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Invited Review

Contributions to the Pfeiffer Effect

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Contents

1. Introduction
2. Contributions to the Pfeiffer Rotation
3. The Non-associative Mechanism
4. The Diastereoisomeric Mechanism
5. Comparison of the Two Mechanisms
   A. ORD–CD Studies
   B. Kinetic Studies
   C. Effect of Charge
   D. Temperature Effects
   E. Lability
   F. Solvent
6. Source of Configurational Activity
7. References

1. Introduction

The resolution of the two enantiomers A′, A″ of a chiral species by exploiting the different solubilities of the two diastereoisomers A′B, A″B formed by their association with another chiral species B is well known. A related phenomenon is the gradual change in the optical rotation of a solution of a racemate when another chiral organic species is added, from that of the racemate and the chiral species separately before mixing.[1,2] This is attributed to the following changes:

$$\begin{array}{c} A' + A'' + B \\ \Big\downarrow \ \text{(on solution)} \\ A'B + A''B \\ 50\% \ \uparrow\!\downarrow \ 50\% \ \text{(equilibration)} \\ A'B + A''B \\ (50+x)\% \ (50-x)\% \end{array} \qquad [1]$$

The diastereoisomers differ in stability because of their different spatial demands in solutions, and therefore at equilibrium are no longer in equal concentrations. A partial resolution is thus effected.

Such an effect has also been observed however with ionic systems in dissociating solvents. For example, if a racemate of labile $Ni(phen)_3^{2+}$ ions (which has no net rotation) is added to an aqueous solution of *d*-bromcamphorsulphonate$^-$ ions, the optical rotation of the solution (suitably corrected for the overall volume change) changes significantly. This is an example of what has become known as the Pfeiffer effect (after Pfeiffer[3], who first noted the effect). The molar Pfeiffer rotation P_m at a particular temperature and wavelength may be defined as[4]

$$P_m = \frac{P}{[e][c]l}$$

where

$$P = \pm\,(\alpha_{e+c} - \alpha_e)$$

P is the observed Pfeiffer rotation (degrees), α_{e+c} the rotation of the solution containing both the environment compound (e) and the complex (c), α_e that for (e) only, and the sign chosen for P is that for the (e) solution. Molar concentrations of (e) and (c) are respectively [e] and [c], and l is the solution path length in metres.

Speculations on the mechanism of the Pfeiffer effect have produced a steady stream of papers, especially in recent years. In the process, a wide variety of systems that exhibit the effect have been reported. In this review, the various mechanisms are carefully defined and the possible sources of the phenomenon discussed in the light of recent developments in the area.

2. Contributions to the Pfeiffer Rotation

Two basic mechanisms have been postulated as the source of the Pfeiffer effect. These are best understood by first discussing the general processes that could occur in the mixed solution. If we now let A′, A″ be the *dextro* and *laevo* forms of the complex ion, B the chiral environment ion, and A'B, A"B the diastereoisomers of A', A" with B, the solvent being achiral, the following processes could occur:

(A) Association:

$$A' + B \xrightleftharpoons{K_a'} A'B$$

$$A'' + B \xrightleftharpoons{K_a''} A''B$$

(B) Diastereoisomeric Equilibration:

$$A'B \xrightleftharpoons{K_d} A''B$$

(C) Enantiomeric Equilibration:

$$A' \xrightleftharpoons{K_e} A''$$

Step (A) involves the formation of definite diastereoisomers or associates. Because of the different contact interactions of the two enantiomers with the chiral B ion, the stoichiometric equilibrium (or association) constants K_a', K_a'' are not necessarily equal. Once formed, the diastereoisomers are distinct chemical species, each having its own characteristic shape and properties. The equilibration steps (B), (C) can only take place if the species A and AB are labile. Step (B) is the result of the different chemical activities of the two diastereoisomers; this activity difference is essentially the consequence of their different shapes, and hence their different interactions with the chiral solvent. It is thus a property of the diastereoisomer as a whole, and not of the interactions between A and B that cause the formation of the associate. Step (C) arises from the different activities of the enantiomers of A due to their long range interactions with the chiral species B. This is the result of the interaction of A' and B being different from that of A" and B, even when they are separated by large distances in the solution. This was first termed configurational activity by Dwyer.[5] As A is labile, the equilibrium shifts to the enantiomer which has the greater stability in the chiral environment.

