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AN NMR STUDY OF OPTICAL ISOMERS IN SOLUTION

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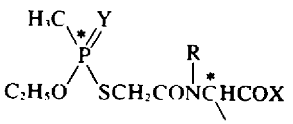
Abstract—NMR $^{31}P-\{^1H\}$ spectra of stereoisomeric N - [S - (methylethoxyphosphinyl) - thioglycolyl]valines in solution to reveal association of the molecules, and interaction of the chiral centres. Under fast inter-associate exchange in achiral media, these interactions lead to the following: (i) The chemical shift of the racemic mixture of enantiomers deviates from the shift of the individual species; (ii) the spectra of non-racemic mixtures are doublets; (iii) there are 2^n lines in the spectrum of a mixture containing unequal concentrations of stereoisomers with n asymmetric centres. The integrated intensity ratio is equal to the concentration ratio in all cases. The concept of statistically controlled associate diastereomerism (SCAD) is introduced and the respective formalism is given to describe the spectral effects accompanying variations of temperature and concentration. It is also shown applicable to more complicated cases involving ion exchange of chiral fragments between stereoisomers.

In recent years diastereomeric anisochronism (DA) (magnetic non-equivalence of nuclei in diastereomeric systems) has received a great deal of attention.[1] This problem includes magnetic non-equivalence of nuclei in diastereomeric molecules; DA spectra of the kind are employed in assigning absolute configurations[2] and in determination of enantiomeric purities.[3] Another example is DA of enantiomers in chiral solvents[4] or in achiral solvents containing chiral additives,[5] for instance, chiral shift reagents.[6] Finally, there is DA of enantiomers in achiral solvents, the enantiomer concentrations being not equal.[7-11] The latter type of DA will be discussed in more detail below.

Earlier we studied the DA of diastereomer mixtures of *N* - [*S* - (methylethoxythiophosphinyl) - thioglycolyl]valine **1**, its ethyl ester **2**, the respective *N*-methylated derivatives **3** and **4**, and simpler analogues.[12] Certain intramolecular factors affecting the appearance and variation of DA as well as solvation effects exerted by molecules of magnetically anisotropic solvents were established. The results obtained are, on the whole, interpretable in terms of the Mislow and Raban[13] representation although a special approach was necessary in certain cases, e.g. with the phenomenon of aromatic solvation-induced diastereomeric anisochronism (ASIDA).


$C_2H_5O(H_3C)\overset{*}{P}(=Y)SCH_2CON(R)\overset{*}{C}H(C_3H_7\text{-}i)COX$

1: $Y = S$, $R = H$, $X = OH$
2: $Y = S$, $R = H$, $X = OC_2H_5$
3: $Y = S$, $R = CH_3$, $X = OH$
4: $Y = S$, $R = CH_3$, $X = OC_2H_5$
5: $Y = O$, $R = H$, $X = OH$
6: $Y = 0$, $R = H$, $Y = OC_2H_5$

DA in diastereomer mixtures dissolved in chloroform or benzene results in the doubling of the multiplicity of NMR ^1H or ^{31}P spectra. In conditions of proton decoupled NMR ^{31}P spectra, DA is exhibited in the form of well-resolved phosphorus doublets. Therefore, further study was carried out with the $^{31}P-\{^1H\}$ NMR method. The necessity of a deeper study of DA in the mixtures mentioned above and analogous systems became apparent after establishing unusual concentration, temperature, and mixing effects on $^{31}P-\{^1H\}$ NMR spectra in **1**–**4** and, especially, in their monothio analogues **5** and **6**.

These molecules contain two asymmetric centres, phosphorus and carbon. Consequently, four stereoisomers are possible: *RR*, *SS*, *RS* and *SR*. In a sample of the dithioester **2** representing a mixture of all four stereoisomers DA is not affected by dilution in chloroform, the chemical shifts difference ($\Delta\delta$) in the phosphorus doublet remains unchanged (Fig. 1). In the free acid **1** the $\Delta\delta$ difference decreases on dilution. This can be readily explained on the basis of the effect of intermolecular hydrogen bonding on DA studied by Mateos and Cram.[14] Indeed, one may assume that dilution causes decomposition of hydrogen bonds, makes the system more flexible, releases the frozen degrees of freedom, and therefore, DA is decreased by the resulting averaging.

In a striking manner, dilution of solutions of monothio derivatives **5** and **6** (each of the samples was also a mixture of the four stereoisomers) led to an increase in the DA stronger in the case of the former compound, and weaker for the latter one (Fig. 1). The temperature dependence patterns were even more complicated (Fig. 2). The dithio derivatives **1** and **2** revealed the natural decrease in $\Delta\delta$ with increase of temperature. In solutions of monothio derivatives **5** and **6**, $\Delta\delta$ decreases from −60° to ~−45°, but furthher heating (up to +50°) leads to a steady increase in $\Delta\delta$. At about −45° $\Delta\delta$ is equal to zero within the resolution of the instrument. The experiment provides us only with the absolute magnitude, not the sign of $\Delta\delta$, so the alternative conclusion was that $\Delta\delta$ rose steadily from −60° to +50° and changed its sign at −45°.

To rationalise the complicated patterns obtained, the mixtures containing four stereoisomers (two racemic diastereomers each) should be replaced by simpler systems. This is difficult to perform with the dithio derivatives since they acquire their chiral centres at the moment of synthesis and separation of the diastereomers

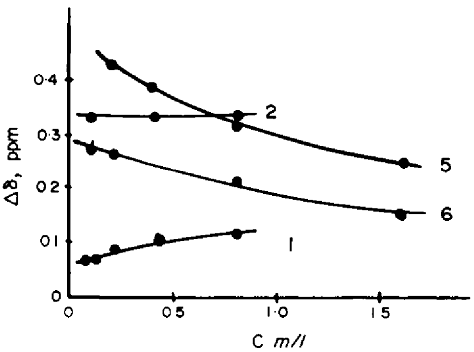


Fig. 1. DA vs concentration in four-isomer mixtures. NMR $^{31}P\text{-}\{^1H\}$, $CHCl_3$, 20°C and 25°C for 5. The curve numeration correspond to compound numeration in the text.

