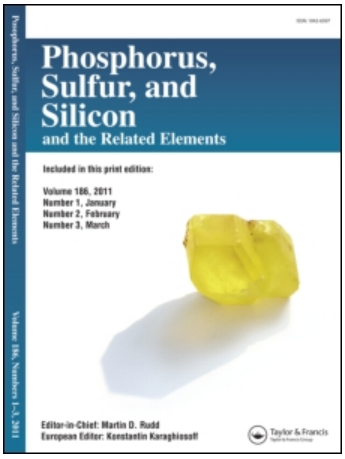

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ASSOCIATE DIASTEREOMERISM OF ORGANOPHOSPHORUS COMPOUNDS

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ASSOCIATE DIASTEREOMERISM OF ORGANOPHOSPHORUS COMPOUNDS †

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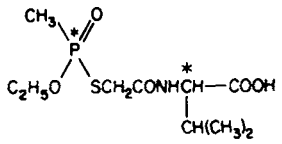
This report will deal with SCAD, statistically controlled associate diastereomerism of enantiomers in solution. The compounds used are derivatives of methylthiophosphonic acid containing an amino acid (valine) group in the thio site.



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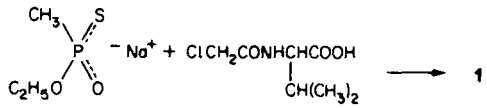
In the beginning these compounds drew our interest as potential insecticides,[1] but the nmr spectra were so strikingly peculiar that we felt a more extensive study was necessary.

The formula shows that there are two chiral centers, a phosphorus and a carbon. Accordingly all four possible stereoisomers have been synthesized,[2] *via* optically active salts of methylthiophosphonic acid and optically active chloroacetyl valines.



Absolute configurations of the starting compounds are known;[3,4] the asymmetry centers are not affected by the reaction when carried out under conditions ruling out any racemization; therefore the configurations of the resulting stereoisomers are beyond doubt. Their properties are listed in Table I.

TABLE I

Configuration		$[\alpha]_g^{25}$ †	N. Eq.	
P	C		Found	Calcd
S	S	-17.5	301.0	297.3
R	R	+18.0	300.5	"
S	R	-35.0	298.0	"
R	S	+35.5	300.5	"

† C1, C_2H_5OH

The stereoisomers are, naturally, pairwise enantiomeric. Our method of studying the SCAD is the measurement of diastereomeric anisochronism in the nmr spectra of the enantiomers. Diastereomeric anisochronism is the magnetic non-equivalence of atoms and groups in diastereomers. The phenomenon is well known.[5,6]

† Plenary Lecture. The Vth International Conference of Organic Phosphorus Chemistry, Gdansk, Poland, September 1974.

Earlier, differences between the nmr spectra of enantiomers were observed only in the presence of a chiral agent[7-9] as shown in Figure 1.

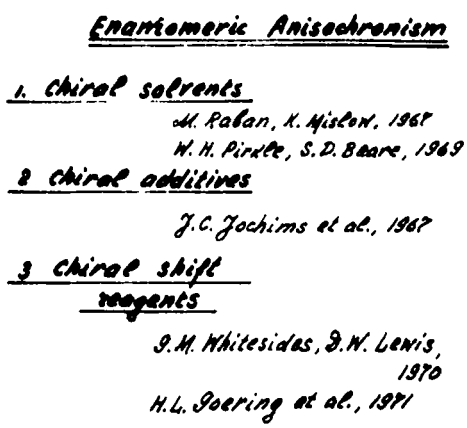


FIGURE 1

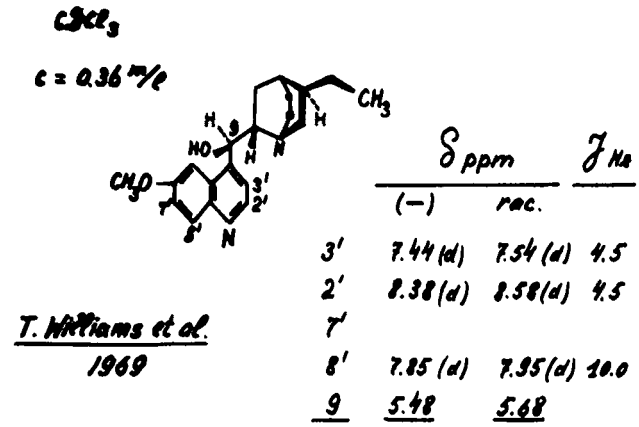


FIGURE 2

In an achiral medium containing no chiral additives, however, the nmr spectra of enantiomers and their racemates were always assumed to be identical. The first exception to this rule has been found by Williams and coworkers.[10] They studied the nmr spectra of optically active (−)-dihydroquinine (Fig. 2), racemic dihydroquinine, and their mixtures in deuteriochloroform and found the following:

(i) The nmr spectra of (−)-dihydroquinine and racemic dihydroquinine are not identical. The difference between the chemical shifts may be as high as 0.2 ppm.