In this general case, then, the observed Pfeiffer rotation can be ascribed to three main factors: (i) the formation of diastereoisomers which will have different rotations than the dissociated species, and the resulting difference in concentrations of the free ions due to the different association constants [step (A)]. This occurs also for inert species[6], and is not usually considered as being a Pfeiffer rotation; (ii) the equilibration of the diastereoisomers thus formed. This disturbs the diastereoisomeric proportions of step (A), leading to changes in the overall rotation; (iii) the equilibration of the enantiomers in the chiral environment. This equilibrium shift introduces a new net rotation due to the excess of the more stable enantiomer.

Some other contributions are also possible. For example, the species B may induce optical activity in A (and *vice versa*) by long range interactions. This is possible even if A is achiral.[7,8] This contribution, though interesting in its own right, is usually small and may be neglected in Pfeiffer systems.

The papers in the literature are polarised in support of two mechanisms, which are particular cases of the above scheme. It is stressed at the outset that the two mechanisms describe two quite different sources of the Pfeiffer effect. Thus the purpose of this review is not to suggest that one or the other is a better way of looking at the Pfeiffer effect; rather it is to compare them, and thus better define the methods by which it is possible to ascertain which mechanism is effective in a given experimental system. The two mechanisms may be referred to as the non-associative and diastereoisomeric mechanisms respectively. We discuss these in turn.

3. The Non-associative Mechanism

Referred to in the literature as the 'equilibrium shift' mechanism (which is ambiguous as both mechanisms involve an equilibration step), this mechanism neglects steps (A) and (B) entirely, and hence it is assumed that no association occurs. This was postulated in terms of the configurational activity picture by Dwyer and co-workers,[5,9,10] and has more recently been supported by Kirschner.[4,11]

In order to discuss this mechanism in detail, we consider the equilibration

$$A' \underset{k''}{\overset{k'}{\rightleftharpoons}} A''$$

in the presence of a fixed amount of B in an achiral solvent. k', k" are the rate constants for the *dextro* to *laevo*, *laevo* to *dextro* processes respectively, and m', m" the concentrations of A', A" at equilibrium. The molar free energy of A' may be written as

$$G_{A'} = G^{o}_{A'} + RT \ln a'$$

where

$$a' = m'\gamma'$$

a' is the activity of species A', γ' the activity coefficient, and $G^{o}_{A'}$ the standard molar free energy of A'. A similar expression may be written for A", and it follows that we may define a discrimination free energy Δ^e (which is essentially the free energy difference of A', A" in the chiral environment) by the equation

$$\Delta^e = \frac{[G_{A'} - G_{A''}]}{RT} = \ln \frac{\gamma'}{\gamma''} \quad (\text{if } m' = m'')$$

The standard state has been chosen to be that of infinite dilution (when all interactions between A′ and B, A″ and B, vanish) so that, for the above reaction at equilibrium

$$\Delta G^\circ = -RT\ln K_{th} = 0$$

where K_{th} (= 1) is the thermodynamic equilibrium constant defined as $K_{th} = a''/a'$. It thus follows that equilibrium is reached when the activities of A′, A″ become equal, and this is the theoretical expression of Dwyer's initial configurational activity concept. It follows immediately that

$$\frac{m''\gamma''}{m'\gamma'} = 1,\ K_e = \frac{m''}{m'} = \frac{k''}{k'},\ \text{and}\ \Delta^e = RT\ln K_e$$

The discrimination free energy may be expressed in terms of separate enthalpy and entropy contributions so that

$$\Delta^e = \Delta_h{}^e - T\Delta_s{}^e$$

It follows that these separate contributions may be determined directly from a temperature study of the stoichiometric equilibrium constant K_e.