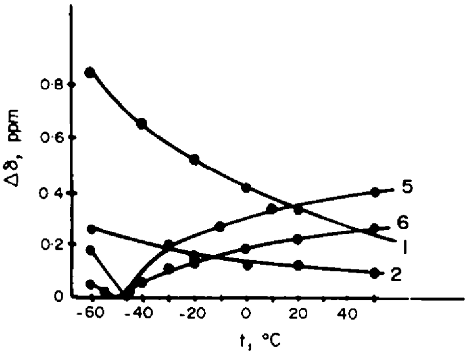


Fig. 2. DA vs temperature in four-isomer mixtures. NMR $^{31}P\text{-}\{^1H\}$, $CHCl_3$, C = 0·4 mole/l. The curve numeration corresponds to compound numeration in the text.

and resolution of the racemates are rather difficult. With a monothio derivative 5, the situation is more favourable since enanthiomeric (*R* and *S*) monothio acids of phosphorus are readily available[15] and so are enantiomeric (*R* and *S*) chloroacetyl valines, while the synthesis of 5 from the starting compounds mentioned does not affect the asymmetric centre and is carried out in conditions which ensure that racemisation does not occur. Thus, all four stereoisomers (*RR*, *SS*, *RS* and *SR*) of 5 are obtainable in pure form, and NMR $^{31}P\text{-}\{^1H\}$ spectra of their chloroform solutions at various concentrations of either individual compounds or of their mixtures can be recorded. Synthesis of the stereoisomers has been described elsewhere.[8]

It was found that the value of $\Delta\delta$ determined as the difference between the chemical shifts obtained for solutions of individual stereoisomers of 5 was not equal to the chemical shift difference obtained for solutions of the stereoisomer mixtures at the same total concentration. The difference $\Delta\delta$ for the *SS* and *SR* compounds measured separately was 0·84 ppm while the mixture gave 0·04 ppm at the same total concentration. The effect was as high as 1·05 ppm in the case of the *SS* + *RS* mixture.

Further, it was found that the spectrum of a mixture containing unequal concentrations of all four species displayed four signals, with the intensity ratio being equal to the concentration ratio. Finally, the temperature dependence of spectrum of a equimolecular mixture of the four isomers differs from the DA dependences obtained for the components.

The difference found between NMR spectra of individual stereoisomers in solution and their mixtures may be explained only assuming interaction of the dissolved molecules. This interaction should depend on whether molecules of identical configuration (homo interaction) or molecules of antipodal configurations (cross interaction), or diastereomeric molecules interact.

In solvents of low polarity such as chloroform or carbon tetrachloride, molecules of the monothio acid 5 are strongly associated. This follows from the IR spectra[17] strongly varying with dilution. The dithio ester 2 is not at all associated in chloroform and its NMR spectrum reveals no anomalous alterations on dilution or temperature variation.

Thus, we concluded that multiplicity and frequency arrangement in DA spectra of stereoisomers depends on association and its stereoselectivity. Consequently, stereoisomer association and its stereoselectivity can be studied on the basis of NMR spectra.

BINARY SYSTEMS

Mixtures of enantiomers[8–10]

Since NMR techniques were first applied to the study of stereochemical problems, there was always an assumption that in achiral media NMR spectra of antipodes were identical and coincided with NMR spectra of their mixtures. This assumption is equivalent to denying the existence of racemic compounds in solutions or, in general, of association stereoselectivity. On the other hand a considerable number of investigations have been directed towards the study of the interaction of optical isomers in solution by other methods. Most of the studies dealing with the problem are cited in Ref. 11.

In 1969 Williams, Pitcher, Bommer, Guitzwiller and Uskokowic[7] studying PMR spectra of (−)-dihydroquinine and racemic dihydroquinine in deuterochloroform found that the respective proton chemical shifts differed by 10–20 Hz (at 100 MHz) while in a (−) - dihydroquinine + racemic - dihydroquinine mixture (1:1) the signal multiplicities doubled at the intensity ratio of 3:1 in the doublets. The authors proposed a qualitative interpretation of the phenomenon based on the assumption[7] that the increase of the multiplicity was due to interaction of the molecules in solution and to the different environment of molecules of each enantiomer—identical, enantiomeric or diastereomeric environment. Recently we described a similar phenomenon observed in NMR $^{31}P\text{-}\{^1H\}$ spectra of enantiomer mixtures of 5, and proposed a statistical theory of this phenomenon.[8,9] Almost simultaneously Horeau and Guette[11] studying PMR spectra of α,α-methylethyl- and α,α-methylisopropylsuccinic acids in $CDCl_3$ found a similar difference in spectra of pure antipodes and 1:1 (racemic) and 3:1 mixtures. The authors also consider that the phenomenen is caused by association of the enantiomers, however, they believe that the chemical shift variation can be explained assuming different stability of diastereomeric associates of the enantiomers in solution.

In terms of the NMR time scale, there are associates of two types, long-lived and short-lived. With the first type, the DA spectra multiplicity should be determined by the number of varieties of long-lived associates while the intensity ratio by the relative concentrations of the long-lived species. The multiplicity equal to two and the intensity ratio equal to the enanthiomer concentration ratio may result only by mere chance.

The other possibility is connected with formation of short-lived associates via fast inter-associate exchange.

This is statistically controlled associate diastereomerism (SCAD).

Here, the DA multiplicity should be equal to two while the intensity ratio in the elementary DA doublet should be invariably equal to the antipode concentration ratio.

An NMR ^{32}P-{^{1}H} spectrum of *RR*- and *SS*-enanthiomers of 5 recorded in chloroform at 0·4 mole/l and −60°C displays narrow singlets the chemical shifts of which (homo shifts, δ_h) coincide within the experimental error of ±0·1 Hz. Below, this signal will serve as a reference for other chemical shifts. The spectrum of the racemic mixture (1 : 1) recorded at the same temperature and total concentration reveals one singlet as well, however, its position (δ_r) differs by 0.35 ppm (13.2 Hz) from the homo shift, δ_h. At [*RR*] : [*SS*] ratio of 7 : 3 there are two signals (at 0.25 and 0.42 ppm) with an intensity ratio of 7 : 3 (Fig. 3). An identical spectrum is observed at the concentration ratio of 3 : 7.

Similar patterns are observed for the *RS* + *SR* pair under the same conditions. At −60°C δ_h is 0·84 ppm while the racemic singlet is at 0·46 ppm; at concentration ratios of 7 : 3 and 3 : 7 two identical doublets are observed at 0·38 and 0·58 ppm with intensity ratios of 3 : 7. Similar relationships are observed at other temperatures (Table 1). These data allow us to make the following qualitative conclusions.