(ii) The multiplicity in the spectrum of a mixture of the racemic and (−)-compounds rises by a factor of two.

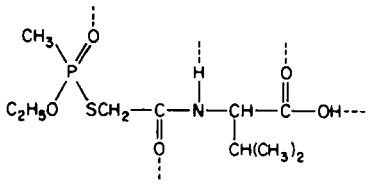
(iii) The effect vanishes on diluting the solution. It becomes weaker when the compounds are acetylated or methanol is used as solvent.

The conclusion of Williams and coworkers was that the effect is caused by interaction of enantiomer molecules in solution.

In our laboratory L. L. Morozov and E. I. Fedin[11] have considered this effect in terms of diastereomeric anisochronism. One of their conclusions is that the spectral multiplicity of enantiomer mixtures may arise owing to the association in solution. Judged by the nmr time scale two types of interaction of enantiomers may occur in solution, namely, the formation of long-lived or short-lived associates. In the first case the increment in multiplicity should be governed by the number of types of long-lived species and the intensities ratio by the ratio of concentrations of these species. To the best of our knowledge this has never been observed. The short-lived associates may form *via* fast inter-associate exchange. We thus come to SCAD. In this case the multiplicity should increase by exactly a factor of two, whereas the doublet intensities ratio should be equal to the ratio of antipode concentrations in the solution.

We have found SCAD in solutions of the methylthiophosphonates mentioned above. The compounds are indeed strongly associated in solution. The molecules contain two proton donor centers, COOH and NH group groups, and three proton acceptor centers, P = O and two C = O groups.

Nmr ^{31}P spectra of the compounds have been studied[2] under total proton decoupling conditions. The spectra of the RR and SS isomers reveal the same narrow signal whose position is invariable with an accuracy up to 0.1 Hz. Let us call this a homo signal, and the respective chemical shift a homo shift; $\delta_h^{SS} = \delta_h^{RR}$. Similarly in the SS/RR (1/1) racemic mixture, only one signal is observed under the following conditions: −60°, $CHCl_3$, 0.4 mole/1. Its chemical shift, δ_r, differs by 0.35 ppm (13.2 Hz) from the homo shift.



Another RR/SS mixture, e.g. 7/3, gives two signals shifted by 0.25 and 0.42 ppm with respect to the homo signal. The intensities ratio is 7/3. The inverse concentration ratio RR/SS of 3/7 leads to exactly the same doublet. This is shown in Figure 3.

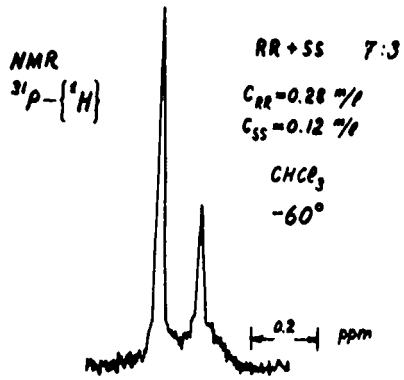


FIGURE 3

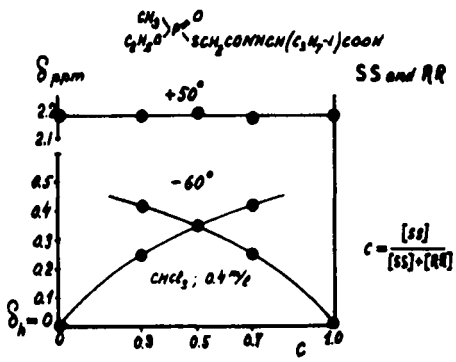


FIGURE 4

Figure 4 presents chemical shifts of the RR/SS mixture as a function of the relative SS concentration at $-60°$ and $+50°$, the total concentration being constant and equal to 0.4 mole/1. The relative concentrations are on the x-axis, and the chemical shifts on the y-axis. The zero on the y-axis is arbitrarily taken as the chemical shift of pure enantiomer in solution. The figure demonstrates that at $-60°$ just one signal is observed at the racemic point where the SS concentration is 0.5. In all other cases there are two signals. In contrast at $+50°$ there is only one signal at any of the concentrations and no SCAD effect at all.