The contribution to the Pfeiffer rotation from this equilibration is readily found by assuming that

$$\delta m = (m''-m') \ll m'$$

so that

$$\Delta^e = RT\ln\frac{m''}{m'} \cong RT\frac{\delta m}{m'}$$

P_m is thus directly proportional to this change in concentration δm which may be written as

$$\delta m = \frac{m'}{R}\left[\frac{\Delta_h{}^e}{T} - \Delta_s{}^e\right]$$

As $\Delta_h{}^e$, $\Delta_s{}^e$ are constants for a given system, the temperature dependence of P_m is immediately defined from the above. In particular, it changes sign in going through what we may call the inversion temperature

$$T_i{}^e = \Delta_h{}^e/\Delta_s{}^e$$

and is zero at that temperature.

A comprehensive study[12] of the racemization of *d*- and *l*-$Ni(phen)_3{}^{2+}$ ions in aqueous solutions of *d*-bromcamphorsulphonate$^-$ (referred to as I) and *d*-cinchoninium^{++} (II) ions has been done by Davies and Dwyer. Both kinetic and equilibrium studies yield the following results:

$$\Delta^e(I) = -318 + 0.87T$$
$$\Delta^e(II) = 386 - 1.03T\ (\text{cals mol}^{-1})$$
$$T_i{}^e(I) = 365\ K \quad T_i{}^e(II) = 376\ K$$

Estimation of δm follows directly from the above equations. Pfeiffer studies on this system agree closely with these racemization studies, supporting the mechanism for such systems.

4. The Diastereoisomeric Mechanism

This mechanism was first suggested by Turner and Harris,[1] and is still actively supported by Brasted and co-workers.[13] Association is postulated as a prerequisite in the Pfeiffer system, and the change in rotation with time is assumed to be the result of diastereoisomeric equilibration [step (B)]. The scheme is analogous to that of equation (1). The association is assumed *complete* on mixing, so that the difference in association constants is neglected, and the concentration of free enantiomer assumed to be zero. Note that the total rotation arises in this case from contributions (i) and (ii) of section 2, but the change in rotation from the time of mixing (which is the Pfeiffer rotation) arises from contribution (ii) only.

We have noted that in this case the equilibrium shift [step (B)] arises because of the different activities of the two diastereoisomers, which is due to their different interactions with the achiral solvent (because of their different shapes). In this case we can define a diastereoisomeric free energy difference

$$\Delta^d = RT\ln K_d$$

in the same way as we defined Δ^e in the previous section, except that Δ^d now is a measure of the difference in free energies of the two diastereoisomers in the achiral solvent. Definitions of $\Delta_h{}^d$, $\Delta_s{}^d$ as before indicate that the difference in molarities of A′B, A″B may again be written in the approximate form

$$\delta M = (M'-M'') \cong \frac{M'}{R}\left[\frac{\Delta_h{}^d}{T} - \Delta_s{}^d\right]$$

so that the Pfeiffer rotation arising from this equilibration will have the same temperature dependence as before, but with quite different constants $\Delta_h{}^d$, $\Delta_s{}^d$, and $T_i{}^d$.

5. Comparison of the Two Mechanisms

In order to determine which mechanism is operating in a given system, it is necessary to analyse carefully the different features of the two equilibrations. In this section, therefore, there is no attempt to collate all the available data on the Pfeiffer effect; instead, attention is focussed on those methods which are particularly useful in elucidating the possible mechanisms involved.

A. ORD–CD Studies

The measurement of Pfeiffer rotations at a single wavelength has been superceded, with the introduction of ORD and CD techniques, by Pfeiffer ORD and CD studies. Such studies were first discussed in this context by Kirschner,[4,11] and more recently by Kan and Brewer,[15] and Brasted.[14] The advantage of using ORD–

CD curves lies in their characteristic shape for a given optically-active species. The free enantiomer will have quite a different ORD–CD curve from that of the associate AB. For example, in some Pfeiffer systems, the Pfeiffer ORD and CD curves were found to be practically identical to those of the pure enantiomer thought to be produced in excess, suggesting that the enantiomeric equilibration mechanism was operating in these systems.[4,11] Kan and Brewer,[15] and more recently Mayer and Brasted,[14] have also used ORD to show that in some other systems the rotation is purely due to association, and in Pfeiffer systems due to the diastereoisomeric equilibration. In this way it should be possible by systematic studies to classify environment compounds B into essentially associating and non-associating classes for given ionic systems.