(i) Narrow singlets are observed in solutions of enantiomers recorded separately. As every molecule in the associates is surrounded only by identical molecules and is subject to fast inter-associate exchange, therefore the local fields built up on the indicator nucleus (phosphorus) are averaged out regardless of the number and stability of associates. Hence narrow singlets. Magnetic field is achiral, so the antipode signals are identical.

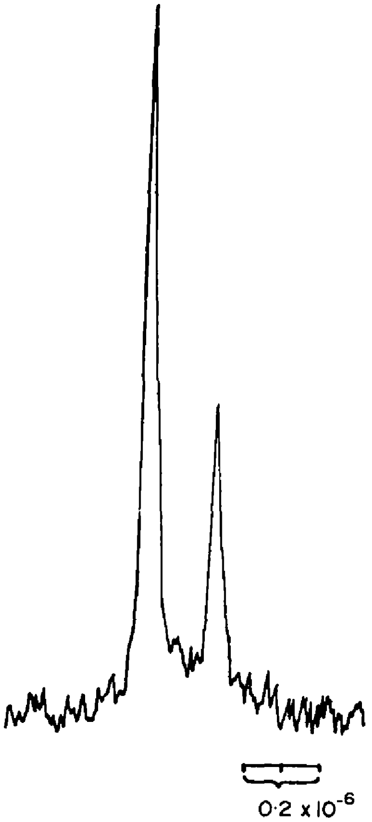


Fig. 3. NMR ^{31}P-{^{1}H} spectrum of *SS* + *RR* mixture at concentration ratio of 7 : 3, CHCl$_3$, C = 0·4 mole/l, −60°C.

(ii) In a racemic solution, molecules of each of the enantiomers are surrounded both by identical and antipode molecules. Homo and cross associations may or may not be thermodynamically equivalent. The fast inter-associate exchange makes cross interactions contribute, alongside with the homointeractions, in the exchange statistics; this affects the resulting magnetic field at the indicator nucleus and, consequently, the chemical shift of each of the enantiomers. Situations for the enantiomers are mirror reflections of each other, so the

Table 1. Chemical shifts in enantiomer mixtures† (CHCl$_3$, C = 0·4 mole)l)

(a) *SS* + *RR*

$C = \frac{[SS]}{[SS]+[RR]}$	δ	Relative integral intensity	t (°C) −60	−50	−40	−30	−20	−10	0
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
	δ_{RR}	0·7	0·25	0·13	0·09	0·06	0·03	0	0

(b) *SR* + *RS*

$C = \frac{[SR]}{[SR]+[RS]}$	δ	Relative integral intensity	t (°C) −60	−50	−40	−30	−20	−10	0	10	20	30	40	50
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	−0·05	−0·03	0·03	0·08	0·16	0·26	0·30	0·33	0·36
	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

**RR* and *RS* signals are identical to *SS* and *SR* signals in a racemic mixture or in pure state.

†The reference signal is homo shift of *SS* molecule at the given temperature.

‡The spectra of mixtures are identical at the C of 0·7, but assignment of the two lines changes.

chemical shifts coincide to give one signal, δ_r, which differs from δ_h.

(iii) At unequal concentrations of the antipodes, each of these is characterised by its own admixture of cross-interaction to homo-interaction. If homo association prevails in one of the antipodes, cross association will prevail in the other. In this case the mirror reflection pattern does not operate and an NMR doublet with intensity ratio equal to the antipode concentration ratio appears in the spectrum.

The qualitative representation exposed above may be formalised to give a quantitative interpretation of DA spectra of enantiomer mixtures subject to SCAD. To calculate the (+)- and (−)-enantiomer signals (δ^+ and δ^-) as a function of the relative concentration, it is necessary to include statistical averaging of the effect exerted by homo and cross interactions on the shielding of indicator nuclei in antipode molecules under fast inter-associate exchange. If W_+^+ is the statistical weight of the homo contribution to δ^-, W_+^- the statistical weight of the cross contribution to δ^+ and W_-^- and W^+ are the homo and cross contributions to δ^- then

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

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

where δ_h is the homo shift, identical for both antipodes, δ_c the cross shift, also identical for the (+)- and (−)-molecules.

Statistical weights of the homo and cross interactions depend on the relative content of antipode molecules in the mixture, $C = [+]/([+]+[-])$, and on the stability parameters of the homo and cross contacts, α_h and α_c that are functions of the cross and homo interaction energies:

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

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

Since experimental data do not provide us with the α_c and α_h values but only with their ratio, α_c/α_h, a characteristic of stereospecificity of association of the antipodes, eqns (1) and (2) may be rewritten in the following form

$$\delta^+ = [C\delta_h + (\alpha_c/\alpha_h)(1-C)\delta_c]/[C + (\alpha_c/\alpha_h)(1-C)] \quad (5)$$

$$\delta^- = [(1-C)\delta_h + (\alpha_c/\alpha_h)C\delta_c]/[(1-C) + (\alpha_c/\alpha_h)C]. \quad (6)$$

Formulae (5) and (6) describe the $\delta^+(C)$ and $\delta^-(C)$ curves as having neither extremes nor inflection points through the entire concentration range. At $C = 0$, $\delta^+ = \delta_c$ and $\delta^- = \delta_h$, while at $C = 1$, $\delta^+ = \delta_h$ and $\delta^- = \delta_c$; only one signal is observed in both cases since signal δ_c is experimentally unobservable. At $C = 0.5$ (racemic mixture) there is also only one signal that is shifted with respect to the homo signal. All other concentrations should lead to two signals. Each of these belongs to a specific antipode, so the intensity ratio should be equal to $C/(1-C)$.

Curvature of $\delta^+(C)$ and $\delta^-(C)$ depends on α_c/α_h, i.e. on stereospecificity of homo and cross interactions. At $\alpha_c/\alpha_h = 1$ the curves become straight lines. However, the essential features of the pattern are retained, viz. there is one signal at $C = 0$, $C = 1$ and at $C = 0{\cdot}5$ whereas there are two signals at any other relative concentration. Thus, we have come to a very important conclusion: the appearance of two signals in an NMR spectrum of an antipode mixture which contains unequal concentrations of the species is not due to association stereoselectivity for example a tendency to racemate formation, but is caused by SCAD proper.

The data of Table 1 have been processed via (5) and (6). The parameters δ_c and α_c/α_h were found for each of the temperatures. These parameters, together with experimental δ_h, provide a complete description of a DA spectrum. They are listed in Table 2. Curves calculated from (5) and (6) using the parameters found are presented in Figs. 4 and 5. The experimental data are also plotted therein and, as can be seen, are in good agreement with the theory.

