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Optical Isomers in Solution Investigated by Nuclear Magnetic Resonance

M.I.Kabachnik, T.A.Mastryukova, E.I.Fedin, M.S.Vaisberg, L.L.Morozov, P.V.Petrovskii, and A.E.Shipov

Work during recent years on the n.m.r. spectroscopy of solutions of optical antipodes and their mixtures with each other and with epimers is surveyed. The phenomenon of statistically controlled anisochronism of diastereomeric association (SCADA) is described. Several factors—the nature of the stereoisomers, the solvent, the temperature, etc.—affect the multiplicity of the diastereomeric anisochronism spectra. The above phenomenon is not observed in the absence of association. A theory of the phenomenon is given, and theoretical calculations are compared with experimental results. A list of 41 references is included.

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I. INTRODUCTION

Aspects of the stereoselectivity of the molecular association of optical antipodes in solution have recently been attracting the attention of research workers. They are closely connected with the problem of the existence of racemic compounds in solution and in the liquid phase in general. There are a large number of papers and many reviews on this topic (for an excellent review see Ref. 1). Differences in the interactions of identical chiral molecules (e.g. S...S or R...R) or of antipodal molecules (i.e. S...R) have been studied theoretically by quantum-chemical methods [2] and in terms of the three-body problem [3]. Spatial relations were taken into account in applying statistical thermodynamics [4]. A similar treatment has been made to the classic approximation [5].

Experimental methods for studying the association of chiral molecules—measurement of density, molecular mass, viscosity, dipole moments, surface tension, heats of mixing, refractive indices of solutions, absorption spectra, etc.[1]—have not given unambiguous results. Polarimetric investigations have given more precise information. Horeau [6] was the first to show that the optical purity P of a mixture of antipodes of $\alpha\alpha$-ethylmethylsuccinic acid $HO.CO.CH_2.C(CH_3)(C_2H_5).COOH$ may vary non-linearly with the enantiomeric purity Q. Here

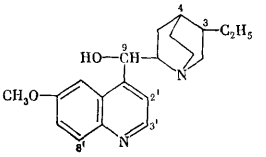
$$P = [\alpha]^t_\lambda/[\alpha_0]^t_\lambda; \quad Q = ([D]-[L])/([D]+[L])$$

where $[\alpha]^t_\lambda$ and $[\alpha_0]^t_\lambda$ are the angles of rotation of the mixture and of an optically pure specimen, while [D] and [L] are the corresponding concentrations of the antipodes in the mixture. Horeau attributed this non-linearity to different contributions by diastereomeric association complexes to the observed angle of rotation of the plane of polarisation, which served as basis for using polarimetry to investigate the interaction of antipodes in solution.

The nuclear magnetic resonance method occupies a special place in these investigations. The reason is that separate signals for diastereomeric forms can be observed in n.m.r. spectra. It has been known for a long time that the n.m.r. spectra of diastereomers may differ in the chemical shifts of signals from indicator nuclei [7,8], and this difference has been termed *diastereomeric anisochronism*. Quite recently it has become known that such anisochronism can be observed in solutions not only of diastereomeric molecules but also of diastereomeric association complexes of enantiomers, even with rapid exchange between the complexes (see below). Diastereomeric anisochronism has two independent parameters—the diastereomeric chemical shift, determined by spatial independent differences in the chemical environment of the indicator nucleus in the diastereomers, and the relative integral intensity in the diastereomeric doublets, representing the relative content of the given diastereomeric form in the solution.

We are thus concerned with the laws of diastereomeric anisochronism—the magnetic non-equivalence of nuclei in diastereomeric systems—in the narrow sense in diastereomeric molecules [7,8]; spectra of this kind are used to determine absolute configuration [9] and enantiomeric purity [10]. It includes also diastereomeric anisochronism of enantiomers in chiral solvents [11] or in achiral solvents but in the presence of chiral additives [12], which in particular may even be chiral shift reagents [12]. Finally, it includes the dynamic anisochronism of enantiomers in achiral solvents when the concentrations of the enantiomers are unequal, which is the type that will be surveyed in the present Review.

In 1969 Williams et al. [13] found that the multiplicity of the spectrum of a 1 : 1 mixture of racemic and optically active *laevo*-dihydroquinine was doubled in an achiral solvent. They felt it necessary, of course, to compare the ^1H n.m.r. spectrum (in deuterochloroform) of the racemic dihydroquinine



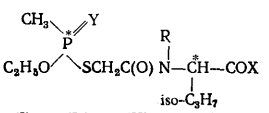
obtained on repeating Rabe's well known multistage synthesis, with the spectrum of natural (−)-dihydroquinine. The comparison showed that the signals from protons 2', 3', 8', and 9 did not coincide but differed by 0.1 − 0.2 ppm. The spectrum of 1 : 1 mixture of racemic and optically active dihydroquinines showed a doubled multiplicity of these signals. The intensity ratio of the components of the doublets was 3 : 1, which corresponded to the concentration ratio of (−)- and (+)-dihydroquinines. The effect

diminished on dilution and on replacement of deuterochloroform by deuteromethanol as solvent, and it decreased substantially when the hydroxy-group was acetylated. These observations were correctly interpreted[13] as evidence that, in a solution of the pure enantiomers, the racemate, and their mixtures, molecules of each individual enantiomer are situated in an identical environment, enantiomeric and diastereomeric respectively.

In a series of publications the Reviewers have reported an analogous phenomenon and a detailed study[15-20] of solutions of compounds containing two chiral centres, of the type $C_2H_5O.\overset{*}{P}O(CH_3).S.CH_2.CO.NH.\overset{*}{C}HR.COOH$. At the same time an axiomatic theory was constructed for the spectra of states of diastereomeric systems that were due to the stereospecificity of interaction of their chiral fragments[21]. One deduction from this theory was the theoretical possibility that the multiplicity of the diastereomeric anisochronism spectra of solutions of enantiomers in an achiral medium would be increased with a non-racemic concentration ratio of the antipodes. The effects studied by Williams et al.[13] indicated that the diastereomeric anisochronism observed in these cases was due to the short lifetime of association complexes of chiral molecules with rapid exchange between the complexes, i.e. with statistical control of the system. The phenomenon of the n.m.r. non-equivalence of enantiomers, occurring in such systems in an achiral medium with rapid averaging due to exchange between association complexes, has been termed *statistically controlled anisochronism of diastereomeric association* (SCADA). This is a physical aspect of statistically controlled diastereomeric association. The experimental and theoretical results of research on the former phenomenon discussed below throw light on interesting features of the latter phenomenon.

II. DIASTEREOMERIC ANISOCHRONISM IN ORGANOTHIOPHOSPHORUS DEPSIPEPTIDES

Studies of mixtures of stereoisomers of *P*-ethoxy-*P*-methylphosphinothioylthiologlycolloylvaline (I), its ethyl ester (II), the corresponding *N*-methylated derivatives (III) and (IV)



Compound	(I)	(II)	(III)	(IV)	(V)	(VI)
Y	S	S	S	S	O	O
R	H	H	CH_3	CH_3	H	H
X	OH	OC_2H_5	OH	OC_2H_5	OH	OC_2H_5

and a few of their simpler analogues[18,19] have revealed several intramolecular factors influencing the occurrence and variation of diastereomeric anisochronism, as well as solvation effects by molecules of a magnetically anisotropic solvent. The results were in general consistent with the views of Mislow and Raban[22], although certain facts required special treatment, e.g. the phenomenon of diastereomeric anisochronism induced by aromatic solvation[17].

In the mixtures of diastereomers investigated in solution in chloroform or benzene diastereomeric anisochronism is evident in a doubling of the multiplicity of the ^1H or ^{31}P n.m.r. spectra. In the latter spectra under conditions of wide-band suppression of spin–spin interactions with protons it is apparent as a well resolved phosphorus doublet. We therefore used $^{31}P-\{^1H\}$ n.m.r. in subsequent investigations. The impetus to a more profound study of diastereomeric anisochronism spectra in these and analogous systems was provided by observation of the unusual influence of the concentration and temperature, and also mixing[7], of solutions of the diastereomers on the $^{31}P-\{^1H\}$ n.m.r. spectra both of compounds (I)–(IV) and especially of their monothio-analogues (V) and (VI).

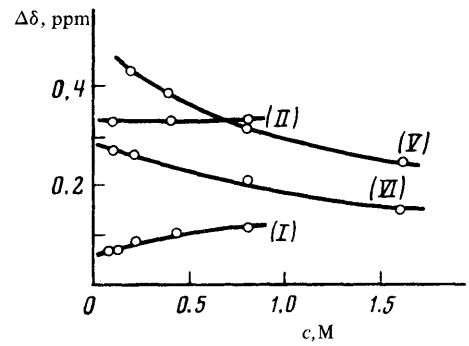


Figure 1. Concentration dependence of diastereomeric anisochronism in $^{31}P-\{^1H\}$ n.m.r. spectra of mixtures of four isomers in chloroform at 20°C (V at 25°C). The numbering of the curves corresponds to that of the compounds in the text.