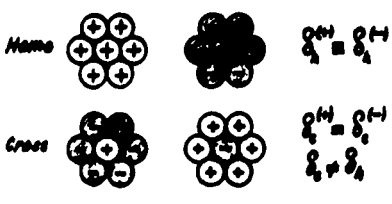


FIGURE 5

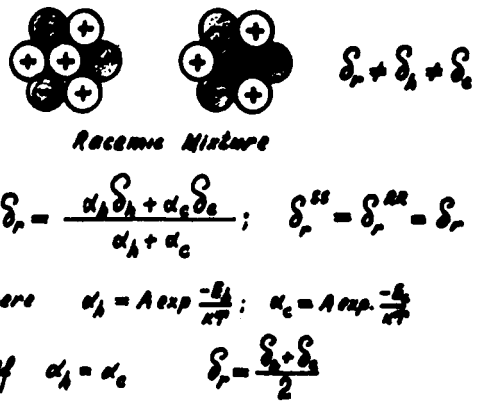


FIGURE 6

Let us make some structural analyses.[2] In a solution of a pure enantiomer, each of the molecules is associated only with identical molecules (homo-association). The characteristic chemical shift is a homo-shift, δ_h. Naturally it has the same value in either of the antipodes. The second line of Figure 5 describes a hypothetical case in which the (+)-antipode molecule associates only with the (−)-molecules, or *vice versa*. This may be termed cross-association. Similar relations arise when there is a small admixture of one of the enantiomers with the other. The chemical shift of the (+)-molecule will now be different; it may be termed a cross-shift, δ_c. Of course it has the same value in either of the enantiomers but it differs from the homo-shift.

In the racemic mixture (Fig. 6) each of the enantiomers associates with (+)- and (−)-molecules. A fast exchange between the associates leads to a chemical shift δ_r formed through averaging the homo- and cross-shifts in each of the enantiomers independently. Consequently the racemic shift of the mixture equals neither homo- nor cross-shifts. However in both the antipodes the situations are mirror reflections of each other; naturally their racemic shifts are equal

$$\delta_r^{(+)} = \delta_r^{(-)}$$

and their coalescence results in one signal (δ_r). On the other hand although the (+)- and (−)-concentrations are equal, the homo- and cross-associations are not identical as to their relative contributions in the averaging. Let α_h and α_c denote statistical weights of homo- and cross-interactions in associates with the antipode concentrations in the solution being equal. They may be expressed exponentially through the energy of the elementary association event (the energy is averaged over all types of association).

$$\alpha_h = A_h \exp(-E_h/kT) \quad ; \quad \alpha_c = A_c \exp(-E_c/kT) \quad .$$

The chemical shift of the racemic mixture may be written as follows (cf. Ref. 12),

$$\delta_r = \frac{\alpha_h \delta_h + \alpha_c \delta_c}{\alpha_h + \alpha_c} \quad .$$

If $\alpha_h = \alpha_c$, then

$$\delta_r = \frac{\delta_h + \delta_c}{2} \quad .$$

Now we may consider a mixture of enantiomers whose concentrations are not equal (Fig. 7).

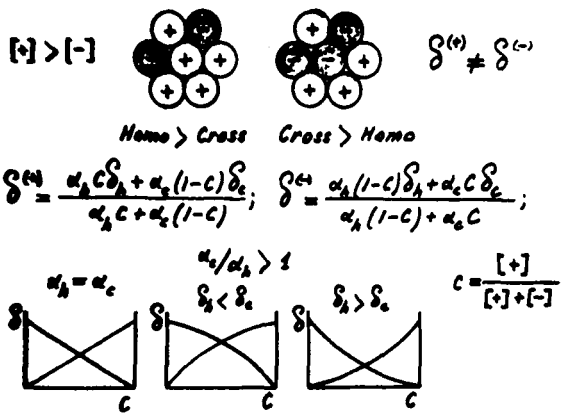


FIGURE 7

Let the (+)-antipode concentration be higher than the (−)-concentration. Identical molecules will then tend to prevail in the vicinity of the (+)-species whereas, in the vicinity of the antipode, the neighboring molecules will be antipodal with respect to the latter. The homo arrangement of the closest environment will predominate in the first case; the cross arrangement in the second case. Consequently the averaged shifts of the (+)- and

(–)-molecules are no longer equal and two signals will appear with the ratio of intensities being equal to the ratio of the (+)- and (–)-concentration.

