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NUCLEAR MAGNETIC RESONANCE SPECTRA, CONFIGURATION AND CONFORMATION OF DIASTEREOMERS—II[1]

ETHYL ESTERS OF 3-SUBSTITUTED 2,3-DIPHENYLPROPANOIC ACIDS: MAGNETIC NONEQUIVALENCE INDUCED BY TWO ASYMMETRIC CENTRES

S. L. SPASSOV

Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia 13, Bulgaria

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Abstract—The NMR spectra of the *erythro* and *threo* forms of the esters $PhCH_aXCH_b(Ph)COOC_2H_5$, where X = OH, NH_2, NHPh, and $NHCONH_2$ have been investigated in $CDCl_3$, DMSO-d_6, benzene and pyridine solutions. Study of the conformational distribution based on the values of the vicinal coupling constants J_{ab} showed that the conformer with antiperiplanar methine protons is the favored one for both diastereomers. Some chemical-shift criteria permitting the assignment of relative configuration of diastereomeric compounds of such type were established. It was shown by use of suitable model compounds that the magnetic nonequivalence of the methylene protons observed in some solvents might be attributed not to either of the asymmetric centres taken alone, but rather to the dissymmetry of the molecule as a whole.

IN THE previous paper,[1] the *erythro* and *threo* forms of a series of 2,3-diphenylpropanoic acids and their methyl esters containing various substituents at C-3 were studied by NMR. It was shown that the favored conformation for both diastereomeric forms is that with antiperiplanar methine protons. Some chemical-shift criteria permitting the determination of the relative configuration of similar compounds as well as the quantitative analysis of mixtures of diastereomers have been also developed.

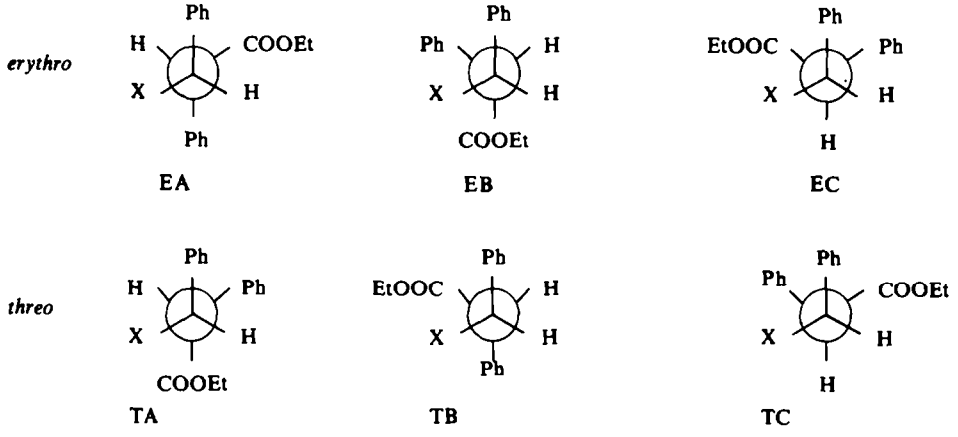
The present paper reports the results of the NMR study of ethyl esters of diastereomeric derivatives of 2,3-diphenylpropanoic acid in various solvents. The position of the conformational equilibria as well as the possibilities for determination of the relative configuration of compounds of such type on the basis of the NMR parameters are discussed. The origin of the magnetic nonequivalence of the ester methylene protons observed in some solvents is investigated by using suitable model compounds.

RESULTS AND DISCUSSION

The NMR parameters of the *erythro* and *threo* forms of the esters $PhCH_aXCH_b(Ph)COOC_2H_5$ (X = OH, NH_2, NHPh, $NHCONH_2$, Br) determined from the room temperature spectra measured in $CDCl_3$ and DMSO-d_6 are given in Table 1. As expected, the two methine protons give a typical AB spectrum, which for compounds **1**, **3** and **4** in DMSO-d_6 and **4** in $CDCl_3$ shows additional splitting of the H_a-signal owing to the coupling with the adjacent proton of the substituent X.