The molecules of these compounds contain two asymmetric atoms—phosphorus and carbon—so that four stereoisomers—RR, SS, RS, and SR—are possible. Dilution of a chloroform solution of a specimen of the ethyl ester (II) of the dithio-derivative, which was a mixture of all four stereoisomers, had no effect at all on the diastereomeric anisochronism: the difference Δδ in the chemical shifts in the phosphorus doublet remained constant (Fig. 1). For the free acid (I) the difference diminished on dilution, which could easily be explained by the influence[23] of intermolecular hydrogen bonds on the anisochronism: dilution tends to rupture the hydrogen bonds, diminish the rigidity of the system, liberate frozen degrees of freedom, and diminish diastereomeric anisochronism by averaging.

It was found unexpectedly that dilution of solutions of the monothio-derivatives (V) and (VI) (each specimen also a mixture of four stereoisomers) produced increases in diastereomeric anisochronism, respectively strong and less marked, while the difference Δδ increased (Fig. 1). Still more complicated relations were evident with variation in temperature (Fig. 2). The dithio-derivatives (I) and (II) showed a decrease in Δδ with rise in temperature. In solutions of the monothio-derivative (V) and (VI) a rise in temperature from −60 to −45°C was accompanied by decrease in Δδ, but further rise to +50°C by a continuous increase. At about −45°C the difference Δδ became zero (or smaller than the resolving power of the instrument). Since only the absolute value was measured in such an experiment, not the sign of the difference, an alternative

conclusion was that the function increased monotonically with rise in temperature from −60 to +50°C but changed sign at −45°C.[19,20]

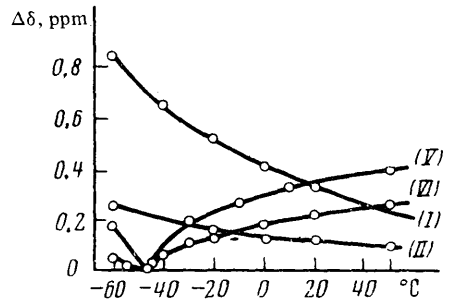


Figure 2. Temperature dependence of diastereomeric anisochronism in $^{31}P-\{^1H\}$ n.m.r. spectra of 0.4 M mixtures of four isomers in chloroform. The numbering of the curves corresponds to that of the compounds in the text.

To understand such complicated relations it is necessary to simplify the test systems consisting of mixtures of four stereoisomers (two racemic diastereomers). This was difficult with dithio-derivatives, since the phosphorus chiral centre arose at the instant of formation of the compound, but the separation of diastereomers and the resolution of racemates were quite complicated tasks. The monothio-derivative (V) provided a more favourable situation: enantiomeric (R and S) monothio-acids of phosphorus are readily available[24], as are also enantiomeric (R and S) chloroacetylvalines[25]; preparation of (V) from them leaves the centres of asymmetry unaffected, and is conducted under conditions under which no racemisation of chiral centres is observed. It thus became possible to obtain in pure form all four stereoisomers of (V) [15]—RR, SS, RS, and SR—and to investigate the $^{31}P-\{^1H\}$ n.m.r. spectra of their chloroform solutions both individually and in mixtures of various relative concentrations.

The value of Δδ calculated as the difference between the chemical shifts in the spectra of solutions of pure diastereomers of (V) taken separately was not identical with the difference in chemical shifts in solutions of mixtures of the same diastereomers at the same total concentration. In the spectra of the stereoisomers SS and SR taken separately the difference Δδ = 0.84 ppm, whereas a mixture of the same total concentration gave Δδ = 0.04 ppm, but mixing the stereoisomers SS and RS separated the signals of the doublet to Δδ = 1.05 ppm.

Furthermore, the spectrum of a mixture of all four stereoisomers in unequal concentrations contains four signals exhibiting intensity ratios equal to the corresponding concentration ratios. Finally, the temperature dependence of the spectrum of an equimolecular mixture of the four stereoisomers differs from that for the stereoisomers taken separately[20]. Fig. 3 illustrates the temperature dependence of the chemical shifts of signals due to the stereoisomers SS and SR of compound (V), together with that of $\Delta\delta = \delta_{SR} - \delta_{SS}$.

The reason for such a difference between individual stereoisomers and their mixtures with respect to the n.m.r. spectra of the solutions could only be interaction between the dissolved molecules. In solvents of low polarity, such as chloroform and tetrachloromethane, indeed, molecules of (V) are strongly associated[26]. The dithio-ester (II) is not associated at all in chloroform, and its n.m.r. spectrum exhibits no anomalous changes on dilution or change in the temperature of the solution.

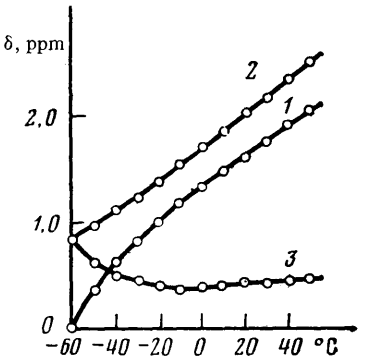


Figure 3. Temperature dependence of chemical shifts of signals from isomers of compound (V) in separate 0.4 M solutions in chloroform: 1) SS; 2) SR; 3) Δδ.

Thus the multiplicity and the frequency spacing of the signals in the diastereomeric anisochronism spectra of stereoisomers depend on association and its stereoselectivity. Hence n.m.r. spectra can be used to study the association of stereoisomers and its stereoselectivity.

III. DIASTEREOMERIC ANISOCHRONISM IN BINARY MIXTURES OF STEREOISOMERS

1. Mixtures of Enantiomers

The Reviewers investigated the n.m.r. spectra of a mixture of enantiomers of *P*-ethoxy-*P*-methylphosphinothioylthiologlycolloylvaline during 1973 and 1974.[15-18] Two fundamentally different types of association complexes of enantiomers—long and short lived—may exist with respect to the n.m.r. time scale. In the former the multiplicity of the diastereomeric anisochronism spectrum should be determined by the number of varieties of such long-lived complexes, and the intensity ratio of the signals by their relative concentrations. It would be completely fortuitous for the multiplicity to be 2 and the intensity ratio equal to the concentration ratio of the enantiomers. The other possibility—formation of short-lived association complexes with rapid exchange between them—represents the above case of statistically controlled diastereomeric association. The multiplicity of the spectrum should then be 2 (provided that the resolving power of the instrument is adequate), and the intensity ratio of the signals in an elementary doublet equal to the concentration ratio of the antipodes[16].

The $^{31}P-\{^1H\}$ n.m.r. spectrum of the enantiomers RR and SS of compound (V) in a 0.4 M solution of chloroform at −60°C contains narrow singlet signals, whose chemical shifts (homo-shifts δ_h) coincide within the limits of experimental error (±0.1 Hz). This signal will henceforward be adopted as reference point, from which other chemical shifts will be reckoned. The n.m.r. spectrum of a racemic mixture (1 : 1) of the same total concentration at the same temperature also contains a single singlet, but its position δ_r differs by 0.35 ppm (13.2 Hz) from the homo-shift δ_h. With the concentration ratio [RR] : [SS] = 7 : 3 two signals are observed, at 0.25 and 0.42 ppm, whose integral intensities are in the ratio 7 : 3. An identical spectrum is observed with the concentration ratio 3 : 7.

Similar relations are observed for the pair of antipodes RS + SR under the same conditions. At −60°C the homo-shift δ_h = 0.84 ppm, but the singlet signal of the racemic mixture is located at 0.46 ppm. Their concentration ratios 7 : 3 and 3 : 7 reveal two identical doublets at 0.38 and 0.59 ppm with the intensity ratio 3 : 7. Analogous relations are found at other temperatures. The following qualitative conclusions can be drawn from the data in Table 1.

Table 1. Chemical shifts of signals in spectra of mixtures of enantiomers of compound (V) in 0.4 M solution in chloroform (I_{rel} = relative integral intensity)*.

c_1	δ, ppm	I_{rel}	t, °C											
			−60	−50	−40	−30	−20	−10	0	10	20	30	40	50
SS+RR														
1.00	δ_h	1	0	0	0	0	0	0	0	—	—	—	—	—
0.50	δ_r	1	0.35	0.20	0.13	0.10	0.05	0.03	0	—	—	—	—	—
0.30	δ_{SS}	0.3	0.42	0.24	0.17	0.12	0.08	0.05	0.02	—	—	—	—	—
0.30	δ_{RR}	0.7	0.25	0.13	0.09	0.06	0.03	0	0	—	—	—	—	—
SR+RS														
1.00	δ_h	1	0.84	0.61	0.50	0.44	0.39	0.36	0.39	0.40	0.43	0.44	0.45	0.46
0.50	δ_r	1	0.46	0.21	0.10	0.03	0.07	0.13	0.18	0.22	0.26	0.32	0.36	0.41
0.30	δ_{SR}	0.3	0.38	0.10	0.00	−0.05	−0.03	0.03	0.08	0.16	0.26	0.30	0.33	0.36
0.30	δ_{RS}	0.7	0.59	0.34	0.23	0.18	0.19	0.22	0.26	0.30	0.32	0.36	0.38	0.43

*The antipodes RR and RS have signals identical with those of SS or SR in a racemic mixture and in the pure state. The quantity

$$c_1 = [SS]/([SS]+[RR]) \text{ or } c_1 = [SR]/([SR]+[RS]).$$

The homo-signal of SS molecules at the given temperature has been adopted as reference signal.