The results obtained lead to interesting conclusions. In the *RS* + *SR* system phosphorus shielding non-equivalence ($\delta_h - \delta_c$) in the homo and cross associates changes rather slowly with temperature increase from −60 to +50° whereas association stereoselectivity (devia-

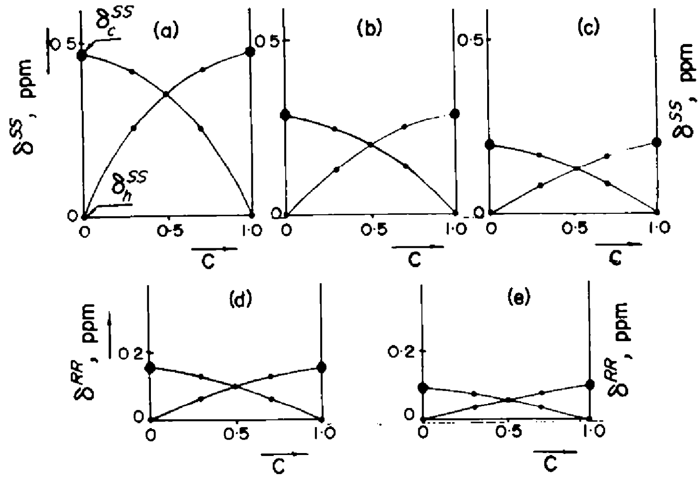


Fig. 4. *SS* and *RR* chemical shifts vs *SS* relative concentration at various temperatures. The curves are calculated, the points are experimental values. The origin of the system of coordinates is homo shift at a given temperature, for each of the curves. (a) t = −60°C; (b) t = −50°C; (c) t = −40°C; (d) t = −30°C; (e) t = −20°C. Measured in $CHCl_3$ at C = 0·4 mole/l.

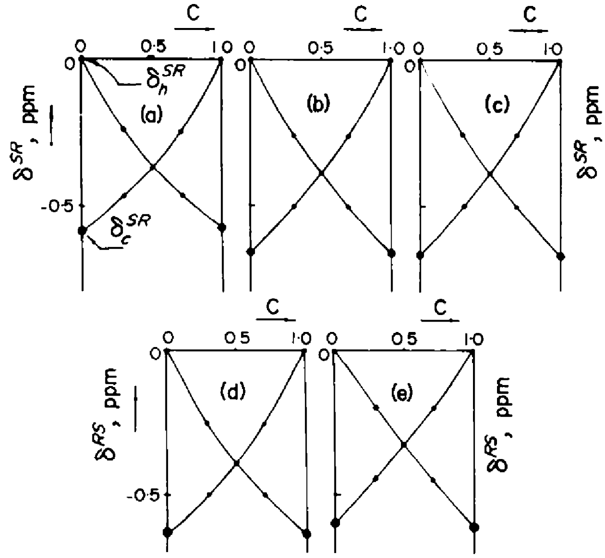


Fig. 5. *SR* and *RS* chemical shifts vs *RS* relative concentration at various temperatures. The curves are calculated, the points are experimental values. The origin of the system of coordinates is homo shift at a given temperature. Measured in $CHCl_3$ at C = 0·4 mole/l. (a) t = −60°C; (b) t = −50°C; (c) t = −40°C; (d) t = −30°C; (e) t = −20°C.

Table 2. SCAD parameters for *SS* + *RR* and *SR* + *RS* enantiomer mixtures in $CHCl_3$ at C = 0·4 mole/l. The reference signal is δ_{SS}^{SS} observed at the given temperature

Mixture		t (°C)				
		−60	−50	−40	−30	−20
SS + *RR*	δ_c	0·50	0·31	0·22	0·17	0·10
	α_c/α_h	2·4	1·7	1·4	1·2	1·0
SR + *RS*	δ_c	0·26	−0·07	−0·18	−0·20	−0·21
	α_c/α_h	1·8	1·7	1·6	1·4	1·2

tion of α_c/α_h from unity) vanishes at about 0°C. In the *RR* + *SS* system, both the quantities disappear rapidly on heating and SCAD is not observed in NMR spectra recorded above 0°C. Only one singlet is present at any relative concentration of antipodes in the mixture. Consequently, an NMR observation of SCAD may be made only under certain conditions that depend on the structure of enantiomers and on thermodynamic characteristics of the system. If these conditions are violated, the NMR SCAD effect will be lower than instrument resolution. This is why, probably, the literature data interpretable as SCAD are rather scarce. Equations (5) and (6) allow one to process the data reported on dihydroquinine[7] and α,α-methylethylsuccinic acid.[11] Unfortunately, the data[7] are somewhat incomplete; the authors[7] point out that the aromatic proton signals are very sensitive to total concentration and coalesce on dilution. More reliable are the data[7] on the H^9 signals whose positions depend mainly on relative concentration of the antipodes. The δ curves plotted as a function of C are linear, in other words, there is no association stereoselectivity. The parameters calculated from eqns (5) and (6) are listed in Table 3. Good linearity has also been found for the data of Horeau and Guette.[11]

Table 3. Processing of experimental data presented in Refs 7 and 11 using eqns (5) and (6)

No.	Enantiomers	Signal	$\delta_c - \delta_h$	α_c/α_h
1	Dihydroquinine	$\delta_{(H^9)}$	+0·4 ppm	1·0
2	α,α-methylethyl-succinic acid	δ_1	−4·6 Hz	1·0
		δ_2	−5·7 Hz	1·0

Epimer mixtures

Equations (1) and (2) do not impose any conditions on stereochemical relations of the components. In contrast, eqns (5) and (6) are applicable to enantiomers only. If the components i and j are diasteromers rather than antipodes, then (5) and (6) should be generalised to (7) and (8).

$$\delta_i = \frac{\alpha_i^i C_i \delta_i^i + \alpha_i^j (1 - C_i) \delta_i^j}{\alpha_i^i C_i + \alpha_i^j (1 - C_i)} \tag{7}$$

$$\delta_j = \frac{\alpha_j^j (1 - C_i) \delta_j^j + \alpha_j^i C_i \delta_j^i}{\alpha_j^j (1 - C_i) + \alpha_j^i C_i}. \tag{8}$$

The C_i and C_j concentrations are normalised to unity; the subscript denotes the isomer treated, the superscript the isomer interacting with it in the associates.