As can be seen from Table 1, the values of the vicinal coupling constant J_{ab} for the compounds **1**–**4** are in the range 7·5–10·9 Hz. Considering each diastereomer as

existing in the form of an equilibrium mixture of three rapidly interconverting staggered conformers (shown below), an *approximate* quantitative estimation of the conformer distribution is possible on the basis of the J_{ab}-values. Assuming[1, 3] the values J_t = 12 ± 1 Hz for the vicinal coupling constant between the antiperiplanar protons in EA and TA, and J_g = 2 ± 1 Hz for that between the synclinal protons in EB, EC, TB and TC, one can calculate[3] the population of the conformation with antiperiplanar protons EA, resp. TA (Table 1; deviation range ± 10%). In spite of the ambiguity concerning the choice of J_t and J_g, these population values could be used at least for comparison purposes with closely related compounds. In a recent paper Reuvers *et al.*[4] recommend for 1,2-diarylethanes the values J_t = 12 Hz and J_g = 5 Hz. However, the latter value seems to be high even in comparison with the corresponding coupling constants in cyclohexane (2·96–3·65 Hz),[5] and in our case it should be reduced anyway owing to



the presence of electronegative substituents which according to their spatial orientation are expected to influence more J_g than J_t.[6, 7] The assumed values for these constants appear to be reasonable also in view of the results obtained recently by Abraham and Gatti[8] for 1,2-disubstituted ethanes.

Thus, it may be seen from Table 1, that in almost all cases the favored (more than 65%) conformation for both diastereomers is that with antiperiplanar protons (EA, resp. TA). This is in agreement with our previous results for the corresponding acids and methyl esters and is observed also for other series of 1,2-diphenylethane derivatives.[1] Notable exceptions are the lower J_{ab}-values for *erythro*-**1** and *threo*-**3** in $CDCl_3$, observed also for the methyl esters.[1] In the case of *erythro*-**1**, the apparent reason is the possibility for intramolecular H-bonding between the hydroxyl and the ester group which should stabilize conformations EB and EC. The existence of such bonding was confirmed by infrared studies of **1** in dilute CCl_4 solution. Beside the free OH-band at 3625 cm^{-1}, the spectra showed another broad band centred at 3550 (*erythro*-**1**) and 3520 (*threo*-**1**) cm^{-1}; as expected, this band is stronger for the *threo* form, since in this case the intramolecular H-bonding can be realized in the favoured conformation TA. Coupling constants of similar magnitude were recorded by Heublein *et al.*[9] for some *erythro*-1,2-diaryl-2-bromoethanols (J_{ab} = 5·6–6·7 Hz in $CDCl_3$), where the existence of intramolecular H-bonds was proved in a similar manner. On the other hand, the

lower coupling constant for *threo*-**3** might be attributed to an attractive charge-transfer interaction between PhN and Ph when synclinal to each other.

The observed larger J_{ab}-values in the more polar solvent DMSO-d_6 in comparison with $CDCl_3$ (Table 1) may be explained, as in the case of the methyl esters,[1] with the better solvation capabilities of conformations EA and TA. The significant solvent as well as temperature dependence of J_{ab}[1] is an indication for the real existence of conformational mixtures, rather than a single angle-distorted conformer, as suggested for *meso*- and (±)-2,3-bis(2,6-dimethylphenyl)butanes.[4]

It is interesting to note that in all cases for both diastereomers J_{ab} of the ethyl esters **1**–**4** is by 0·1–0·7 Hz lower than that of the corresponding methyl esters.[1] Since the difference in electronegativity of COOMe and COOEt is negligible, the effect is apparently due to conformational changes which are not easily conceivable.

As can be expected, the chemical shifts of the methine protons of compounds **1**–**4** are almost identical with those of the respective methyl esters (difference less than ±0·05 ppm).[1] On the other hand, the chemical shifts of the ester methyl and methylene protons as well as of the phenyl groups fall into intervals characteristic for each diastereomeric form (Table 2), thus offering the possibility to determine the relative configuration of related compounds even in cases when only one of the diastereomers is available.[10] The chemical-shift difference for a given *erythro-threo* pair is large enough to permit convenient quantitative analysis via intergration of the appropriate signals, which proved useful for the investigation of the stereochemical course of some reactions yielding diastereomers.[11]

The chemical-shift regularities given in Table 2 may be explained qualitatively on the basis of the shielding contributions of the phenyl groups in the different *erythro* and *threo* conformations in a similar manner as before.[1]

As can be seen from Tables 1 and 2, our results support the relative configurations tentatively ascribed by Buchan and Watson[2] to the bromo-esters **5** (*erythro*, m.p. 134°, and *threo*, m.p. 60°) on the basis of the NMR data for this single pair.