1. Narrow singlet signals are observed in solutions of individual enantiomers. Since every molecule in an association complex is surrounded solely by identical molecules, and rapid exchange takes place between complexes, local fields induced at the indicator nucleus (in the present case phosphorus) are completely averaged out, regardless of the number and stability of the various complexes. Hence the signal is a narrow singlet. Since the magnetic field is achiral, the signals of antipodes, are, of course, identical.

2. In a solution of a racemic mixture the molecules of each enantiomer are surrounded both by identical and by antipodal molecules. Homo- and cross-association may be thermodynamically either equivalent or non-equivalent. With rapid exchange between complexes the statistics of exchange results in contamination of homo-interactions by cross-interactions at each enantiomer. This changes the resultant local field at the indicator nucleus of the enantiomer molecule and hence the chemical shift of the n.m.r. signal. Since the situations for the two enantiomers have a mirror-image relation, the chemical shifts of their signals are identical, and they merge into a single signal δ_r differing from δ_h. This difference, which is termed the *deviation* $D = \delta_r - \delta_h$, is a characteristic feature of SCADA.

3. When the concentration of antipodes in the solution are unequal, they exhibit different extents of contamination of homo- by cross-interactions: if homo-association predominates at one antipode, cross-association predominates at the other. The situations are not now those of mirrow-images, and a doublet appears in the spectrum, in which the intensity ratio of the components is equal to the concentration ratio of the antipodes.

In calculating the specific form of dependence of the signals of (+)- and (−)-enantiomers, i.e. δ^+ and δ^-, on the relative concentration of the enantiomers in the mixture we must take into account the statistical averaging, with rapid exchange between complexes, of the effects of homo- and cross-interactions on the shielding of the indicator nuclei in the molecules of the antipodes. If W_+^+ is the statistical weight of the contribution to δ^+ by homo-interaction, W_+^- is that of cross-interaction, and correspondingly W_-^- and W_-^+ are the statistical weights of the contributions to δ^- by homo- and cross-interactions, the chemical shifts of the signals due to (+)- and (−)-molecules are given by the formulae

$$\delta^+ = (W_+^+\delta_h + W_+^-\delta_c)/(W_+^+ + W_+^-), \quad (1)$$

$$\delta^- = (W_-^-\delta_h + W_-^+\delta_c)/(W_-^- + W_-^+) \quad (2)$$

in which δ_h is the homo-shift, identical for the two antipodes, and δ_c the cross-shift [also identical for (+)- and (−)-molecules].

The statistical weights of the contributions by homo- and cross-interactions are determined, of course, by two factors: the relative content of antipodal molecules in the mixture can be expressed as $c = [+]/([+]+[-])$; and the stability characteristics of homo- and cross-contacts can be represented by the functions of homo- and cross-interaction energies

$$\alpha_h = A_h \exp(-E_h/kT), \quad (3)$$

$$\alpha_c = A_c \exp(-E_c/kT). \quad (4)$$

The condition of rapid exchange between association complexes is indicated by the equations

$$\alpha_h = \langle\alpha_h\rangle,\ \alpha_c = \langle\alpha_c\rangle,\ \delta_h = \langle\delta_h\rangle,\ \delta_c = \langle\delta_c\rangle, \quad (5)$$

where the symbol $\langle\rangle$ denotes averaging over all types of association complexes containing the given interaction. We can then write

$$W_+^+ = \alpha_h c,\ W_+^- = \alpha_c(1-c),\ W_-^- = \alpha_h(1-c),\ W_-^+ = \alpha_c c. \quad (6)$$

Since experimental data do not yield values of the parameters α_c and α_h but only their ratio $\alpha_c/\alpha_h = m$ representing the stereospecificity of association of the antipodes, Eqns. (1) and (2) can be finally written

$$\delta^+ = [c\delta_h + m(1-c)\delta_c]/[c + m(1-c)], \quad (7)$$

$$\delta^- = [(1-c)\delta_h + mc\,\delta_c]/[(1-c) + mc]. \quad (8)$$

Inspection of formulae (7) and (8) indicates that both extrema and points of inflection are absent from both δ^+-c and δ^--c curves throughout the concentration range. When $c = 0$, we find that $\delta^+ = \delta_C$ and $\delta^- = \delta_H$; and when $c = 1$, that $\delta^+ = \delta_H$ and $\delta^- = \delta_C$; in both cases only one signal is observed, since δ_C cannot be observed. When $c = 0.5$, i.e. in a racemic mixture,

$$\delta^+ = \delta^- = (\delta_h + m\delta_c)/(1 + m), \qquad (9)$$

and one signal is also observed, which is displaced by the deviation relative to the homo-signal. At all other concentrations two signals should be observed. Since each belongs to a definite antipode, the ratio of the integral intensities of these signals should be $c/(1 - c)$.

For both functions $\delta^+(c)$ and $\delta^-(c)$ the curvature depends on m, i.e. on the stereospecificity of homo- and cross-interactions. If $m = 1$ (i.e. $\alpha_C = \alpha_H$), the relations become linear:

$$\delta^+ = \delta_c - (\delta_c - \delta_h)c, \qquad (10)$$

$$\delta^- = \delta_h + (\delta_c - \delta_h)c. \qquad (11)$$

However, the main characteristics of the phenomenon are preserved: the spectrum contains one signal when c is 0, 1, or 0.5, and two signals at all other relative concentrations. This is a very important conclusion: the appearance of two signals in the n.m.r. spectrum of a mixture of unequal concentrations of antipodes is not a consequence of stereoselectivity of association (e.g. a tendency to racemate formation) but is caused by SCADA itself.

Table 2. SCADA parameters of the enantiomeric pairs SS + RR and SR + RS of compound (V) in 0.4 M solution in chloroform*.

t, °C	−60	−50	−40	−30	−20	−60	−50	−40	−30	−20
	SS+RR					SR+RS				
δ_c	0,50	0.31	0.22	0.17	0.10	0.26	−0.07	−0.18	−0.20	−0.21
α_c/α_h	2.4	1.7	1.4	1.2	1.0	1.8	1.7	1.6	1.4	1.2

*The reference signal adopted was δ_{SS} at the given temperature.

If δ_H is adopted as reference signal, Eqns. (7) and (8) permit a simple linear transformation giving the formulae

$$\frac{1}{\delta^+} = \frac{1}{\delta_c} + \frac{1}{m\delta_c}\cdot\frac{c}{1-c}, \qquad (12)$$

$$\frac{1}{\delta^-} = \frac{1}{\delta_c} + \frac{1}{m\delta_c}\cdot\frac{(1-c)}{c} \qquad (13)$$

which were used to treat the experimental data in Table 1. The parameters δ_C and

$$m_{SS}^{RR} = \alpha_{SS}^{RR}/\alpha_{SS}^{SS},\ m_{SR}^{RS} = \alpha_{SR}^{RS}/\alpha_{SR}^{SR}. \qquad (14)$$

were found for each temperature, where the subscript denotes the stereoisomer whose signal is under consideration, and the superscript the stereoisomer that interacts with it in the association complex. Together with experimental values of δ_C these parameters give a complete description of the diastereomeric anisochronism spectra.

Table 2 gives the SCADA parameters, which were used in Eqns. (7) and (8) to calculate the curves in Fig. 4. Good agreement is evident between calculation and experiment.

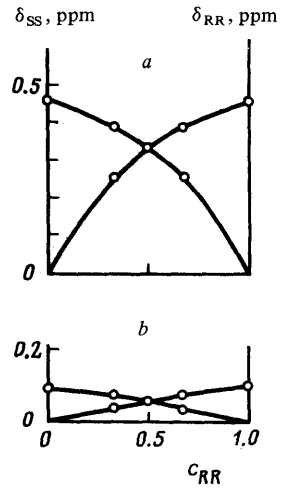


Figure 4. Dependence of chemical shifts of signals from SS and RR enantiomers of compound (V) on relative concentration of RR isomer at different temperatures: *a*) −60°C; *b*) −20°C. The curves have been obtained theoretically; the points on them represent experimental values. Each curve was reckoned from the homo-shift at the given temperature.

From the results the interesting conclusions can be drawn that for the RS + SR system the non-equivalence of shielding of the phosphorus atom in homo- and cross-complexes, i.e. $\delta_C - \delta_H$, varies comparatively slowly with rise in temperature from −60 to +50°C, while the stereoselectivity of association (the difference between m and unity) vanishes at ~0°C. In the RR + SS system both the non-equivalence of shielding and the stereoselectivity of association disappear rapidly with rise in temperature, and above 0°C the SCADA phenomenon is completely absent from the n.m.r. spectra: a single singlet signal is observed at any relative concentration of antipodes in the mixture. Thus conditions depending on the structure of the enantiomers and the thermodynamic characteristics of the system must be satisfied for SCADA to be observed in the n.m.r. spectra; otherwise the magnitude of the phenomenon in the n.m.r. will become smaller than the resolving power of the instrument. This is evidently the reason for the fewness of published examples of SCADA.