B. Kinetic Studies

Further differences in the two mechanisms may be probed by kinetic studies. Configurational activity effects are small perturbations on free-ion properties, depending on discriminations in long range interactions with the environment compound. Diastereoisomeric effects however are the result of the chemical properties of the new diastereoisomeric species, and the effects cannot really be viewed as small perturbations of free-ion properties. To illustrate this point and its manifestations, we look at the rates of equilibration for the two mechanisms:

$$\text{(B)}\quad A'B \underset{k_l}{\overset{k_d}{\rightleftharpoons}} A''B$$

$$\text{(C)}\quad A' \underset{k''}{\overset{k'}{\rightleftharpoons}} A''$$

Consider first the enantiomeric equilibration (C). In the absence of B we have $k'=k''=k$ where k is the rate constant for A in pure solvent. As B is added, long range interactions favour one enantiomer, so that one constant increases, the other decreases. Qualitatively we can write

$$k' \cong k + \delta k, \quad k'' \cong k - \delta k$$

The rate constants are not greatly different from those in pure solvent, as the equilibration mechanism is still occurring in a solvent sphere, unimpeded by contact interactions with large environmental species. That this occurs for certain Pfeiffer systems is illustrated by the experiments of Kirschner and Ahmad.[11] For the diastereoisomeric equilibration however the inversion of the complex (which involves motion of at least two of the chelate ligands[16]) must occur while the complex is in intimate contact with the environmental compound (which is by no means small). In such cases, we might expect larger differences in k_d and k_l, and, furthermore, we would not necessarily expect them to bear any simple relation to the free-ion rate constant k.

C. Effect of Charge

That contact interactions are not important in all instances is strongly suggested by the appearance of discrimination even in systems where A and B carry the same charge. For example, large discriminations have been found for positive complex ions A using such environment compounds as *d*-cinchoninium$^+$, Co (en)$_3^{+++}$.[17] On the other hand, doubly-negative tartrate and relatively high concentrations of *d*-bromcamphorsulphonate$^-$ are more likely to favour the diastereoisomeric mechanism.[15] The study[12] of the dependence of the discrimination of *d*- and *l*-Ni(phen)$_3^{++}$ on the concentration of *d*-bromcamphorsulphonate$^-$ suggests that association does not become important in this case except at relatively high concentrations of the environment compound (> 5%).

D. Temperature Effects

The temperature dependence of the effect has been studied by Brasted *et al.*[13] It follows from the discussion of previous sections however that this is not a good criterion for differentiating between the two mechanisms, as they both predict the same functional behaviour, which agrees closely with experiment. On the other hand, as the inversion temperatures for the two mechanisms may be quite different, it is possible to compare the inversion temperature from a Pfeiffer study with that of direct racemisation studies. If T_i is the same for both cases, then the same mechanism is involved.

E. Lability

The effect of the lability of the complex on the effect has been studied,[18] and found in some cases to lead to an increase in Pfeiffer rotation with increasing lability of the complex. This was used to support the enantiomeric mechanism. Such correlation is however coincidental for the equilibrium shift depends only on the discrimination energy, which is not at all a function of lability.

F. Solvent

Use of different achiral solvents[18] can cause large changes (even in sign) in the Pfeiffer rotation. This has several possible interpretations however so that it is not really a good criterion for supporting particular mechanisms. The occurrence of the effect in water, acetic acid, and DMF but not in alcohols could be due to the lability of the complexes in the former dipolar solvents. Alternatively, and this is suggested in that the sign of the effect is different for different solvents[18]), the solvents could stabilise different conformers of the complexes, yielding different enantiomeric equilibrium constants (see next section). A further possibility is that the solvent structure transmits the asymmetry between the complex and the environment molecules; in this case energy differences could be the result of interactions of asymmetrically induced solvent sheaths.