The spectra of the ethyl esters **1**–**4** measured in $CDCl_3$ showed broadening or even slight splitting of some of the components of the methylene quartet, which however in most cases remained unresolved (spectrometer resolution ca. 0·5 Hz). It turned out that in aromatic solvents (benzene or pyridine), an increased multiplicity of the methylene signal could be clearly observed. Apparently the effect is due to a manifested non-equivalence of the methylene protons which appear as a part of an ABX_3 spectrum. Since the chemical-shift difference $\Delta\nu$ between the CH_2 protons happened to be small (<6 Hz at 60 MHz), instead of the four quartets theoretically expected,[12] their spectrum looked more or less like a quartet with doubled components, similar to some of the spectra measured and calculated by Meyer *et al.* for ethyl esters of decalin derivatives.[13] This conclusion is supported by the 100 MHz-spectrum of *threo*-**2** in benzene which after decoupling of the Me protons revealed the expected AB spectrum with $\Delta\nu$ = 9 Hz and J_{gem} = 10 Hz. The latter value is in agreement with literature data for geminal coupling constants in acyclic methylene groups.[13, 14]

Some of the NMR parameters of the diastereomeric esters **1**–**4** measured in aromatic solvents are given in Table 3. Since the complete analysis of the CH_2 spectra was rendered difficult by the overlap of the H_b-doublet, the methylene group non-equivalence was characterized quantitatively by the splitting of the quartet components $\Delta\nu'$ (Hz) directly measured from the spectra.

Many cases of nonequivalent methylene protons have been described in the literature;[12, 15] the effect is usually attributed to molecular asymmetry and differences in the conformational population.[16] In most cases, however, the nonequivalent methylene group was separated from the asymmetric centre by no more than two bonds, further increase of the separation usually cancelling the effect.[17] Three-bond separation nonequivalence, as in our case, has been reported by Meyer *et al.* in their aforementioned paper,[13] where the effect has been explained with the different shielding of the CH_2 protons by the rigid decalin system which fixes the ester group in an appropriate conformation.

Since the esters studied by us contain two asymmetric carbons, it seemed interesting to find out which of them or, more exactly, which of their substituents exerts the main influence on the methylene protons in the sense of their nonequivalence. For this purpose, the model compounds **6**, **7** and **8** were prepared, which could be regarded as analogues of **2** (showing the largest CH_2 nonequivalence) in which the substituents at C-2 and C-3 were systematically replaced by H-atoms. However, it turned out that neither of these compounds showed anything more than a simple sharp-component quartet for the CH_2 group in $CDCl_3$ and benzene solutions. Thus it seems that the

$PhCH(NH_2)CH_2COOEt$	$H_2NCH_2CH(Ph)COOEt$	$PhCH_2CH(Ph)COOEt$
6	**7**	**8**

methylene nonequivalence of the ethyl esters **1–4** might be attributed to neither of the individual asymmetric centres, but rather to the dissymmetry of the molecule as a whole.

From NMR data for the *erythro* and *threo* PhCH(NHPh)CH(Et)COOEt measured in CCl_4 one can deduce that nonequivalence of the ester CH_2 group has not been observed for these closely related to **3** esters.[18]

As indicated in Table 3 and in the text above, the CH_2 nonequivalence $\Delta\nu$ decreases in the following order of solvents: benzene > pyridine > $CDCl_3$ > DMSO-d_6 and acetone (no peak broadening was observed in the latter two solvents). This order is in agreement with the literature data,[14] according to which $\Delta\nu$ is approximately reversely proportional to the dielectric constant ε of the solvent. As an exception of this rule, in our case $\Delta\nu$ is larger in pyridine ($\varepsilon = 12$) than in $CDCl_3$ ($\varepsilon = 5$). This suggests a probable relation between the CH_2 magnetic nonequivalence and the possibility of complex formation between the esters **1–4** and aromatic solvents as benzene and pyridine, similar to that assumed for a number of carbonyl compounds.[19] The decrease in $\Delta\nu$ observed at elevated temperatures (Table 3, footnote *d*) might be connected either with the decomposition of such a complex, or with a conformational averaging at higher temperatures.