The energy difference between averaged cross- and homo-contacts in association complexes can be elucidated from the temperature dependence of α_C/α_H. Thus if

$$\alpha_c = A_c e^{-E_c'/RT} \qquad \alpha_h = A_h e^{-E_h/RT},$$

we have

$$\lg(\alpha_c/\alpha_h) = \lg(A_c/A_h) + (E_h - E_c)/2.3RT.$$

A linear plot of $\lg(\alpha_C/\alpha_H)$ against $1/T$ should be observed, with a slope

$$\tan\alpha = (E_h - E_c)/2.3R,$$

whence $E_h - E_c$ can be calculated. Such linear relations are indeed found. For the pair SS + RR the difference $E_h - E_c \simeq 2$ kcal mole^{-1}, whereas the difference is ~1 kcal mole^{-1} for SR + RS. In both cases cross-interaction is appreciably more effective than homo-interaction[19,20].

A very interesting paper by Horeau and Guette[1] appeared at almost the same time as the publications by Soviet workers. As mentioned above, Horeau had earlier made a systematic study of the optical and enantiomeric purity of enantiomers. This was why he investigated the interaction of antipodes in solution and the effect of this interaction on physical constants. It has also been mentioned above that in 1969 departures from additivity were found for the angle of rotation of the plane of polarisation by solutions of a mixture of the enantiomers of α-ethyl-α-methylsuccinic acid[6]. Horeau and Guette found that such departure was still more strongly marked for solutions of the enantiomers of α-isopropyl-α-methylsuccinic acid HC.CO.C(CH_3)(iso-C_3H_7).CH_2.COOH in chloroform or dichloromethane.

When discussing this result, the authors[1] refer to the work of Jurczak and Zamojski[27], who observed that the rotatory power of dimethyl malate in methanol was not a linear function of the enantiomeric composition. However, Horeau and Guette were working in non-polar solvents—chloroform and dichloromethane—and the use of methanol, ethanol, pyridine, diglyme, and acetonitrile completely depresses the non-linearity effect. Even additions of 4–6% of ethanol to chloroform were sufficient for the dependence of optical purity on enantiomeric composition to be linear. Hence it was concluded[1] that the divergence from a linear dependence of the rotatory power of a mixture of enantiomers on enantiomeric composition was due to differences in stability between diastereomeric association complexes of the antipodal molecules in the solution, so that the phenomenon could be observed only in non-ionising solvents. However, this does not extend to stable complexes, which may give deviations even in aqueous solution. Thus in the presence of ammonium molybdate $(NH_4)_6Mo_7O_{24}.4H_2O$ a solution of (+)-mandelic acid has an angle of rotation $[\alpha_0]_D^{22} = +45.6°$. For a mixture of 75% of the dextrorotatory acid and 25% of the laevorotatory acid $[\alpha]_D^{22} = -19°$. This value requires for the pure enantiomer an angle of rotation $[\alpha_E]^{22} = +38°$, instead of the observed +45.6°: i.e. non-linearity is apparent.

Table 3. Diastereomeric anisochronism in associated solutions of α-ethyl-α-methylsuccinic acid.

Substance	δ_A, Hz	$\Delta\delta_A$, Hz	δ_B, Hz	$\Delta\delta_B$, Hz	J_{AB}, Hz
Optically pure enantiomer	251.4	0	234.9	0	16.5
Mixture of antipodes (75:25)	250.4	1.0	233.5	1.4	16.9
	247.7	3.7	230.5	4.4	17.2
Racemate	248.9	2.5	231.9	3.0	17.0

However, intermolecular interactions of antipodes are most clearly indicated by results obtained by Horeau and Guette[1] in a study of the ^{1}H n.m.r. spectra of the above acids. These workers investigated the spectra of solutions of α-ethyl-α-methylsuccinic acid in deuterochloroform at a working frequency of 100 MHz. The protons of the methylene group give two doublets characteristic of an AB system. The magnetic non-equivalence of the two antipodes does not affect the doublet in a strong field. Table 3 gives chemical shifts and spin–spin interaction constants for the doublet in a weak field. The racemate differs appreciably in chemical shifts (by 2.5–3.0 Hz) from the optically pure enantiomers, but two signals appear in a non-equimolecular mixture of antipodes. An appreciable though smaller difference is observed for the spin–spin interaction constants. Similar results were obtained for α-isopropyl-α-methylsuccinic acid. The authors[1] interpret their findings as evidence of differences in the stability of diastereomeric interactions of enantiomers in solution.

In order to demonstrate energy differences between D...L and D...D or L...L interactions a calorimetric investigation was made[1] of solutions of enantiomers of α-ethyl(isopropyl)-α-methylsuccinic acids, and heats of mixing of antipodes at 25°C were found to be respectivelv 33.5 and 50 cal mole^{-1}. It is significant that the interaction of antipodal molecules is more advantageous energetically than is the interaction of identical molecules (this contradicts deductions made by other workers[2,3]).

Table 4. Treatment of experimental results[1,13] by means of Eqns. (12) and (13).

Enantiomers	Signal	$\delta_c - \delta_h$, Hz	α_c/α_h
Dihydroquinine α-Ethyl-α-methyl-succinic acid	H (9)	40	1.0
	δ_A	−4.6	1.0
	δ_B	−5.7	1.0

As has been shown above, diastereomeric anisochronism can be observed in solutions of enantiomers even in the absence of energy differences between homo- and cross-interactions. The appearance of an elementary diastereomeric doublet in the spectra of solutions of unequal concentrations of antipodes is due to non-equivalence of the stereochemical environment of antipodal molecules under conditions of statistical control with rapid exchange between association complexes. This non-equivalence is caused by the unequal concentration of the antipodes. It depends also, of course, on the energy parameters of association, but may arise even with equal parameters for identical and diastereomeric contacts. In this sense the conclusions of Horeau and Guette need to be refined. Equations (7) and (8) can be used to treat the experimental results for dihydroquinine[13] and α-ethyl-α-methylsuccinic acid[1]. Unfortunately, the results obtained by Williams et al.[13] are very incomplete: the authors note that the signals of aromatic protons are extremely sensitive to change in the total concentration, and coalesce on dilution. Data on the chemical shifts in the signals of 9-H protons are more reliable, their position depending mainly on the relative concentration of the antipodes. Linear plots of δ against c are obtained: i.e. stereoselectivity of association is absent. Parameters calculated by means of Eqns. (12) and (13) are listed in Table 4. Good linearity is observed also for the results of Horeau and Guette[1]. For the enantiomers of α-ethyl-α-methylsuccinic acid $m = 1$, which also supports the view that stereospecificity of association is either absent or very slight.

Thus no appreciable preference for homo- or cross-association of enantiomers is evident in solutions of dihydroquinine and of α-ethyl-α-methylsuccinic acid. In the *P*-ethoxy-*P*-methylphosphinylthiologlycolloylvalines investigated by Soviet workers cross-association, i.e. racemisation, occurs preferentially [15].

Table 5.

Amide	A	A	B	C
t,°C	15	26	15	15
δ_c	1.41	1.60	1.54	1.62
m	0.21	0.33	0.35	1.0

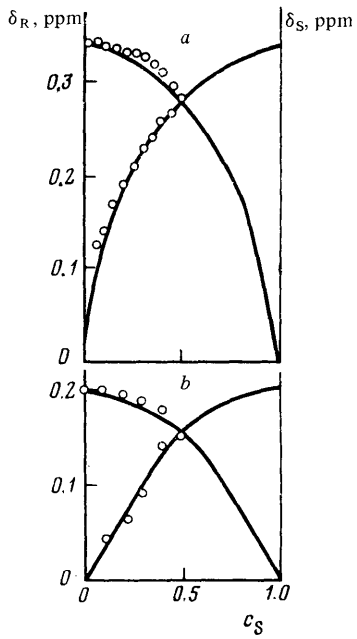
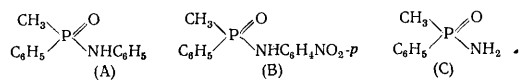
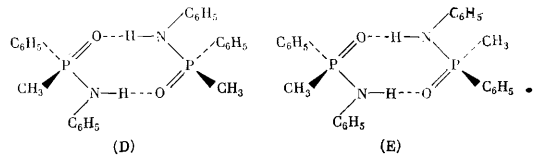


Figure 5. SCADA in deuterochloroform solution of *P*-methyl-*NP*-diphenylphosphinamide (A) at: *a*) 15°C; *b*) −26°C. The curves have been calculated theoretically; and the points represent experimental values.

