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CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOISOMERS

VI. RELATIVE RETENTIONS OF THE DIASTEREOISOMERS OF 3-HYDROXY-2,3-DIARYLPROPIONATES ON SILICA GEL AND THEIR THEORETICAL INTERPRETATION

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SUMMARY

Separations by thin-layer chromatography on silica gel have been achieved for fifteen diastereoisomeric pairs of the type Ar–CH(X)–CH(COOR)–Ar′ (X = OH, OAc or NHPh; R = Me, iso-Pr, n-Bu, iso-Bu or tert.-Bu) which have known relative configurations. R_F values of the compounds studied have been measured as a function of the concentration of diethyl ether in mixtures with heptane. Thus, the values of a parameter, related to the adsorption pattern, have been found. The relative retentions of the diastereoisomers $R_{F(erythro)} > R_{F(threo)}$ and $R_{F(threo)} > R_{F(erythro)}$ within those compounds where X = OH and R = tert.-Bu have been explained. Four different patterns of adsorption have been discussed. The data and the conclusions permit further outlining of the scope of each of the two retentions; they also support the previously elaborated criteria for thin-layer chromatographic assessment of the relative configurations of other diastereoisomeric pairs of tetrasubstituted ethanes.

INTRODUCTION

Separation of diastereoisomeric compounds by liquid–solid chromatography (LSC) on polar adsorbents such as silica gel and alumina is widely practised[1–23] (see also references cited in the previous papers of the present series[24–28]). The techniques used are thin-layer chromatography (TLC), column chromatography and normal-phase high-performance liquid chromatography, the last being lately of increased importance. The separation itself has been the main problem as it enables isolation of each isomer in pure form. In some cases of related compounds, one isomer moves faster than its diastereoisomer. More comprehensive treatment of this phenomenon is given by Helmchen and co-workers[5–7,17] and by Pirkle and co-workers[2,3]. The most difficult point of this problem is the inversion, *i.e.* a few of the diastereoisomers have a reverse relative retention[8].

In our series[24-28], diastereoisomeric tetrasubstituted ethanes, $>CH-CH<$ and related cyclic compounds. which have known relative configurations, have been investigated. Our efforts have been directed to performing TLC separation on the same silica gel and thus to establish experimentally the relative retention of the diastereoisomers. The retention orders have been elucidated on the basis of LSC theory[29-35]. As far as tetra-substituted ethanes are concerned, the retention $R_{F(erythro)}$ $> R_{F(threo)}$ and the opposite alternative, $R_{F(threo)} > R_{F(erythro)}$, are both possible, depending mainly on the nature of the substituents. The purpose of our studies is to outline the scope of each pattern of retention. So far, semi-empirical criteria have been given[25,28] for using the order $R_{F(erythro)} > R_{F(threo)}$ to assess the relative configurations of some diastereomeric tetrasubstituted ethanes. Since the diastereoisomeric species investigated showed mainly the latter order, it was of utmost importance to find compounds having the opposite order. This paper reports the TLC behaviour of diastereoisomeric 3-hydroxy-2,3-diarylpropionates and their O-acetyl derivatives which offer such a possibility.

In our opinion, any differences in the chromatographic behaviour of diastereoisomers deserves detailed investigation since they could be highly informative. For instance, the reverse retentions of a given set of diastereoisomers obtained on two separate silica gels[11] are probably due to secondary adsorbance effects (see p. 140 of ref. 29); a study of intramolecular hydrogen bonding in the solutes could be of significance. It is of importance to clarify the factors responsible for the inversion of the retention sequence due only to replacement of CH_3 by C_2H_5 in a mevalonate series[8]. It should be mentioned that the retentions established in the present paper and in refs. 25 and 26 were even more surprising than those in ref. 8. Besides, the interpretation of $R_{F(threo)} > R_{F(erythro)}$ established[18] for eight diastereoisomeric pairs of type 1 (see the formulae below, X = OH or derivatives, Y = CH_3 or CH_2HgCl, Ar = Z = Ph or $4-CH_3OC_6H_4$) requires further investigations.