The comparison of the data in Tables 1 and 3 reveals that the J_{ab}-values in $CDCl_3$ and benzene in most cases do not differ substantially. The same constants in pyridine for both *erythro* and *threo* **1–4** are higher by 0·1–2 Hz than the values in $CDCl_3$ and are very close to those in DMSO-d_6. This might be an indication for a similar solvation of the conformers in $CDCl_3$ and benzene (nonpolar solvents) on the one hand, and in DMSO-d_6 and pyridine (polar solvents) on the other.

TABLE 1. NMR PARAMETERS OF DIASTEREOMERIC ETHYL ESTERS OF 3-SUBSTITUTED 2,3-DIPHENYLPROPANOIC ACIDS

$PhCH_aXCH_b(Ph)COOCH_2CH_3$

Comp. No.	X	Config.	Solvent[a]	J_{ab} (Hz)	%EA or TA	Chemical shifts (ppm relative TMS)					
						H_a	H_b	CH_3[b]	CH_2[b]	Ph[c]	OH, NH, NH_2
1	OH	*erythro*	$CDCl_3$	7·5	55	5·26	3·85	1·00	3·97	7·3d	2·6
			DMSO-d_6	8·6	66	5·08	3·90	0·85	3·81	7·3s	5·4 (J_{CHOH} = 5 Hz)
		threo	$CDCl_3$	8·9	69	5·17	3·85	1·17	4·17	7·1d	3·3
			DMSO-d_6	9·8	78	5·13	3·85	1·16	4·12	7·15s	5·7 (J_{CHOH} = 4·5 Hz)
2	NH_2	*erythro*	$CDCl_3$	9·4	74	4·58	3·78	0·90	3·85	7·35m	1·3
			DMSO-d_6	9·6	76	4·37	3·78	0·78	3·75	7·35m	2·2
		threo	$CDCl_3$	9·8	78	4·50	3·78	1·20	4·18	7·1s	1·8
			DMSO-d_6	10·5	85	4·38	3·83	1·12	4·11	7·1s	2·1
3	NHPh	*erythro*	$CDCl_3$	9·6	76	4·90	3·80	0·91	3·85	6·2–7·5[d]	
			DMSO-d_6	10·5	85	5·03	4·10	0·79	3·75	6·4–7·8[d]	6·05 (J_{CHNH} = 9·4 Hz)
		threo	$CDCl_3$	7·7	57	4·90	3·93	1·10	4·08	6·4–7·3[d]	
			DMSO-d_6	10·5	85	5·15	4·03	1·09	4·09	6·3–7·4[d]	(J_{CHNH} = 10 Hz)
4	$NHCONH_2$	*erythro*	$CDCl_3$	9	70	5·38	4·10	0·97	3·95	7·35s	NH 5·55 (J_{CHNH} = 9 Hz), NH_2 4·2
			DMSO-d_6	10·9	89	5·32	4·06	0·82	3·77	7·35m	NH 6·45 (J_{CHNH} = 9·4 Hz), NH_2 5·2
		threo	$CDCl_3$	8·6	66	5·35	3·98	1·11	4·08	7·2d	NH 6·85 (J_{CHNH} = 9·1 Hz), NH_2 4·9
			DMSO-d_6	9·0	70	5·25	4·05	1·09	4·01	7·15d	NH 6·75 (J_{CHNH} = 9·4 Hz)
5	Br[e]	*erythro*	$CDCl_3$	12	100	5·43	4·36	0·90	3·90	7·2–7·7	
		threo	$CDCl_3$	12	100	5·54	4·40	1·28	4·25	7·0–7·3	

[a] Concentration of the solutions ca. 0·3 M

[b] $J_{CH_3CH_2}$ is in all cases in the interval 6·8–7·1 Hz

[c] Centre of the signal: s-singlet, d-doublet, m-multiplet

[d] Very broad and complex multiplet caused by superposition of the PhN-signals

[e] Data taken from Ref. 2

TABLE 2. CHEMICAL SHIFTS INTERVALS OF SOME PROTON GROUPS IN THE *erythro* AND *threo*-ESTERS **1-5** (BASED ON THE DATA PRESENTED IN TABLE 1)

Group	Solvent	*Erythro*	*Threo*
CH_3	$CDCl_3$	0·90–1·00	1·10–1·28
	DMSO-d_6	0·78–0·85	1·09–1·16
CH_2	$CDCl_3$	3·85–3·97	4·08–4·25
	DMSO-d_6	3·75–3·81	4·01–4·12
$2C_6H_5$	$CDCl_3$ and DMSO-d_6	7·3–7·35	7·1–7·2