Harger [28] has investigated the ^{1}H n.m.r. spectra of amides of methylphenylphosphinic acid—the phenylamide (A), *p*-nitrophenylamide (B), and unsubstituted amide (C)



Deviation of the chemical shift for the racemic mixture of antipodes and doubling of the multiplicity of the doublet signals of *P*-methyl protons with unequal concentrations of enantiomers were observed in all cases in deuterochloroform solution. Citing Refs. 1, 13, and 15–20, Harger gives a qualitative treatment of his results that follows completely from our views. In his opinion [28] the magnetic non-equivalence of the indicator nucleus in the enantiomer molecules with statistical non-equivalence of homo- and cross-contacts and rapid exchange between complexes underlie the observed phenomenon. From infrared spectral data Harger refines the character of the diastereomeric association complexes as the dimeric



Although he gives only qualitative consideration to his results, his numerical data are susceptible to a quantitative treatment based on formulae (7) and (8). Table 5 gives values that the Reviewers have thus calculated for the SCADA parameters in the n.m.r. spectra of the phosphinamides. The curves in Fig. 5 have been calculated theoretically by the Reviewers, whereas the points have been taken from Harger's experiments [28]. It is obvious that he had investigated a typical SCADA phenomenon, with $m = \alpha_c/\alpha_h < 1$ in all cases other than the last, so that homo-association had occurred preferentially.

2. Mixtures of Epimers

Equations (1) and (2) do not involve any restrictions on the stereochemical relations of the mixture components. Equations (7) and (8), on the other hand, are applicable to mixtures only of enantiomers. If the components i and j are not antipodes but diastereomers, formulae (7) and (8) should be replaced by the more general [19,20]

$$\delta_i = \frac{\alpha_i^i c_i \delta_i^i + \alpha_i^j (1-c_i)\,\delta_i^j}{\alpha_i^i c_i + \alpha_i^j (1-c_i)}, \qquad (15)$$

$$\delta_j = \frac{\alpha_j^j (1-c_i)\,\delta_j^j + \alpha_j^i c_i \delta_j^i}{\alpha_j^j (1-c_i) + \alpha_j^i c_i} \qquad (16)$$

in which the concentrations c_i and c_j have been normalised to unity and the subscript corresponds to the isomer whose signal is under consideration, while the superscript denotes the isomer with which it interacts in the association complexes. Thus α_i^i, α_j^j and α_i^j, α_j^i are association stability characteristics; the latter two, of course, are the same for the two epimers: i.e. $\alpha_i^j = \alpha_j^i$. The chemical shifts δ_i^i and δ_j^j are homo-shifts; when $c = 1$ and $c = 0$, they equal respectively δ_i or δ_j. These shifts are unequal; furthermore $\delta_i^j \neq \delta_j^i$. In the case of enantiomers we have

$$\alpha_i^i = \alpha_j^j = \alpha_h; \quad \alpha_i^j = \alpha_j^i = \alpha_c,$$
$$\delta_i^i = \delta_j^j = \delta_h; \quad \delta_i^j = \delta_j^i = \delta_c.$$

The ^{31}P–{^{1}H} n.m.r. spectra of mixtures of epimers SS + SR and SS + RS of compound (V) were investigated. Their mirror-image mixtures RR + RS and RR + SR were enlisted only to determine the error in the measurements. Table 6 gives experimental values obtained at various relative concentrations of the epimers and of the mixture and at various temperatures. Treatment by means of formulae (15) and (16) [20] yielded all the parameters of the diastereomeric anisochronism spectra of the systems (Table 7). They are identical, of course, with the parameters of the corresponding mirror-antipodal pairs RR + RS

and RR + SR. These parameters carry all the information on the influence of association on the n.m.r. spectra of binary mixtures of the diastereomers. In contrast to mixtures of enantiomers, the signals of epimers at equal concentrations naturally do not merge into one, and two signals are observed throughout the range of relative concentrations.

Table 6. Chemical shift of signals in $^{31}P-\{^1H\}$ n.m.r. spectrum of mixtures of epimers of (V) with c = 0.4 M in chloroform (I_{rel} is the relative integral intensity and $c_1 = [SS]/([SS] + [SR])$ or $c_1 = [SS]/([SS] + [RS])$

c_1	δ, ppm	I_{rel}	t, °C											
			−60	−50	−40	−30	−20	−10	0	10	20	30	40	50
							SS+SR							
0.7	δ_{SS}	0.7	0.33	0.22	0.14	0.09	0.05	0.03	0.02	0	0	0	0	0
	δ_{SR}	0.3	0.48	0.25	0.13	0.13	0.13	0.15	0.17	0.20	0.23	0.26	0.31	0.33
0.5	δ_{SS}	0.5	0.50	0.26	0.24	0.17	0.12	0.08	0.05	0.03	0	0	0	0
	δ_{SR}	0.5	0.54	0.30	0.18	0.16	0.17	0.20	0.26	0.26	0.30	0.32	0.35	0.39
0.3	δ_{SS}	0.3	0.61	0.45	0.35	0.27	0.17	0.13	0.09	0.06	0.03	0.01	0	0
	δ_{SR}	0.7	0.62	0.36	0.23	0.24	0.22	0.24	0.26	0.30	0.32	0.35	0.37	0.39
							SS+RS							
0.7	δ_{SS}	0.7	−0.22	−0.15	−0.09	−0.05	−0.04	−0.01	0	0	0	0	0	0
	δ_{RS}	0.3	0.70	0.42	0.30	0.25	0.24	0.26	0.27	0.29	0.32	0.35	0.38	0.41
0.5	δ_{SS}	0.5	−0.30	−0.22	−0.15	−0.08	−0.06	−0.04	0	0	0	0	0	0
	δ_{RS}	0.5	0.73	0.44	0.35	0.28	0.26	0.27	0.29	0.31	0.33	0.34	0.37	0.41
0.3	δ_{SS}	0.3	−0.36	−0.26	−0.18	−0.12	−0.08	−0.06	−0.03	0	0	0	0	0
	δ_{RS}	0.7	0.75	0.50	0.39	0.31	0.30	0.33	0.34	0.37	0.39	0.41	0.41	0.41

*The reference signal adopted was δ SS at the given temperature.

Table 7. SCADA parameters for binary mixtures of epimers SS + SR and SS + RS of (V) in 0.4 M solution in chloroform at various temperatures.

t, °C	−60	−50	−40	−30	−20
δ_{SS}^{SR}	0.77	0.61	0.52	0.49	0.55
δ_{SS}^{RS}	−0.41	−0.31	−0.24	−0.16	−0.10
δ_{SR}^{RR}	0.69	0.39	0.27	0.21	0.19
δ_{SR}^{SS}	0.44	0.21	0.09	0.07	0.07
$\alpha_{SS}^{SR}/\alpha_{SS}^{SS}$	1.8	1.3	0.8	0.5	0.2
$\alpha_{SS}^{RS}/\alpha_{SS}^{SS}$	2.6	2.0	1.3	1.0	1.0
$\alpha_{SR}^{RR}/\alpha_{SR}^{SR}$	3.3	2.7	2.0	2.1	1.6
$\alpha_{SR}^{SS}/\alpha_{SR}^{SR}$	3.0	3.4	3.6	2.4	1.8

Figs. 6–9 contain theoretical curves representing the dependence of the parameters of the diastereomeric anisochronism spectrum for the mixtures of epimers SS + RS and SS + SR at various temperatures. Good agreement is evident between calculated and observed values.

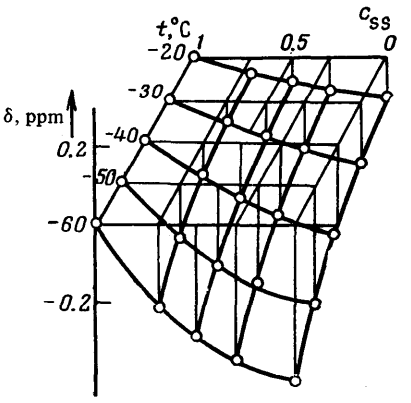


Figure 6. Dependence of chemical shifts in signals from SS isomer of (V) mixed with RS isomer in 0.4 M solution in chloroform on relative concentration at various temperatures. Each curve has been reckoned from the homoshift of the signal from SS molecules at the given temperature. The curves have been obtained theoretically, and the points represent experimental values.

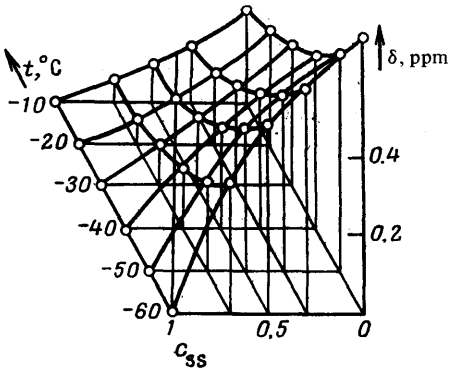


Figure 7. Dependence of chemical shifts in signals from SS isomer of (V) mixed with SR isomer in 0.4 M solution in chloroform on relative concentration at various temperatures. Each curve has been reckoned from the homoshift δ SS at the given temperature. The curves have been obtained theoretically, and the points represent experimental values.