Accordingly, α_i^i, α_j^j, α_i^j, α_j^i are parameters of stability of associates, the latter two being identical for both epimers ($\alpha_i^j = \alpha_j^i$). The chemical shifts δ_i^i and δ_j^j are homo shifts equal to δ_i or δ_j at C = 1 or C = 0. There is no equality between the homo shifts, nor between δ_i^j and δ_j^i.

NMR ^{31}P-$\{^1H\}$ spectra of *SS* + *SR* and *SS* + *RS* epimer mixtures of compound **5** were studied. Their mirror reflections, *RR* + *RS* and *RR* + *SR* mixtures, were used only for determining experimental inaccuracies. Table 4 contains experimental data obtained at various relative epimer concentrations and at various temperatures. The data were processed according to formulae (7) and (8).

All the DA parameters were found (Table 5). They are, naturally, identical with the parameters of the mirror antipode pairs *RR* + *RS* and *RR* + *SR* and describe completely the association effect on NMR spectra of binary mixtures of the diastereomers studied.

Unlike enantiomers, the signals do not coalesce at equal epimer concentrations and two signals are observed in the entire range of relative concentrations.

Table 4. ^{31}P-{^1H} chemical shifts in epimer mixtures ($CHCl_3$, C = 0·4 mole/l). The computing origin is the δ_{SS}^{SS} signal at a given temperature

(a) *SS* + *SR*

$C = \frac{[SS]}{[SS]+[SR]}$	δ	Relative integral intensity	t (°C)											
			−60	−50	−40	−30	−20	−10	0	10	20	30	40	50
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	0·36	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	0·22	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

(b) *SS* + *RS*

$C = \frac{[SS]}{[SS]+[RS]}$	δ	Relative integral intensity	t (°C)											
			−60	−50	−40	−30	−20	−10	0	10	20	30	40	50
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	0·42

Table 5. SCAD parameters for binary epimer *SS* + *SR* and *SS* + *RS* mixtures ($CHCl_3$, C = 0·4 mole/l)

δ_i^j, α_i^j/α_i^i	−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

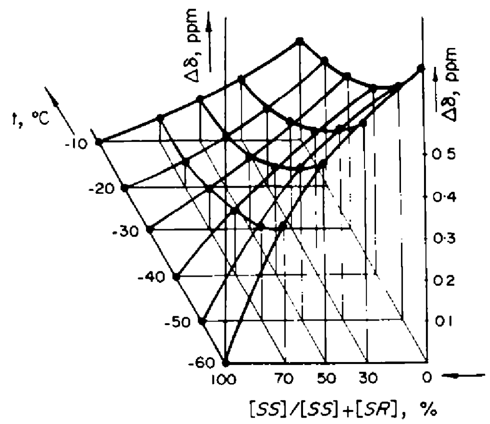


Fig. 6. *SS* chemical shifts vs [*SS*]/([*SS*]+[*SR*]) at various temperatures. The origin of the system of coordinates is *SS* homo shift at a given temperature. The curves are calculated, the points correspond to experimental values. Measured in $CHCl_3$ at C of 0·4 mole/l.

Typical theoretical DA curves obtained for *SS* + *SR* mixture at various temperatures are shown in Fig. 6 where experimental data are also plotted. The agreement is again quite satisfactory.

MORE COMPLICATED SYSTEMS

General

Set-theory formalism applied to DA study in this laboratory[18] showed that DA multiplicity for mixtures of stereoisomers containing n chiral sites may be equal to the number (2^{n-1}) of antipode pairs but may also lie above this magnitude. An increase in the DA multiplicity may be caused by non-degeneracy and mirror non-invariance of the action operators corresponding to stereoisomers. In achiral media under statistically controlled association, in other words, at fast inter-associate exchange, the DA multiplicity may be as high as 2^n for n chiral centres since each stereoisomer has, under these conditions, its own signal averaged over all possible associates.

For an N-component mixture of optical isomers in an achiral solvent the SCAD-induced chemical shift of the nucleus in the i-th component may be written as follows

$$\delta_i = \sum_{j=1}^{N} \alpha_i^j C_j \delta_i^j \Bigg/ \sum_{j=1}^{N} \alpha_i^j C_j. \tag{9}$$

Equation (9) includes statistical contribution of the pairwise ij contacts under fast inter-associate exchange. More complex contacts may also be included.

A statistical theory of such second-order complexity systems is possible to construct; the necessity of such complexity can only be determined experimentally. We have shown above that a good agreement exists between calculated and experimental values of chemical shifts in binary systems while using formulae (7) and (8) for epimers, (5) and (6) for enantiomers. All these equations take account of direct pairwise contact only. A four-component mixture will be calculated below using formula (9).

A four-component system

For a mixture of four stereoisomers containing two chiral centres each, eqn (9) may be written for phosphorus chemical shift in each isomer.

The total number of $\delta_i{}'$ and $\alpha_i{}'$ parameters at $N = 4$ amounts to 32. These are arranged in two square matrices presented in Fig. 7. The lines correspond to the stereoisomers whose chemical shift is studied (subscripts) the columns to the stereoisomers interacting in pairwise elementary contact with the former isomers. The left matrix contains the parameters describing fields induced on the indicator nucleus in associates, the right matrix—the parameters describing stereospecificity of pairwise contacts in the associates.

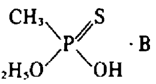
$$\begin{array}{c|c|c|c|c|}
 & RR & SS & RS & SR \\
\hline
RR & \delta_{RR}^{RR} & \delta_{RR}^{SS} & \delta_{RR}^{RS} & \delta_{RR}^{SR} \\
\hline
SS & \delta_{SS}^{RR} & \delta_{SS}^{SS} & \delta_{SS}^{RS} & \delta_{SS}^{SR} \\
\hline
RS & \delta_{RS}^{RR} & \delta_{RS}^{SS} & \delta_{RS}^{RS} & \delta_{RS}^{SR} \\
\hline
SR & \delta_{SR}^{RR} & \delta_{SR}^{SS} & \delta_{SR}^{RS} & \delta_{SR}^{SR} \\
\hline
\end{array}
\qquad
\begin{array}{c|c|c|c|c|}
 & RR & SS & RS & SR \\
\hline
RR & \alpha_{RR}^{RR} & \alpha_{RR}^{SS} & \alpha_{RR}^{RS} & \alpha_{RR}^{SR} \\
\hline
SS & \alpha_{SS}^{RR} & \alpha_{SS}^{SS} & \alpha_{SS}^{RS} & \alpha_{SS}^{SR} \\
\hline
RS & \alpha_{RS}^{RR} & \alpha_{RS}^{SS} & \alpha_{RS}^{RS} & \alpha_{RS}^{SR} \\
\hline
SR & \alpha_{SR}^{RR} & \alpha_{SR}^{SS} & \alpha_{SR}^{RS} & \alpha_{SR}^{SR} \\
\hline
\end{array}$$

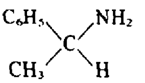
Fig. 7. SCAD parameters in a system of two-centre stereoisomers.

