism for the transmission of chiral information in solution (Bosnich and Watts 1975, Schipper 1975 a, 1978, Gillard 1979). Schipper (1978) notes that while the question of chiral solvent sheaths remains open to investigation, the theory developed can still take it into account.

Despite the success of the non-associative model in explaining some Pfeiffer-active cases, others require a different appraisal. In fact some of the same arguments mentioned above can be used to support an associative mechanism (1) to (3). Here the observed antiracemization is due to the different activities of the diastereoisomeric species ΔE and ΛE . This model was first proposed by Turner and Harris (1948) and has been advocated by Brasted *et al.* (1969). Pfeiffer O.R.D. and C.D. curves in certain systems can be shown to arise from diastereoisomeric equilibration alone (Kan and Brewer 1971, Mayer and Brasted 1973). A noteworthy example is provided by Kirschner *et al.* (1979). The C.D. spectra of solutions of $[\text{Co}(\text{phen})_3]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ (0.04 M) with either (+)-cinchoninium chloride, (-)-tartaric or (-)-malic acid (0.08 M) are somewhat dissimilar and, most importantly, do not exhibit isodichroic null points.

Clearly in some cases therefore, intermolecular ion pairs or associates do form between the Pfeiffer and environment substances in solution.

The question then remains as to the specific nature of the interactions which are involved. Fortunately, some evidence is available along these lines, especially in light of the fact that some Pfeiffer-active systems show chiral discrimination energies far in excess of those calculated for the equilibrium shift model (Miyoshi *et al.* 1985). It should of course be remembered that with close contacts, many of the weak interactions become highly discriminating.

Hydrogen bonding between the Pfeiffer and environment compounds might be important. In this connection it is worth recalling that Ogino and Saito (1967) reported that an overall C.D. is induced in systems which are not labile, but which have different diastereoisomeric association constants. This is akin to the picture drawn by (1) and (2) with $K_\Delta \neq K_\Lambda$. More to the point are the experiments of Norman and Mason (1965), who showed that an induced C.D. could be observed in the visible spectrum of $[\text{Co}(\text{NH}_3)_6]^{3+}$ in an aqueous solution containing a large excess of (+)-tartrate ion. In a similar vein, analogous effects were found in systems involving $\Delta, \Lambda\text{-}[\text{Co}(\text{en})_3]^{3+}$ with (+)-tartaric acid or (-)-malic acid (Kirschner *et al.* 1979). Perhaps more intriguingly, the same authors note that protonated chiral hydroxyacids of this type lead to greater Pfeiffer effects than do their deprotonated congeners. In this case it was suggested that hydrogen bonding to the π -electron system of the diimine ligands in the Pfeiffer compounds used could account for the variable chiral discriminations found with varying pH.

Other workers have pointed to the implications of hydrophobic bonding. Such interactions can be in part correlated with some of the solvent dependencies of the Pfeiffer effect (Brasted *et al.* 1969, Yoneda *et al.* 1974). In particular, the recent work of Miyoshi *et al.* (1985) stands out. Large discriminations in systems containing Δ, Λ -[Co(ox)₂(phen)]⁻ (ox = oxalate dianion) and *Cinchona* alkaloids were observed. These could be ascribed to a combination of hydrogen bonding between the environment substance and coordinated oxalate ligands and to hydrophobic interactions between coordinated 1,10-phenanthroline and the quinolyl fragment of the environment species. A striking feature of the experiments they describe is that virtually no discrimination is found in corresponding systems containing the Δ, Λ -[Co(ox)₂(en)]⁻ anion. We should also like to draw attention to the work of Barton *et al.* (1984) which describes chiral discriminations between the kinetically inert species Δ, Λ -[Ru(phen)₃]²⁺ and DNA. More recently, a study over the whole visible range of the spectrum using C.D. techniques has shown that significant chiroptical effects are produced in this case (Vagg and Williams 1985, unpublished). These are a result of hydrophobic stacking interactions with coordinated ligands intercalated into DNA and to electrostatic interactions producing strongly bound aggregates.

Finally, the suggestion that the Pfeiffer effect is due to other kinds of chemical species in those systems containing metal complexes or diimine ligands should be mentioned. Gillard (1975, 1979) has rationalized many of the observations in the field by suggesting that covalent hydrate or pseudobase species, involving attack of H₂O or HO⁻ at the coordinated diimine, could be important. This theory is controversial at present (Constable 1983, Serpone *et al.* 1983). However, it is universally accepted that complexes of 5-nitro-1,10-phenanthroline do form such pseudobases when reacted with nucleophiles (Bartolotta *et al.* 1984 a, b, and references therein). Thus it is intriguing to note that Ru(II) complexes of 5-NO₂-phen display a Pfeiffer effect with chiral hydroxyacid anions only when base is added to produce the appropriate pseudobasic species (Gillard and Williams, unpublished results). The effect, which of course in this case does not involve antiracemization at the metal centre, is not observed in Δ, Λ -[Ru(phen)₃]²⁺ or Δ, Λ -[Ru(bipy)₃]²⁺ and concerns selections of stereochemistry at the pseudobasic centres in a chiral environment. Possibly the selection also concerns hydrogen bonding to the environment compound via the introduced hydroxy groups. It may be that this last mechanism operates in many Pfeiffer systems.

In conclusion we note that the Pfeiffer effect is a complex set of phenomena involving many kinds of discriminating interactions. Some of these have taken a considerable body of experimental work to elucidate, and the studies have been the subject of considerable controversy. However, the effect is a chemical fact which has encouraged a fruitful collaboration between experimentalists and theoreticians. This is indeed a fitting tribute to the subject of this volume, especially as Professor Craig has himself and through his colleagues made such an outstanding contribution to our understanding of chiral discriminations of the kinds mentioned here, as well as others.

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