IV. DIASTEREOMERIC ANISOCHRONISM SPECTRA OF MORE COMPLICATED SYSTEMS

1. General Survey[19,20]

A general discussion of diastereomeric anisochronism spectra in terms of a plurality of theoretical ideas has shown[21] that the multiplicity of the spectra for mixtures of stereoisomers having n chiral fragments may equal the number of antipodal pairs 2^{n-1}, but cannot be less than or

greater than this value. The multiplicity of such a spectrum of a mixture of stereoisomers may be increased if the asymmetrisation operators corresponding to the stereoisomers are non-degenerate and have mirror non-invariance. In achiral media with statistically controlled association, i.e. with rapid exchange between complexes, the multiplicity of the spectrum of a mixture of stereoisomers having n chiral centres may increase to 2^n, since under these conditions each stereoisomer has its own signal averaged over all association complexes of various compositions. If an achiral solvent contains a mixture of optical isomers containing N different components, the chemical shift of a nucleus in the ith component under SCADA conditions can be expressed by the formula

$$\delta_i = \left(\sum_{j=1}^{N} W_i^j \delta_i^j\right) \Big/ \sum_{j=1}^{N} W_i^j. \qquad (17)$$

where δ_i^j is the chemical shift of a nucleus in the ith component in a primary interaction with the jth component and W_i^j is the statistical weight of the contribution to δ_i by this chemical shift, both parameters being averaged over all types of association complexes in which the ij interaction occurs, so that $\delta_i^j = \langle \delta_i^j \rangle$ and $W_i^j = \langle W_i^j \rangle$. As in the discussion of binary systems, it may be supposed that the statistical contribution of the interaction δ_i^j to δ_i is determined by the relative concentration

$$c_j = [j] \Big/ \sum_{j=1}^{N} [j]:$$

and the stability of the pair contacts α_i^j

$$W_i^j = \alpha_i^j c_j. \qquad (18)$$

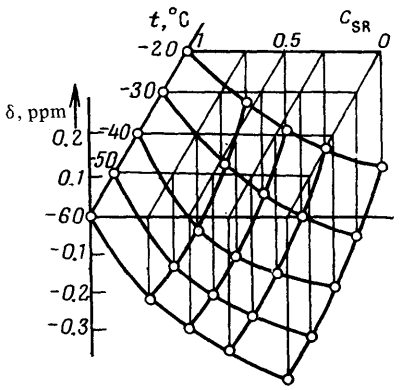


Figure 8. Dependence of chemical shifts in signals from SR isomer of (V) mixed with SS isomer in 0.4 M solution in chloroform on relative concentration of SR molecules at various temperatures. Each curve has been reckoned from the homo-shift δ_{SR} at the given temperature. The curves have been obtained theoretically, and the points represent experimental values.

Thus the chemical shift of the indicator nucleus in the ith component is given by

$$\delta_i = \left(\sum_{j=1}^{N} \alpha_i^j c_j \delta_i^j\right) \Big/ \sum_{j=1}^{N} \alpha_i^j c_j, \qquad (19)$$

and the relative integral intensity of this signal by

$$I_i = [i] / \sum_{j=1}^{N} [j]. \qquad (20)$$

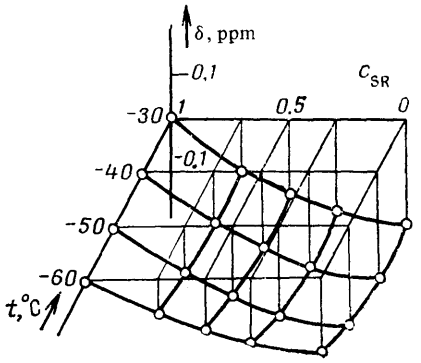


Figure 9. Dependence of chemical shifts in signals from SR isomer of (V) mixed with RR isomer [in 0.4 M solution in chloroform] on relative concentration at various temperatures. Each curve has been reckoned from the homo-shift δ_{SR} at the given temperature. The curves have been obtained theoretically, and the points represent experimental values.

The deduction of formulae (17) and (19) took into account the statistical contribution by pair contacts ij with rapid exchange between association complexes. More complicated contacts of the type ijq can in principle also be taken into consideration, when

$$\delta_i^j = \left(\sum_{q=1}^{N} W_{ij}^q \delta_{ij}^q\right) \Big/ \sum_{q=1}^{N} W_{ij}^q. \qquad (21)$$

This formula covers long-range interactions, since components i and q are not in direct contact. Construction of a statistical theory for such systems of a second order of complexity gives rise to no fundamental difficulties, but the need for such complication can be ascertained only experimentally. It has been shown above that good agreement between calculated and observed chemical shifts of the diastereomeric anisochronism spectrum in binary systems is achieved with calculations based on formulae (15) and (16), or on Eqns. (7) and (8) for a mixture of enantiomers, in which only direct pair contacts are considered. We shall show below that a quaternary system can be completely analysed in terms of formula (19).

2. Four-component Systems [19,20]

For a mixture of four stereoisomers having two chiral centres we can apply Eqn. (19) to the chemical shift of phosphorus in each stereoisomer. With $N = 4$ the total

number of α_i^j and δ_j^i parameters is 32, which are given in the two quadratic matrices

$$\begin{pmatrix} \alpha_{RR}^{RR} & \alpha_{RR}^{SS} & \alpha_{RR}^{RS} & \alpha_{RR}^{SR} \\ \alpha_{SS}^{RR} & \alpha_{SS}^{SS} & \alpha_{SS}^{RS} & \alpha_{SS}^{SR} \\ \alpha_{RS}^{RR} & \alpha_{RS}^{SS} & \alpha_{RS}^{RS} & \alpha_{RS}^{SR} \\ \alpha_{SR}^{RR} & \alpha_{SR}^{SS} & \alpha_{SR}^{RS} & \alpha_{SR}^{SR} \end{pmatrix} \quad \begin{pmatrix} \delta_{RR}^{RR} & \delta_{RR}^{SS} & \delta_{RR}^{RS} & \delta_{RR}^{SR} \\ \delta_{SS}^{RR} & \delta_{SS}^{SS} & \delta_{SS}^{RS} & \delta_{SS}^{SR} \\ \delta_{RS}^{RR} & \delta_{RS}^{SS} & \delta_{RS}^{RS} & \delta_{RS}^{SR} \\ \delta_{SR}^{RR} & \delta_{SR}^{SS} & \delta_{SR}^{RS} & \delta_{SR}^{SR} \end{pmatrix}$$

where the rows correspond to stereoisomers whose chemical shifts are under consideration (subscripts), and the columns to stereoisomers that interact with the former in elementary pair contacts. The right-hand matrix contains parameters describing the fields induced at the indicator nucleus in the association complexes, and the left-hand matrix parameters representing the stereospecificity of pair contacts in the complexes. With the use of these parameters formula (19) can be written for the chemical shift δ_i of each stereoisomer in the form

$$\delta_i = \frac{\alpha_i^{SS} c_{SS} \delta_i^{SS} + \alpha_i^{RR} c_{RR} \delta_i^{RR} + \alpha_i^{RS} c_{RS} \delta_i^{RS} + \alpha_i^{SR} c_{SR} \delta_i^{SR}}{\alpha_i^{SS} c_{SS} + \alpha_i^{RR} c_{RR} + \alpha_i^{RS} c_{RS} + \alpha_i^{SR} c_{SR}}, \quad (22)-(25)$$

in which the subscript i denotes respectively SS, RR, RS, and SR. When symmetry is taken into account, the number of independent parameters in these formulae is greatly diminished. Thus the parameters δ_i^j become equal when both partners in an interaction are replaced by mirror-image antipodes, and the number of such independent parameters decreases to 8. This applies also to the α_i^j parameters, but in this case we also have $\alpha_j^i = \alpha_i^j$, so that the number of these independent parameters diminishes to 6. Each set of 14 parameters corresponds, of course, to given selected conditions of the n.m.r. experiment (solvent, total concentration, temperature).

Table 8. Calculated chemical shifts of signals from stereoisomers SS and SR (or RR and RS) of (V) in a mixture of four isomers in 0.4 M solution in chloroform*.

t, °C	−60	−50	−40	−30	−20	−10	0	10	20	30	40	50
δ_{SS}	0.24	0.13	0.07	0.02	0	0	0	0	0	0	0	0
δ_{SR}	0.46	0.23	0.15	0.17	0.22	0.28	0.31	0.34	0.37	0.39	0.40	0.41
$\delta_{SR}-\delta_{SS}$	0.22	0.10	0.08	0.15	0.22	0.28	0.31	0.34	0.37	0.39	0.40	0.41
$\Delta\delta_{exp}$	0.19	0.09	0.08	0.17	0.24	0.29	0.31	0.34	0.37	0.38	0.39	0.41

*The homo-shift δ_{SS} at the given temperature was adopted as reference signal.

With an instrument of sufficiently high resolving power and with unequal relative concentrations of the four stereoisomers, the diastereomeric anisochronism spectrum should in general contain four signals with different chemical shifts δ_{SS}, δ_{RR}, δ_{RS}, and δ_{SR}. The relative intensities of the components of this quadruplet should be equal to the relative concentrations of the corresponding stereoisomers. If the stereoisomers are present in equal concentrations in the mixture, it is readily seen that the chemical shifts of the enantiomers RR and SS, and also of RS and SR, will become equal, their signals will coalesce, and the spectrum will contain two signals of equal intensity. This has been observed experimentally [20].

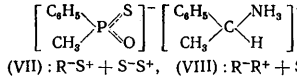
All the fourteen parameters required for the calculation had been determined earlier [20] in experiments on binary systems (Table 2 and 7). Values of $\delta_{SS} = \delta_{RR}$ and $\delta_{SR} = \delta_{RS}$ were calculated for various temperatures (Table 8). It is seen that $\Delta\delta$ actually passes through a minimum at −45°C, as illustrated by Fig. 2 (curve *V*). Agreement is observed between calculated and experimental values of $\Delta\delta$.