Mixing of the chemical shifts δ_h and δ_c will make the statistical contribution of each of the signals depend not only on α_h and α_c but also on the respective concentrations. Hence the following formulae:

$$\delta^{(+)} = \frac{\alpha_h C\delta_h + \alpha_c(1-C)\delta_c}{\alpha_h C + \alpha_c(1-C)} \quad ;$$

$$\delta^{(-)} = \frac{\alpha_h(1-C)\delta_h + \alpha_c C\delta_c}{\alpha_h(1-C) + \alpha_c C} \quad ;$$

where

$$C = \frac{[+]}{[+]+[-]} \quad .$$

The formulae show us that plots of $\delta^{(+)}$ and $\delta^{(-)}$ vs relative (+)-concentration dependences have neither extremes nor inflection points. The curvature sign of the function $\delta(C)$ is governed by the sign of the difference δ_h and δ_c and by the ratio α_c/α_h. At $\alpha_h = \alpha_c$, the functions $\delta(C)$ become linear. It is clear that the value of α_c/α_h characterizes the stereospecificity of the reaction where as the difference $(\delta_h - \delta_c)$ performs the same function for the non-equivalence of the indicator nucleus shielding due to homo- and cross-association.

Linear anamorphosis may be carried out for $\delta^{(+)}(C)$ and $\delta^{(-)}(C)$,

$$\frac{1}{\delta^{(+)}} = \frac{1}{\delta_c} + \frac{1}{m\delta_c} \cdot \frac{C}{1-C} = \frac{1}{\delta_c} + \frac{1}{m\delta_c} \cdot \frac{[+]}{[-]} \quad ;$$

$$\frac{1}{\delta^{(-)}} = \frac{m-1}{m\delta_c} + \frac{1}{m\delta_c} \cdot \frac{1}{C} \quad ,$$

where $m = \alpha_c/\alpha_h$, $\delta_h = 0$ (Fig. 8).

This process readily gives us the parameters δ_c and $m = \alpha_c/\alpha_h$. Figure 9 shows the curves calculated from these parameters. The curves fit well with the experimental points. It has been found that α_c/α_h is 2.4 and δ_c is 0.50 ppm for the RR and SS enantiomers at –60° and 0.4 mole/l.

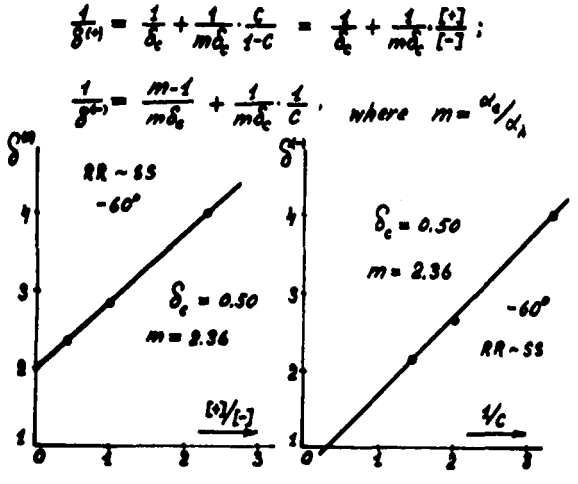


FIGURE 8

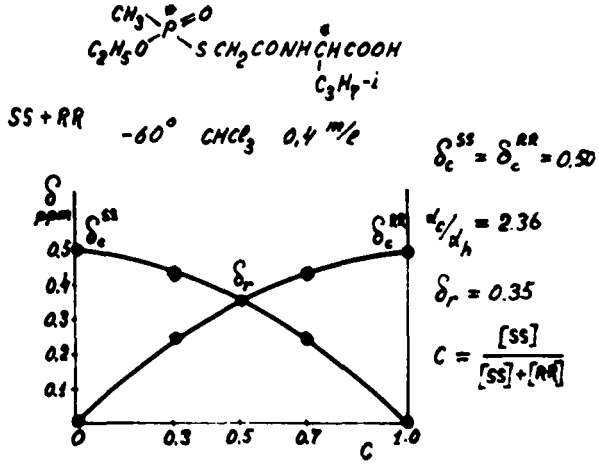


FIGURE 9

The picture is somewhat different for the SR/RS pair. Figure 10 shows that the curves are oriented with the concavity upwards; α_c/α_h is 1.8 and $(\delta_h - \delta_c)$ is 0.59 ppm. The cross-association is, as before, more

favorable than the homo-association but the phosphorus shielding pattern is the reverse of the preceding pattern.