The number of independent parameters may be reduced by applying symmetry considerations. Parameters $\delta_i{}'$ and $\alpha_i{}'$ remain unchanged when the counterparts are replaced by their mirror reflections, moreover $\alpha_i{}' = \alpha_i{}'$, so the number of the independent parameters is reduced to fourteen. In general, at sufficiently high resolution and at unequal relative concentrations of the four stereoisomers the DA spectrum consists of four signals whose chemical shifts δ_{RR}, δ_{SS}, δ_{RS} and δ_{SR} are different. The intensity ratio in the quadruplet is equal to the stereoisomer concentration ratio. If the concentrations are equal, the *RR* and *SS* as well as *RS* and *SR* chemical shifts become equal and the spectrum contains two signals of equal intensity. This is confirmed experimentally.

All the fourteen parameters required for calculation were found in experiments with binary systems (Tables 2 and 5). The quantities $\delta_{SS} = \delta_{RR}$ and $\delta_{SR} = \delta_{RS}$ were calculated at various temperatures. The data obtained demonstrate that Δδ at −45°C does indeed have a minimum (Curve 5 in Fig. 2). The calculated Δδ values (Fig. 8) fit in well with the experimental ones, the mean square deviation of the calculated Δδ(T) curve from the experimental one is 4%.

Table 6. Properties of salts of *O*-ethyl methylthiophosphonic acids



B	Absolute configu-ration at P	Absolute configu-ration at C	M.p. (°C)	$[\alpha]_D{}^t$	t (°C)
	*R*	*R*	139–140	+10·00	22
	S	*S*	139–140	−9·83	22
	R	*S*	107·5–109	+5·33	20
	S	*R*	108–110	−5·00	20
$C_6H_5CH_2NH_2$	R	—	102–103	+7·83	20
	racemate		98–99·5		

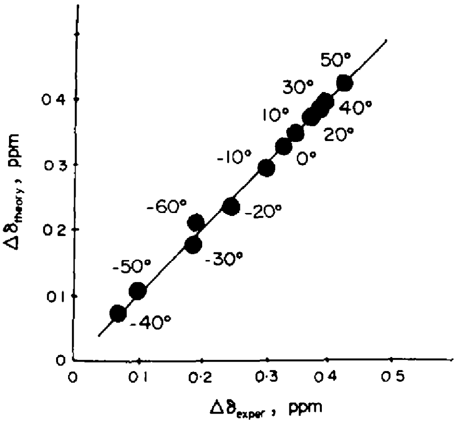
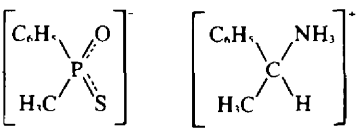


Fig. 8. Calculated and experimental Δδ values in *SS* + *SR* + *RS* + *RR* (1 : 1 : 1 : 1) mixture, C = 0·4 mole/l in $CHCl_3$.

A four-component system with ion exchange

NMR spectra of salt solutions containing chiral cations and anions are very important for experimental stereochemistry. Since Pasteur, such salts were employed for resolution of racemates. Recently, their NMR spectra have been widely applied for the determination of optical purity of enantiomers, in assigning absolute configurations,[19] and in other fields. Therefore, it is important to know how DA operates in the spectra of diastereomeric or enantiomeric salt mixtures and how applicable the NMR criterion is for the solution of the problems mentioned.

NMR chemical shifts in a mixture of salts **7** and **8** were studied by Mikołajczyk *et al.*[20] as a function of the enantiomeric composition.

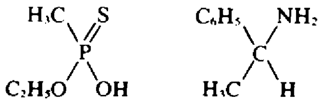


7: $R^-S^+ + S^-S^+$
8: $R^-R^+ + S^-S^+$

where *R* and *S* are absolute configurations of cations (R^+ and S^+) and anions (R^- and S^-).

The proton chemical shift differences Δδ or methyl groups at the phosphorus were found to vary with the relative *SS*-isomer concentration in enantiomer concentration range of 27 to 78%.

We have studied ^{21}NMR $^{31}P\text{-}\{^1H\}$ spectra of salts **9** of enantiomeric *R* and *S* phosphorus-containing acids with *R*- and *S*-α-phenylethylamines in a 1 : 1 chloroform-deuteriochloroform mixture at constant total concentration of 0·5 or 1·0 mole/l at −50 to −10°C. The most detailed study was made at −30° and at the total concentration of 0·5 mole/l.



R and *S* *R* and *S*

9

The enantiomeric *RR* and *SS* salts were obtained by a method described by Boter and Platenburg,[15] the *RS* and *SR* salts by mixing the respective acids and amines. The absolute congurations were assigned on the basis of the work of Mikolajczyk, Para, Ejchart, Jurczak and Omelanczuk.[19] The constants of α-phenylethylammonium and benzylammonium salts of *O*-ethylmethylthiophosphonic acids are listed in Table 6. Figure 9 presents an experimental curve obtained for NMR ^{31}P-{^{1}H} chemical shifts of the R^-R^+ and S^-S^+ salts. The racemic mixture gives only one signal that is displaced by 0·27 ppm with respect to the signal (homo shift) of the individual enantiomers. All other concentrations lead to two signals.

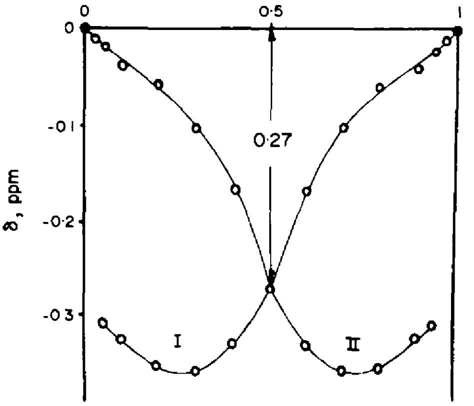


Fig. 9. $\delta_{(S^-)}$ and $\delta_{(R^-)}$ vs *SS* relative content for 9. The origin of the system of coordinates is δ^{SS}_{SS}. Measured in $CHCl_3/CDCl_3$ 1:1, C = 0·5 mole/l, t = −50°C.