It is interesting to note that whereas the difference $\delta_{CDCl_3}-\delta_{benzene}$ is small (0 to $-0{\cdot}2$ ppm) for the methine proton shifts and larger for the CH_3 (ca. $+0{\cdot}3$ ppm) and the CH_2 (ca. $+0{\cdot}2$ ppm) protons, the reverse is observed for the difference $\delta_{CDCl_3}-\delta_{pyridine}$, where the values for CH are $-0{\cdot}2$ to $-0{\cdot}8$ ppm, and for CH_3 and CH_2 $<0{\cdot}2$ ppm, mostly positive (Tables 1 and 3). This means that the solvation in benzene and pyridine occurs with a different geometrical orientation of the solvent. The drastic deshielding of the methine protons in pyridine for X = OH, NHPh and $NHCONH_2$ and the much weaker one for X = NH_2 is in general qualitatively proportional to the proton-donating properties of these groups, i.e. to the possibilities for hydrogen bonding with the solvent.

TABLE 3. NMR PARAMETERS OF ESTERS **1-4** WHEN NONEQUIVALENCE OF THE METHYLENE PROTONS IS OBSERVED
$PhCH_aXCH_b(Ph)COOCH_2CH_3$

Comp. No.	X	Config.	Solvent[a]	J_{ab} (Hz)	%EA or TA	Chemical shifts (ppm) H_a	H_b	CH_3[b]	CH_2[b]	$\Delta\nu'$[c] (Hz)
1	OH	*erythro*	benzene	6·8	48	5·25	3·90	0·68	3·70	1·1
			pyridine	8·6	66	5·70	4·37	0·82	3·88	[d]
		threo	benzene	9·4	74	5·27	3·97	0·83	3·93	1·9
			pyridine	10·3	83	5·72	4·36	1·11	4·20	1·0
2	NH_2	*erythro*	benzene	9·6	76	4·58	3·85	0·60	3·65	2·5[e]
			pyridine	9·6	76	4·77	4·08	0·80	3·81	0·7
		threo	benzene	9·4	74	4·55	3·90	0·86	3·97	2·2
			pyridine	9·9	79	4·74	4·15	1·06	4·13	1·5
3	NHPh	*erythro*	benzene	9·8	78	5·13	3·87	0·63	3·63	2·2
			pyridine	10·4	84	5·54	4·43	0·80	3·86	0·5
		threo	benzene	8·3	63	5·09	3·96	0·80	3·89	0·6
			pyridine	9·8	78	5·53	4·40	1·02	4·13	[d]
4	$NHCONH_2$[f]	*erythro*	pyridine	10·6	86	6·17	4·44	0·75	3·77	0·5
		threo	pyridine	9·1	71	6·08	4·49	1·06	4·11	[d]

[a] Concentration of the solutions ca. 0·3 M
[b] $J_{CH_3CH_2}$ is in the interval 6·8–7·0 Hz
[c] For definition of $\Delta\nu'$, see the text
[d] Only broadening of the peaks observed ($\Delta\nu' < 0{\cdot}5$ Hz)
[e] Temperature dependence: $\Delta\nu' = 1{\cdot}3$ (40°), 0·6 (50°), $<0{\cdot}5$ Hz (60°)
[f] Low solubility in benzene

EXPERIMENTAL

The NMR spectra were measured on a JEOL model JNM-C-60S spectrometer operating at 60 MHz at normal probe temperature (ca. 25°) unless otherwise stated. The 100 MHz-spectra were taken on a Varian HA-100 instrument. The chemical shifts are relative to internal TMS and are believed to be accurate to 0·02 ppm, and the coupling constants to 0·1 Hz.

All diastereomeric compounds studied were analitically and stereochemically pure racemates with independently proved relative configurations. Most samples were generously supplied by the authors of methods for their preparation, as follows: *erythro* and *threo*- **2**,[20] **3**,[21] **4**.[22] *Erythro* and *threo*-**1**, supplied by Dr. N. Berova, were prepared through esterification of the respective acids with EtOH-HCl.[23] The esters **6**, **7** and **8** were prepared by similar esterification of the acids synthesized as follows: 3-amino-hydrocinnamic acid,[24] 3-amino-2-phenylpropanoic acid,[25] and 2,3-diphenylpropanoic acid—through hydrogenation of 2-phenylcinnamic acid in presence of Pd/C catalyst.

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