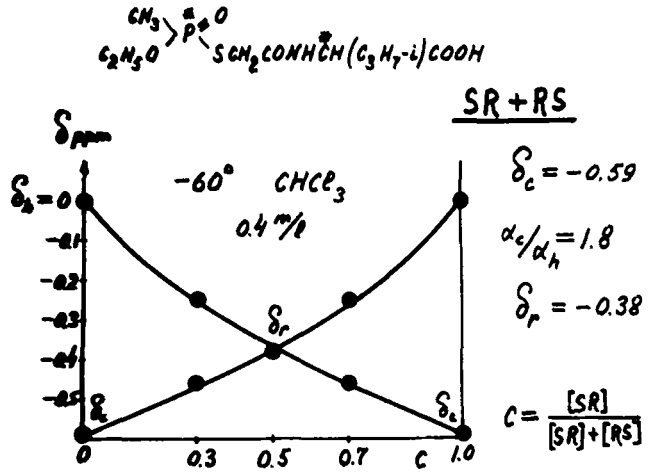


FIGURE 10

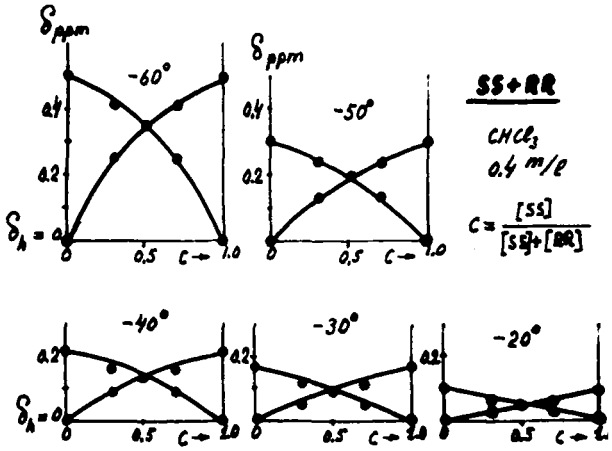


FIGURE 11

A significant difference between the SS/RR and SR/RS pairs has been found in a study of temperature dependences of SCAD. Figure 11 shows enantiomer chemical shifts vs relative concentration at variable temperature. The zero of the scale is always assumed to be equal to the homo-shift δ_h at a given temperature. Raising the temperature from $-60°$ to $-20°$ sharply lowers the difference between the shieldings due to homo- and cross-associations. The stereospecificity α_c/α_h decreases as well and at $-20°$ the dependence is close to linear.

Figure 12 shows the same pattern for the SR/RS pair. In this temperature region δ_h is not equalized with δ_c. Note that no equalization occuts at higher temperatures either. On the other hand, the association-stereospecificity disappears more quickly. Figure 13 lists the respective numerical data.