Naturally, the lower points at the extremities of the plot corresponds to a very weak signal adjacent to a very strong one. The intensity ratio in the central zone of the plot is an exact measure of the enantiomer concentration ratio whereas intensity ratios are less accurate at the extremities. The patterns obtained differ sharply from the SCAD patterns described above (*Mixtures of Enantiomers*); the butterfly-shaped curves display minima and inflection points whereas the typical SCAD curves at rapid inter-associate exchange do not, and cannot, contain either minima or inflection points. At −30° (Fig. 10) the butterfly shape is retained but the width of the wings decreases, in other words, the chemical shift difference $\delta_R - \delta_S$ decreases.

Such salt systems differ from the four-component systems of the preceding Section in that chiral centres in S^-S^-, R^-R^+, S^-R^+ or R^-S^+ stereoisomeric salts are not bonded covalently. In highly polar media, the chiral centres are kinetically independent; in low-polarity media, they form ion pairs or more complex associates which, however, may be subject to a sufficiently fast ion exchange (see, e.g. Ejchart and Jurczak[22]).

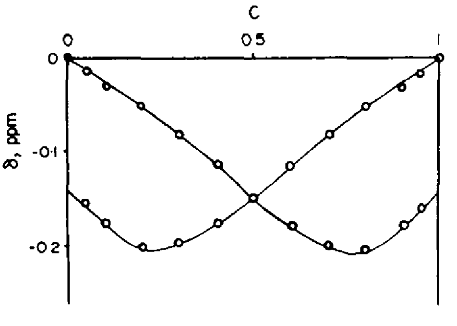


Fig. 10. $\delta_{(S^-)}$ and $\delta_{(R^-)}$ vs *SS* relative content for 9. The origin of the system of coordinates is δ^{SS}_{SS}. Measured in $CHCl_3/CDCl_3$ 1:1, C = 0·5 mole/l, *t* = −30°C. Experimental points on theoretical plots calculated via eqns (10) and (11).

Let us consider a mixture of S^-S^- and R^-R^+ enantiomeric salts at an arbitrary relative concentration with $C^0_{SS} + C^0_{RR} = 1$. The four ion pairs in solution are subject to equilibrium

$$S^-S^+ + R^-R^+ \overset{K}{\rightleftharpoons} S^-R^+ + R^-S^+$$

with constant K:

$$K = C_{SR} \,.\, C_{RS}/C_{SS} \,.\, C_{RR}$$

while

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

At first sight, chemical shifts in such systems can be treated on the basis of the additive contributions of $\delta_{(R^- R^+)}$ and $\delta_{(R^-S^+)}$ to $\delta_{(R^-)}$ and $\delta_{(S^-S^+)}$ and $\delta_{(S^-R^+)}$ to $\delta_{(S^-)}$. However, the curves calculated in terms of this assumption disagree with the experimental δ(C) curve. For salts of the 7–9 type, not only ion pairs but also hydrogen bonded complexes are possible. The phosphorus-containing anion can form only one hydrogen bond and thus fix an ion pair that acts, therefore, as an elementary species in the formation of more complex associates. Consequently, in media with low dielectric constants, DA spectra of stereoisomeric salts are governed by the following factors: (a) formation of ion pairs as stereoisomeric quasi-molecules, (b) ion exchange, in other words, exchange of chiral centres between the quasi-molecules and (c) association of the quasi-molecules. The problem of interpreting such spectra is resolved into the four-by ion exchange. The effect of these factors on the chemical shifts is described by formulae

$$\delta_{(R^-)} = \frac{\Delta_{RR} C_{RR} + \Delta_{RS} C_{RS}}{C^0_{RR}} \tag{10}$$

$$\delta_{(S^-)} = \frac{\Delta_{SS} C_{SS} + \Delta_{SR} C_{SR}}{C^0_{SS}} \tag{11}$$

where $\delta_{(R^-)}$ and $\delta_{(S^-)}$ are the chemical shifts of the indicator nucleus in the R^- and S^- anions while Δ_{RR}, Δ_{RS}, Δ_{SR}, and Δ_{SS} are the chemical shifts of the R^-R^+, R^-S^+, S^-R^+, and S^-S^+ quasi-molecules formed via a SCAD mechanism, i.e. obeying formula (9).

The δ^{SS}_{SS} and δ^{SR}_{SR} parameters are found experimentally by measuring the chemical shifts in solutions of pure *SS* (or *RR*) and *SR* (or *RS*) enantiomers. The problem stated requires thirteen independent parameters to be found. This is performed using $R^-R^+ + S^-R^+$ and $R^-R^- + R^-S^+$ pairs of diastereomeric salts. In the *RR* + *SR* mixture subject to ion exchange in solution, no new species arise, so processing the experimental data via (7) and (8) gives the chemical shift parameters

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

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

The other pair, R^-R^+ and R^-S^+, gives in a similar way the parameters $\delta^{RR}_{RS} = \delta^{SS}_{SR}$ and $\delta^{RS}_{RR} = \delta^{SR}_{SS}$, and the constants: $\alpha^{RR}_{RS} = \alpha^{SS}_{SR} = \alpha^{RS}_{RR} = \alpha^{SR}_{SS}$.

Figures 11 and 12 present experimental chemical shifts as a function of the relative concentration,† measured for the pairs under discussion.

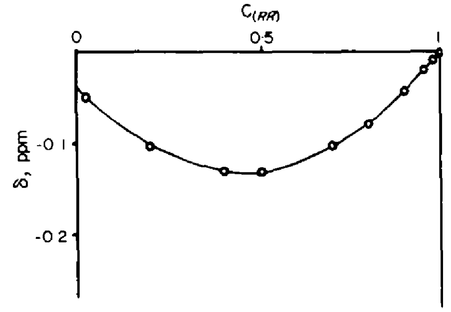


Fig. 11. Chemical shifts in binary salt $RR + RS$ system vs. relative RR concentration; δ^{RR}_{RR} is 0.