6. Source of Configurational Activity

The source of diastereoisomeric activity differences lies in their different shapes and therefore their different interactions with the achiral solvent. Although we have further stated that the configurational activity differences in completely dissociated systems arise from the differences in long range interactions of A′ and A″ respectively with the chiral additive B, it still remains to discuss the nature of the long range interaction responsible for the effect in such ionic systems.

Experimental estimates of the discrimination energies have been made by Dwyer and co-workers in a series of studies on the differences in racemization rates,[12] solubilities[5] and electrode potentials[17] of A′, A″ in aqueous solutions with chiral additives B. Through a simple statistical thermodynamic treatment[19] it has been shown that qualitatively Δ_h^e may be identified as the difference in the intermolecular interactions of A′, A″ with the species B in solution, so that the intermolecular forces responsible for configurational activity must yield interaction energies the order of Δ_h^e, which from Dwyer's experiments is about 300 cal mol^{-1}.

Long range interactions in dissociated systems may be classified as electrostatic, induction and dispersion interactions. Discriminations arising from induction and dispersion energies have been discussed theoretically by Craig, Power and Thirunamachandran.[20,21] Such interactions at long range (order of a few molecular diameters) may be shown to account for discriminations of less than 1 cal mol^{-1}, and thus are unlikely to be important in dissociated systems. The electrostatic terms treated theoretically by Craig and Schipper[22,23] can, however, yield discriminations for model systems that agree in magnitude with that found experimentally for Δ_h^e. This suggests that electrostatic interactions are the source of configurational activity. Some results of the theoretical treatment may be applied directly to the complexes used for the Pfeiffer studies.

It follows from the theory for discrimination in electrostatic interactions[23] that discriminations for ions with symmetry C_n or D_n arise from terms involving the n- and (n+1)-poles of the ions (where the multipoles are expanded about the metal ions as origin). Lower order interactions do not reflect the chirality of the ions, and thus will not discriminate. As an example, for C_2 ions the discrimination arises from quadrupole and octupole terms (2- and 3-pole terms respectively); dipole interactions cannot lead to discrimination alone as a dipole has reflection symmetry. The chemical consequence of this is that the discrimination is weaker the higher the order of the multipoles involved; *i.e.*, Δ_h^e may be said qualitatively to decrease with increasing order n of rotational symmetry of the ion.

An ideal tris-bidentate ion has D_3 symmetry, so that both 3- and 4-poles are required to give discrimination. It has been suggested[19] however that the observed Δ_h^e found experimentally in Pfeiffer systems arises from the stronger interactions involving quadrupole–octupole (2- and 3-pole) terms due to the reduction of the symmetry of these complexes in real solvents to C_2. This is due to the existence of conformers, which is exemplified by $Co(en)_3^{+++}$. The ethylenediamine ligand is buckled, so that two configurations are possible (denoted δ and λ). These give rise to conformers[24,25] of the complex which may be denoted by $\delta\delta\delta, \lambda\lambda\lambda, \delta\delta\lambda, \lambda\lambda\delta$; the $\delta\delta\delta, \lambda\lambda\lambda$ are D_3, and the $\delta\delta\lambda, \lambda\lambda\delta$ both C_2. It is thus possible that the latter two conformers provide the bulk of the discriminations in chiral environments. Whether the less flexible bipyridyl and *o*-phenanthroline ligands can lead to similar conformers due to perturbations by water molecules between the chelate planes is difficult to assess. The suggestion that discriminations arise mainly from C_2 conformers remains speculative; if it has some foundation, however, it could lead to the use of the Pfeiffer effect as a tool in the study of conformers. The importance of solvent in stabilizing certain conformers is thus a possible rationale for solvent effects, as has been previously mentioned.

As a closing comment, we may mention that the point octupole (3-pole) mentioned above is the lowest order moment which takes into account the ligands as separate dipoles. The theoretical work thus supports Dwyer's qualitative suggestions that the configurational activity differences could have their source in long range interactions of electrical origin, the chiral disposition of the ligands presumed reflected in interactions as a chiral disposition of ligand dipoles.

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