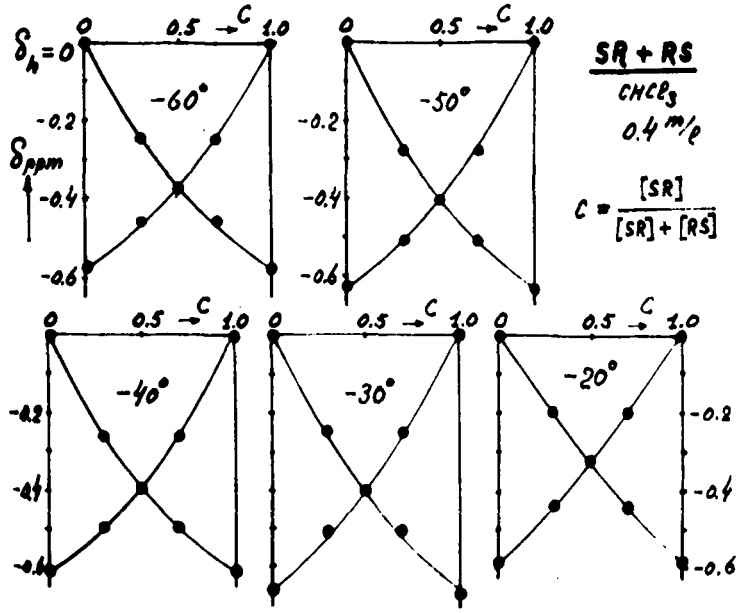


FIGURE 12

SS–RR	−60°	−50°	−40°	−30°	−20°
α_c/α_h	2.4	1.7	1.4	1.2	1.0
$\delta_h-\delta_c$	−0.50	−0.31	−0.22	−0.17	−0.10
SR–RS					
α_c/α_h	1.8	1.7	1.6	1.4	1.2
$\delta_h-\delta_c$	0.58	0.63	0.62	0.66	0.59

FIGURE 13

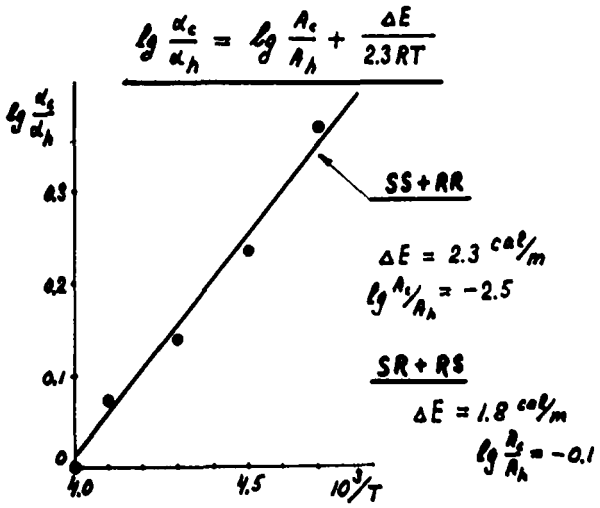


FIGURE 14

The quantity $\log(\alpha_c/\alpha_h)$ is a linear function of the reciprocal temperature $(1/T)$ (Fig. 14):

$$\log(\alpha_c/\alpha_h) = \log\frac{A_c}{A_h} + \frac{\Delta E}{2.3RT},$$

and the equation gives us $\Delta E = 2.3$ kcal/mole for the RR and SS and 1.8 kcal/mole for the RS/SR pair. Consequently the energies of homo- and cross-associations differ markedly.

The difference between the shieldings may be observed in the absence of any association-stereospecificity whatever. The experimental data obtained by Williams and coworkers for dihydroquinine may be plotted in the same way and, however insufficient, they readily fit to the linear δ vs C curve (Fig. 15).

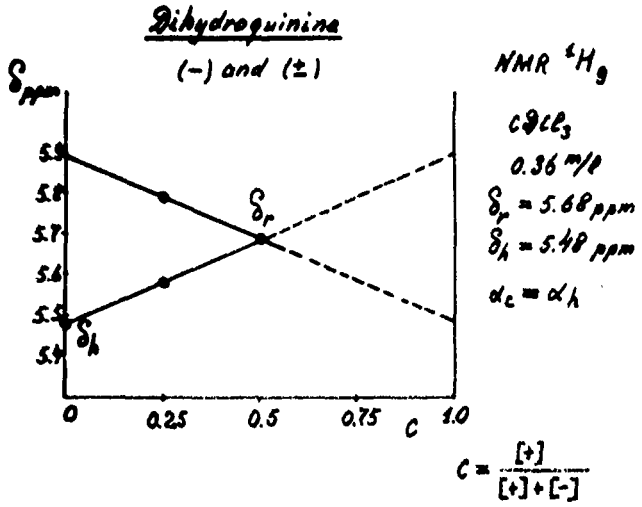


FIGURE 15

Consequently SCAD may be detected by nmr provided certain conditions depending on the enantiomer structures and the thermodynamic parameters of the system are satisfied. If they are not satisfied, the SCAD anisochronism will be lower than the instrumental nmr resolution. If the nmr resolution is high enough, the SCAD effect may give a new method of determination of optical purity without any chiral agent.

My report would be incomplete if I did not mention the other authors of this work. They are: T. A. Mastryukova, A. E. Shipov, M. S. Vaisberg, P. V. Petrovskii, L. L. Morozov, and E. I. Fedin. The results have been discussed by all seven of us; therefire a true picture has been crystallizing rather slowly.

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