EXPERIMENTAL

Silica gel DG (Riedel-de Haen, Hanover, G.F.R.) was used as previously[24-28]. TLC was performed as reported in ref. 24 on 0.5 mm layers without pre-saturation of the tank with the vapours of the solvent system. The developing distance was 18 cm.

As previously[27,28], the dilution method of Soczewiński et al.[32] was also used for elucidation of the adsorption pattern. R_F values of the compounds studied were measured in mixtures of heptane (diluent) and diethyl ether (polar solvent) with increasing concentration, C, of diethyl ether, the latter concentration being proportional to the molar fraction, X_S, of the polar solvent in the equation

$$R_M \left[= \log \left(\frac{1}{\xi R_F} - 1 \right) \right] = \text{constant} - n \log X_S$$

where ξ is a constant depending on the chromatographic conditions. The conversion of R_F into R_M values was done directly by means of the graph shown in Fig. 3 of ref. 32 with $\xi = 1$. The values of the parameter n from the above equation were derived from the slope of R_M versus $\log C$ plots. The absolute values of n are indicative of the

adsorption pattern[36]. In applying this method, the measurements were performed as in ref. 27 with the same reproducibility.

Erythro- and threo-isomers 1–4 and 9–28 (see Table II) have been prepared[37–40] by means of Reformatsky or Ivanoff reactions followed by treatment with diazomethane. The hydroxy-esters 5–8 (m.sp. ca. 50°C) were synthesized by Reformatsky reaction as described for other cases[39,40]. The crude mixtures of 5–6 and 7–8 were separated by repeated column chromatography on a 100-fold quantity of silica gel S (Riedel-de Haen) with heptane–diethyl ether–ethanol (98.5:1:0.5), the separation being controlled by TLC (see Table II). The relative configurations were assessed by the NMR spectra[41] as recommended in ref. 42.

The IR spectra of 1–2 and 9–10, in 10^{-3} M carbon tetrachloride solution, are very similar for each isomer. The bands for free OH (more intense in 1 and 9) appear at 3625 cm^{-1} and those for OH $\cdots$ O = C and OH $\cdots$ Ar are in the region 3400–3600 cm^{-1} (ref. 41).

The anilino-ester 30 has been prepared by Simova and Kurtev[43]. The diastereoisomeric compound 29, characterized by its NMR spectrum[41], has been isolated from the filtrates of the recrystallization of 30.

The preferred conformations of 1–2, 5–10, 21, 22, and 29–30 in CDCl$_3$ are those with antiperiplanar hydrogen atoms[41,42].

RESULTS AND DISCUSSION

The separation of a number of erythro- and threo-3-hydroxy-2,3-diarylpropionic acids and their derivatives has been controlled by TLC on silica gel. Table I shows the R_F values. The data have previously been reported in a dissertation[44] without any interpretation of the retention order of $R_{F(erythro)} > R_{F(threo)}$ in all cases.

Some of the compounds in Table I and the esters 5–8 and 29–30 mentioned in the Experimental section were investigated in detail in the present study. Table II presents the R_F values of compounds 1–30, investigated with four different solvent systems, and the values of the parameter n from R_M versus log C plots. The latter are shown in Fig. 1a–d. Heptane was used as diluent and diethyl ether as the polar solvent when applying Soczewiński's method[32] since these solvents were used in the usual TLC separations. Only heptane–diethyl ether mixtures were used since it was of importance to compare the TLC behaviour of 1–30 and not to study changes in the values of n owing to difverent solvent systems. The values of n are not exactly 1 or 2 which would correspond to one- or two-point adsorption, respectively[36]. This deviation can probably be attributed to solvation effects participating in the main adsorption mechanism[45].

A separation was achieved in all cases studied. With methylene chloride or methylene chloride–diethyl ether (95:5), the separation was excellent for the majority of cases. Table II shows clearly that the order $R_{F(erythro)} > R_{F(threo)}$ is characteristic for all compounds except the tert.-butyl esters 9–10 which have the reverse order. It was surprising that compounds 13–14 and 29–30, which also contain a tert.-Bu group, did not behave as 9–10. Treatment of these results requires a review of our previous papers[24,25,27,28], which will be presented retrospectively.