The molecules of quinine alkaloids contain four asymmetric carbon atoms, at positions 3, 4, 8, and 9. In natural (−)-dihydroquinine the centres at 3 and 4 have the (+) configuration, while 8 and 9 have the (−) configuration. The synthetic racemate, of course, has (±) at all centres. In general, therefore, a mixture of (−)-dihydroquinine and racemic dihydroquinine must be expected to exhibit a maximum of sixteen signals instead of the single signal of a given indicator nucleus. The fact that only two signals appear indicates that all centres of asymmetry other than one have little effect. It is most probably the chiral atom at position 9 that exerts this dominant effect.

3. Four-component Systems with Ion Exchange

An important part in experimental stereochemical investigations is played by the n.m.r. spectra of salts containing chiral cations and anions. Since Pasteur's time such salts have been used for resolving racemates. Their n.m.r. spectra have been widely applied during recent years to determine the optical purity of enantiomers, absolute configurations [9,29], etc. It is therefore important to know how the diastereomeric anisochronism spectrum of a mixture of enantiomeric or diastereomeric salts is formed, and to what extent the n.m.r. criterion is appropriate for solving the above problems.

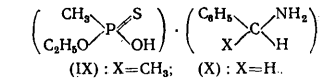
The dependence of the chemical shifts in the n.m.r. spectra of a mixture of the salts (VII) and (VIII)



(VII) : $R^-S^+ + S^-S^+$, (VIII) : $R^-R^+ + S^-S^+$.

on the enantiomeric composition was investigated by Mikolajczyk et al. [30] Here R and S denote the absolute configurations of the cations (R^+ and S^+) and the anions (R^- and S^-). The difference $\Delta\delta$ between the chemical shifts of the *P*-methyl protons were found to vary linearly with the relative concentration of the SS isomer over the range 27–78 mole % of one of the enantiomers.

Shipov et al. investigated [31] the $^{31}P-\{^1H\}$ n.m.r. spectra of salts (IX) of enantiomeric ethyl hydrogen phosphonothionates (R and S) with 1-phenylethylamine (R and S)



(IX) : X=CH_3; (X) : X=H.

at constant total concentrations 0.5 M and 1.0 M in a 1 : 1 mixture of chloroform and deuterochloroform between −50 and −10°C. The most detailed examination was made on a 0.5 M solution at −30°C. The enantiomeric salts RR and SS were prepared by the method of Boter and Platenburg [24], and the salts RS and SR by mixing the corresponding enantiomeric acids and anions. Their absolute configurations were established from data obtained by

Mikolajczyk et al.[29] The constants of the 1-phenylethylammonium and benzylammonium ethyl phosphonothionates investigated are listed in Table 9.

Table 9. Constants for stereoisomeric salts.

Absolute configuration	$[\alpha]_D^t$	t, °C
	(IX)	
RR	+10.00°	22
SS	−9.83°	22
RS	+5.33°	20
SR	−5.00°	20
	(X)	
R—	+7.83°	20
	—	—

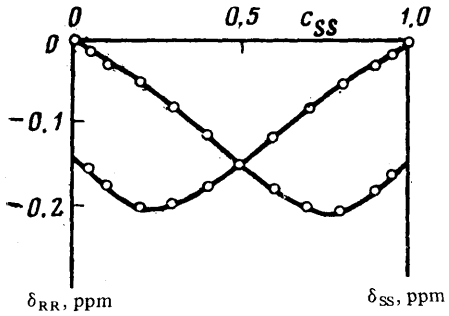


Figure 10. Dependence of δ_S and δ_R on relative content of antipodes of salt (IX) in 0.5 M solution in 1 : 1 $CHCl_3$–$CDCl_3$ at −30°C. The homo-shift δ_{SS} was adopted as reference signal.

Fig. 10 illustrates the experimental dependence of the ^{31}P n.m.r. chemical shifts of mixtures of the R^-R^+ and S^-S^+ enantiomers of the salt (IX) [20] at −30°C. A single signal is observed in the racemic mixture at −50°C, displaced by −0.27 ppm from the signal of the pure enantiomers (i.e. from the homo-shift). At all other concentrations two signals are observed. The curves differ markedly from the above cases of SCADA: they are butterfly-shaped with a minimum and an inflection, whereas typical SCADA curves with rapid exchange between association complexes do not (and cannot) contain either extrema or inflections. At −30°C the curves retain the "butterfly" character, but with narrower wings: i.e. the difference between the chemical shifts $\delta_R - \delta_S$ is smaller (Fig. 10).

Salt systems of this kind differ from the quaternary systems discussed in subsection 2 in the absence of a system of covalent bonds between the chiral centres in the stereoisomeric salts S^-S^+, R^-R^+, S^-R^+, and R^-S^+. In strongly dissociating media the chiral centres are kinetically independent; in media of low polarity they form ion-pairs or higher association complexes, between which, however, quite rapid ion exchange is possible [32].

In a solution of a mixture of the enantiomeric salts S^-S^+ and R^-R^+ in any relative concentrations, i.e. with $c^0_{SS} + c^0_{RR} = 1$, equilibrium is established between four ion-pairs:

$$S^-S^+ + R^-R^+ \overset{K}{\rightleftarrows} S^-R^+ + R^-S^+. \quad (26)$$

with the equilibrium constant

$$K = c_{SR}c_{RS}/c_{SS}c_{RR}, \quad (27)$$

where

$$c_{SR} = c_{RS}; \quad c_{RR} + c_{RS} = c^0_{RR}; \quad c_{SS} + c_{SR} = c^0_{SS}.$$

The chemical shifts in the n.m.r. spectra of such systems could apparently be considered in terms of additive contributions by $\delta_{R^-R^+}$ and $\delta_{R^-S^+}$ to δ_{R^-} and by $\delta_{S^-S^+}$ and $\delta_{S^-R^+}$ to δ_{S^-}. However, the $\delta - c$ relation obtained from theoretical curves calculated on the basis of this hypothesis does not resemble the experimental relation: curves for whose construction only ion exchange has been taken into account differ from the experimental curves in the absence of inflections and extrema at all values of c other than zero and unity. With salts of type (VII)–(IX) not only ion-pairs but also more complicated hydrogen-bonded complexes may be formed. The phosphonate anion is able to form only one hydrogen bond, and thereby fix an ion-pair, which therefore acts as an elementary particle in forming higher association complexes.

Thus in media of low dielectric constant the diastereomeric anisochronism spectra of stereoisomeric salts are produced under the influence of three factors—(*a*) formation of ion-pairs as stereoisomeric quasi-molecules, (*b*) ion exchange, i.e. the exchange of chiral centres between these quasi-molecules, and (*c*) association of the quasi-molecules—so that the problem of interpreting the spectra of such systems simplifies to the four-component problem of subsection 2 complicated by ion exchange [19,20]. The influence of these factors on the chemical shifts is expressed by the formulae

$$\delta_{R^-} = (\Delta_{RR}c_{RR} + \Delta_{RS}c_{RS})/c^0_{RR}, \quad (28)$$

$$\delta_{S^-} = \Delta_{SS}c_{SS} + \Delta_{SR}c_{SR}/c^0_{SS}, \quad (29)$$

in which δ_{R^-} and δ_{S^-} are the chemical shifts of the indicator nucleus in R and S anions, while Δ_{RR}, Δ_{RS}, Δ_{SR}, and Δ_{SS} are those of the quasi-molecules R^-R^+, R^-S^+, S^-R^+, and S^-S^+ produced in conformity with SCADA principles, i.e. formulae (22)–(25). Thus a 33rd parameter—the equilibrium constant K—is added to the 32 parameters of a system comprising four two-centred stereoisomers given above as two quadratic matrices. In this case, too, allowance for symmetry reduces the number of δ^j_i parameters to 8, and of α^j_i to 6. The parameters δ^{SS}_{SS} and δ^{SR}_{SR} are determined directly in an experiment by measuring the chemical shift in solutions of the pure enantiomers RR (or SS) and SR (or RS).

The present problem requires knowledge of 13 independent parameters, to determine which we have used the pairs of diastereomeric salts $R^-R^+ + S^-R^+$ and $R^-R^+ + R^-S^+$. In an RR + SR mixture in solution no new species appear on ion exchange, and treatment of experimental data on the basis of formulae (28), (29), and (19) enables us to isolate the chemical-shift parameters

$$\delta^{RR}_{SR} = \delta^{SS}_{RS}, \quad \delta^{SR}_{RR} = \delta^{RS}_{SS},$$

and also the constants

$$\alpha^{RR}_{SR} = \alpha^{SS}_{RS} = \alpha^{SR}_{RR} = \alpha^{RS}_{SS}.$$

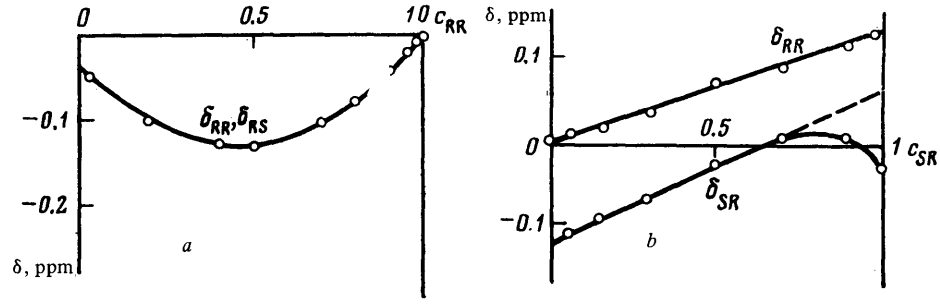


Figure 11. Dependence of chemical shifts of signals in spectra of binary salt systems (IX) on relative concentration: *a*) RR + RS; *b*) RR + SR.