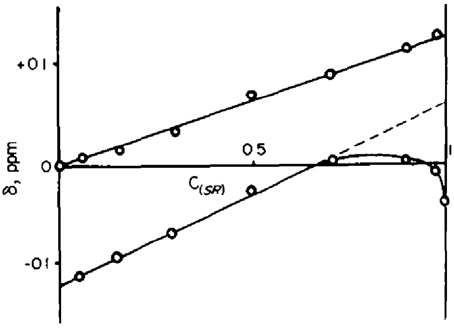


Fig. 12. Chemical shifts in binary salt $RR + SR$ system vs. relative SR concentration; δ^{RR}_{RR} is 0.

Thus, the number of unknown parameters may be reduced to two δ parameters (δ^{SS}_{RR} and δ^{SR}_{RS}), two α parameters (α^{SS}_{RR} and α^{SR}_{RS}), and the equilibrium constant K.

Collation of the theoretical and experimental δ(C) as a function of α^{SS}_{RR} and α^{SR}_{RS} shows that δ(C) is almost independent of the latter two parameters and these may be assumed to be equal to unity, and allows one to find the chemical shifts δ^{SS}_{RR} and δ^{SR}_{RS} and the constant K. The complete set of parameters is given in Fig. 13. The theoretical curve calculated for the values listed is shown in Fig. 10.

Thus, the chemical shifts observed in the salt systems are due to a combined effect of ion exchange equilibrium and SCAD. Consequently, elimination of the equilibrium effect should lead to a pure SCAD.

α

	RR	SS	RS	SR
RR	1	(1)	1·3	1
SS	(1)	1	1	1·3
RS	1·3	1	1	(1)
SR	1	1·3	(1)	1

δ

	RR	SS	RS	SR
RR	0	-0·44	-0·22	+0·01
SS	-0·44	0	+0·01	-0·22
RS	-0·20	-0·14	-0·04	-0·46
SR	-0·14	-0·20	-0·46	-0·04

$K = 1·3$

Fig. 13. Complete set of parameters for the salt system **9**.

We have studied NMR ^{31}P- {^{1}H} spectra of benzylammonium salts **10** of stereoisomeric R and S phosphorus-containing acids. The base in this system is achiral. Therefore, ion exchange cannot have any effect on the chemical shifts. Figure 14 presents the chemical shifts as a function of the relative concentration of the enantiomeric acids. As can be seen, the curve is, indeed, a usual SCAD curve with parameters: $\delta_h = 0$, $\delta_c = 0·25$ ppm and $\alpha_c/\alpha_h = 2·4$.

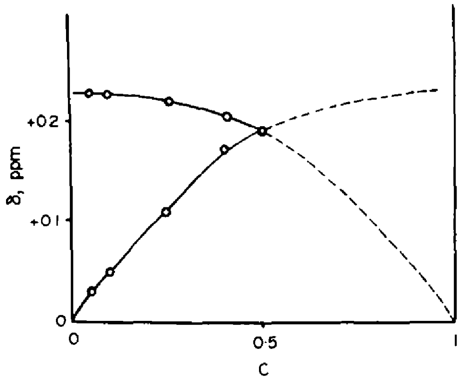
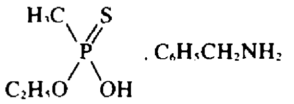


Fig. 14. SCAD in the spectra of the salts **10**, $CHCl_3/CDCl_3$ 1:1; C = 0·5 mole/l, 30°C.



10

CONCLUSION

The matrix elements δ_i^j and α_i^j (and, for salt systems, the value of K) entirely describe association stereospecificity and the association effects on NMR spectra. These parameters provide a better physical characteristic of the systems than does the quantity Δδ whose informativity under these conditions decreases. Temperature variations of the matrix elements have interesting peculiarities on the basis of which certain physical aspects of interaction of chiral molecules involved in an elementary act of association were studied.

The δ(C) curves in binary systems have two parameters, $\delta_i^j - \delta_i^i$ and α_i^j/α_i^i. The first parameter characterises the range of δ(C) variation, the second-deviation of the curve from the straight line formed at $\alpha_c = \alpha_h$, i.e. in the absence of stereospecificity. Tables 2 and 5 show that for SS molecules the ratio $\alpha^i_{SS}/\alpha^{SS}_{SS}$ decreases with temperature increase. On heating, $SS + RR$ and $SS + RS$ mixtures lose their preference for one of the interactions (there is practically no stereospecificity when the SCAD effects are close to vanishing). In contrast, in the $SS + SR$ mixture at lower temperatures interaction of SS molecules with SR molecules is preferential, while at −40° no preference is observed and on further heating the homo interaction of SS molecules with identical SS molecules prevails over SS–SR interaction.

For the SR molecules, heating may either raise the $\alpha^i_{SR}/\alpha^{SR}_{SR}$ value (in the case of $SR + SS$) or diminish it, depending on the counterpart in the mixture. On the whole, the diversity of α_i^j/α_i^i variation for various interactions indicates that the energy of interaction of stereoisomeric molecules subject to intermolecular as-

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†An unexplained variation of the SCAD pattern is observed on Fig. 12 at C close to unity. Probably, higher orders of complexity and/or low inter-associate exchange rates operate at this region.

sociation is not additive with respect to interaction of chiral sites. This conclusion is of fundamental importance.

Interpretation of δ_i^j values and their temperature dependences (Tables 2 and 5) for each elementary associate is a complicated problem. Not entirely discarding the association effect on DA that involves the mechanism of direct induction of additional magnetic fields on the indicator nucleus site it should be considered more probable that DA is primarily affected by conformational alterations induced by the association. The association effect on the position of the signal may be due to fixation in an elementary associate of conformations with different δ values. Of course, we are discussing here not a single pairwise association event but interactions between counterparts which are averaged over all types of associates. It should be also noted that the fixation of conformations at a given δ value implies not a fixed set of conformations but a redistribution of conformation populations which, in general, occurs in terms of an intramolecular hodograph.[18] The conformation population effect may either increase or decrease the δ value, therefore the association may lead to either positive or negative $\delta_i^j - \delta_i^i$ values, in agreement with experiment. Temperature dependence of the chemical shift resulting from each interaction is determined by the variation of averaging the intramolecular hodograph during an elementary association event and by the variation of the association degree in solution, viz., the variation in the effective number of elementary association events in the solution per unit of time. A more detailed study of the mechanisms discussed probably requires further progress in experimental and theoretical methods of quantitative analysis of nuclei shielding in complex molecular structures.

The method of studying complex ensembles of chiral molecules discussed here may provide the basis for investigations of local characteristics of association stereospecificity under statistically controlled conditions.

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