If another pair of diastereomers—R^-R^+ and R^-S^+—is used, the parameters δ_{RS}^{RR} and δ_{RR}^{RS} and the equal δ_{SR}^{SS} and δ_{SS}^{SR}, as well as the parameters

$$\alpha_{RS}^{RR} = \alpha_{SR}^{SS} = \alpha_{RR}^{RS} = \alpha_{SS}^{SR},$$

can be isolated similarly. Fig. 11 illustrates the experimental dependence of the chemical shifts of these pairs on their relative concentration†. Thus the number of unknown parameters can be reduced to two δ parameters (δ_{RR}^{SS} and δ_{RS}^{SR}) and two α parameters (α_{RR}^{SS} and α_{RS}^{SR}), together with K.

Comparison of theoretical and experimental $\delta(c)$ values with variation in the parameters α_{RR}^{SS} and α_{SR}^{RS} showed that these parameters could be taken as unity without any great error, so that the chemical shifts δ_{RR}^{SS} and δ_{RS}^{SR} and the constant K could be evaluated. The complete set of parameters of the system (with $K = 1.3$) is

	α					δ			
	RR	SS	RS	SR		RR	SS	RS	SR
RR	1.0	(1.0)	1.3	1.0	RR	0	−0.44	−0,22	+0.01
SS	(1.0)	1.0	1.0	1.3	SS	−0.44	0	+0.01	−0,22
RS	1.3	1.0	1.0	(1.0)	RS	−0.20	−0,14	−0.04	−0.46
SR	1.0	1.3	(1.0)	1.0	SR	−0.14	−0.20	−0.46	−0.04

Fig. 10 shows the theoretical curve calculated with these values. Thus the chemical shifts observed in salt systems are due to the combined action of chemical equilibrium and SCADA. Consequently exclusion of the influence of the equilibrium factor should reveal pure SCADA. The ^{31}P n.m.r. spectra were investigated of salts of stereoisomeric R and S ethyl hydrogen phosphonothionates and benzylamine[20], in which system (X) the base is achiral. Hence the chemical shifts cannot be affected by ion exchange. In this case the experimental dependence of the chemical shifts on the relative concentration of the enantiomeric acid esters gives the usual SCADA curve with the parameters $\delta_h = 0$, $\delta_c = 0.25$, and $\alpha_c/\alpha_h = 2.4$.

† Divergence from the statistical SCADA rules is observed on the δ_{SR} curve in the region of c_{SR} values close to unity (Fig. 11*b*), the reason for which is not yet clear. Perhaps an inadequate rate of exchange has an influence in this concentration range, and (or) more complicated association complexes play a more important part.

The matrix elements α_i^j and δ_i^j (and K in the case of salt systems) carry the whole of the information on the influence of association on the n.m.r. spectra and its stereospecificity. It is better to use these parameters as physical characteristics of systems instead of the less informative quantity $\Delta\delta$. The temperature variations of the matrix elements have interesting features, on whose basis we can discuss several physical aspects of the interaction of chiral molecules in the primary step of association.

The $\delta - c$ curves of binary systems have two parameters, $\delta_i^j - \delta_i^i$ and α_i^j/α_i^i, the first of which represents the range of variation in $\delta(c)$, and the second the departure of the curve from a straight line that occurs when $\alpha_c = \alpha_h$, i.e. in the absence of stereospecificity of interaction. Tables 2 and 7 show that for SS molecules the ratio $m_{SS}^j = \alpha_{SS}^j/\alpha_{SS}^{SS}$ decreases with rise in temperature. However, if in mixtures of SS with RR or with RS preference for one type of interaction is lost as the temperature rises (at the limit of disappearance of the observed effects stereospecificity is almost absent), in the SS + SR mixture interaction of SS with SR molecules becomes more preferred at low temperatures, a preference which is lost at −40°C, and with further rise in temperature homo-interaction of SS with identical SS molecules occurs in preference to interaction with SR molecules.

For SR molecules, depending on their partner in the mixture, rise in temperature may either increase (SR + SS) or lower the ratio m_{SR}^j. On the whole the great diversity of variation in m for different interactions indicates a non-linear variation in the energy of interaction of chiral molecules on intermolecular association depending on the interaction of individual elements of chirality. This conclusion is of fundamental importance.

The interpretation of the δ_i^j values and their temperature dependence (Tables 4 and 8) for each primary association complex is quite complicated. Without completely rejecting the influence of direct induction of additional magnetic fields at the indicator nucleus on diastereomeric anisochronism during association, nevertheless we must evidently assume that conformational changes are primarily responsible for its establishment and variation. The role of association in changing the position of the signal relative to a possible signal in an isolated molecule may consist in

fixing a conformation with a different value of δ in the primary association complex. This applies, of course, not to a single act of pair association but to interactions between partners averaged over all types of association complexes. Furthermore, the fixation of conformations having a given values of δ implies, not a rigid set of particular conformations, but a redistribution of conformational populations. More detailed investigation of these mechanisms will evidently be possible only on the development of experimental and theoretical methods for quantitative analysis of nuclear shielding in complicated molecular structures.

An interesting series of papers published during 1975 to 1977 by French workers [33-37] reported a comprehensive investigation of the association of dipeptides of alanine, valine, and norvaline of general formula

$$R(1)-C(1)O(1)-N(2)H(2)-C_{\alpha}H_{\alpha}R(2)-C(2)O(2)-N(3)H(3)-R(3).$$

Infrared spectroscopy in tetrachloromethane solution revealed the presence of a conformational equilibrium between conformers A and B. In the former the hydrogen bond H(2)...O(2) completes a five-membered ring, but in conformer B the O(1)...H(3) bond closes a seven-membered ring. Conformer A has a strong intermolecular H(3)...O(1) hydrogen bond, but B is not characterised by association. The atom C_{α} is asymmetric.

Table 10.

R (2)	R (1), R (3)	$K'/2K$
CH_3	t-C_4H_9, iso-C_3H_7	0.9
C_3H_7	t-C_4H_9, iso-C_3H_7	3.3
iso-C_3H_7	t-C_4H_9, iso-C_3H_7	8.5

In full agreement with the results of Williams et al. [13], Horeau and Guette [1], and Soviet authors [15-20], these workers [33-37] observed a doubling of the multiplicity of signals in the n.m.r. spectra in non-equivalent mixtures of antipodes. The treatment that they used [33-37] in calculating Δδ for this specific problem was based on the same principles as the above general calculation of SCADA taking exchange into account. Their equations contain four δ parameters and eight x (concentration) parameters, which were determined from infrared and ^1H n.m.r. spectra. The results for stereoselectivity of association are given in Table 10, in which K' is the cross-dimerisation ($A^D + A^L$) constant, and K the homo-dimerisation ($A^D + A^D$ or $A^L + A^L$) constant. They show that the peptide of alanine is devoid of stereoselectivity of association, whereas those of norvaline and valine form dimers with a high degree of stereoselectivity.

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From the above considerations it is clear that SCADA, apparent in a higher multiplicity of n.m.r. spectral signals in a non-racemic mixture of optical antipodes, is a phenomenon that gives important information on association. When dissociating media (methanol, water) are used, or trifluoroacetic acid, which decomposes association complexes of chiral molecules, is added to non-polar solvents, increase in the multiplicity of n.m.r. spectra is not observed.

Investigation of intermolecular interactions of chiral molecules by other methods lies outside the scope of this Review. We will merely mention a series of studies by Wynberg et al. [38-40], in which the stereoselectivity of interaction of chiral molecules determined the reaction velocity and the proportions of products. Examples chosen were the oxidation of 5,6,7,8-tetrahydro-3,4,8-trimethyl-2-naphthyl ferricyanide, the reductive dimerisation of optically active and racemic camphor, and the reduction of camphor by lithium tetrahydroaluminate to borneol and isoborneol. Research on the spontaneous or seeded separation of racemates into antipodes is obviously of practical importance.

A prolonged "calm", during which solutions of antipodes were regarded in all cases as ideal, so that the possibility that the properties of one antipode would be affected by the presence of the other was thereby rejected *a priori*, has been followed by a period of thorough study of the stereoselectivity of interaction of antipodal molecules—a phenomenon which undoubtedly plays an important part in biological processes and in whose study the n.m.r. method is indispensable.

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Institute of Hetero-organic Compounds, USSR Academy of Sciences, Moscow