TABLE I

R_F VALUES[44] OF DIASTEREOISOMERIC 3-HYDROXY-2,3-DIARYLPROPIONIC ACIDS AND DERIVATIVES OF THE TYPE Ar–CH(X)–CH(Y)–Ar'

Ar	Ar'	X	Y	Solvent system*	$R_{F(threo)}$	$R_{F(erythro)}$
Phenyl	Phenyl	OH	COO-iso-propyl	A	0.37	0.45
2-CH₃C₆H₄	Phenyl	OH	COOCH₃	B	0.16	0.27
4-CH₃C₆H₄	Phenyl	OH	COOCH₃	B	0.17	0.27
2-ClC₆H₄	Phenyl	OH	COOCH₃	B	0.16	0.33
4-ClC₆H₄	Phenyl	OH	COOCH₃	B	0.15	0.25
4-CH₃OC₆H₄	Phenyl	OH	COOCH₃	B	0.07	0.13
α-Naphthyl	Phenyl	OH	COOCH₃	B	0.15	0.24
Phenyl	4-BrC₆H₄	OH	COOCH₃	B	0.12	0.26
2-CH₃C₆H₄	Phenyl	OCOCH₃	COOCH₃	B	0.34	0.41
2-ClC₆H₄	Phenyl	OCOCH₃	COOCH₃	B	0.28	0.38
4-ClC₆H₄	Phenyl	OCOCH₃	COOCH₃	B	0.27	0.39
4-CH₃OC₆H₄	Phenyl	OCOCH₃	COOCH₃	B	0.20	0.27
α-Naphthyl	Phenyl	OCOCH₃	COOCH₃	B	0.21	0.30
Phenyl	4-BrC₆H₄	OCOCH₃	COOCH₃	B	0.22	0.31
2-CH₃C₆H₄	Phenyl	OH	COOH	C	0.38	0.47
4-CH₃OC₆H₄	Phenyl	OH	COOH	C	0.24	0.33
2-ClC₆H₄	Phenyl	OH	COOH	C	0.40	0.50
4-ClC₆H₄	Phenyl	OH	COOH	C	0.37	0.46
α-Naphthyl	Phenyl	OH	COOH	C	0.34	0.40
Phenyl	4-CH₃C₆H₄	OH	COOH	C	0.31	0.41
2-CH₃C₆H₄	4-CH₃C₆H₄	OH	COOH	C	0.37	0.45
4-CH₃OC₆H₄	4-CH₃C₆H₄	OH	COOH	C	0.23	0.33
2-ClC₆H₄	4-CH₃C₆H₄	OH	COOH	C	0.36	0.43
4-ClC₆H₄	4-CH₃C₆H₄	OH	COOH	C	0.32	0.41
Phenyl	4-BrC₆H₄	OH	COOH	C	0.36	0.47
2-CH₃C₆H₄	4-BrC₆H₄	OH	COOH	C	0.33	0.44
4-CH₃OC₆H₄	4-BrC₆H₄	OH	COOH	C	0.28	0.39
2-ClC₆H₄	4-BrC₆H₄	OH	COOH	C	0.34	0.45
4-ClC₆H₄	4-BrC₆H₄	OH	COOH	C	0.35	0.43
Phenyl	2-ClC₆H₄	OH	COOH	C	0.34	0.41
2-ClC₆H₄	2-ClC₆H₄	OH	COOH	C	0.36	0.43

* TLC on silica gel DG (Riedel-de Haen). Solvent systems: A = benzene–diethyl ether (7:1); B = heptane–diethyl ether (2:1); C = light petroleum–benzene–diethyl ether–acetic acid (9:1:10:0.5).

The relation $R_{F(erythro)} > R_{F(threo)}$ on silica gel was established for 60 diastereoisomeric pairs of type 1:

Ar–CH(X)–CH(Y)–Z   X and Y = NH₂, OH, COOH and their derivatives
type 1   Z = Ar' or R
     Ar and Ar' = phenyl, 4-alkoxyphenyl, 3,4-dialkoxyphenyl or carbazyl
erythro and *threo*   R = CH₃ or C₂H₅

According to the Snyder–Soczewiński theory[29-35], most widely adopted in LSC, the relative retention of non-ionic compounds depends on the difference between the diastereoisomeric pair of four factors (see eqn. 2 in ref. 25) having the
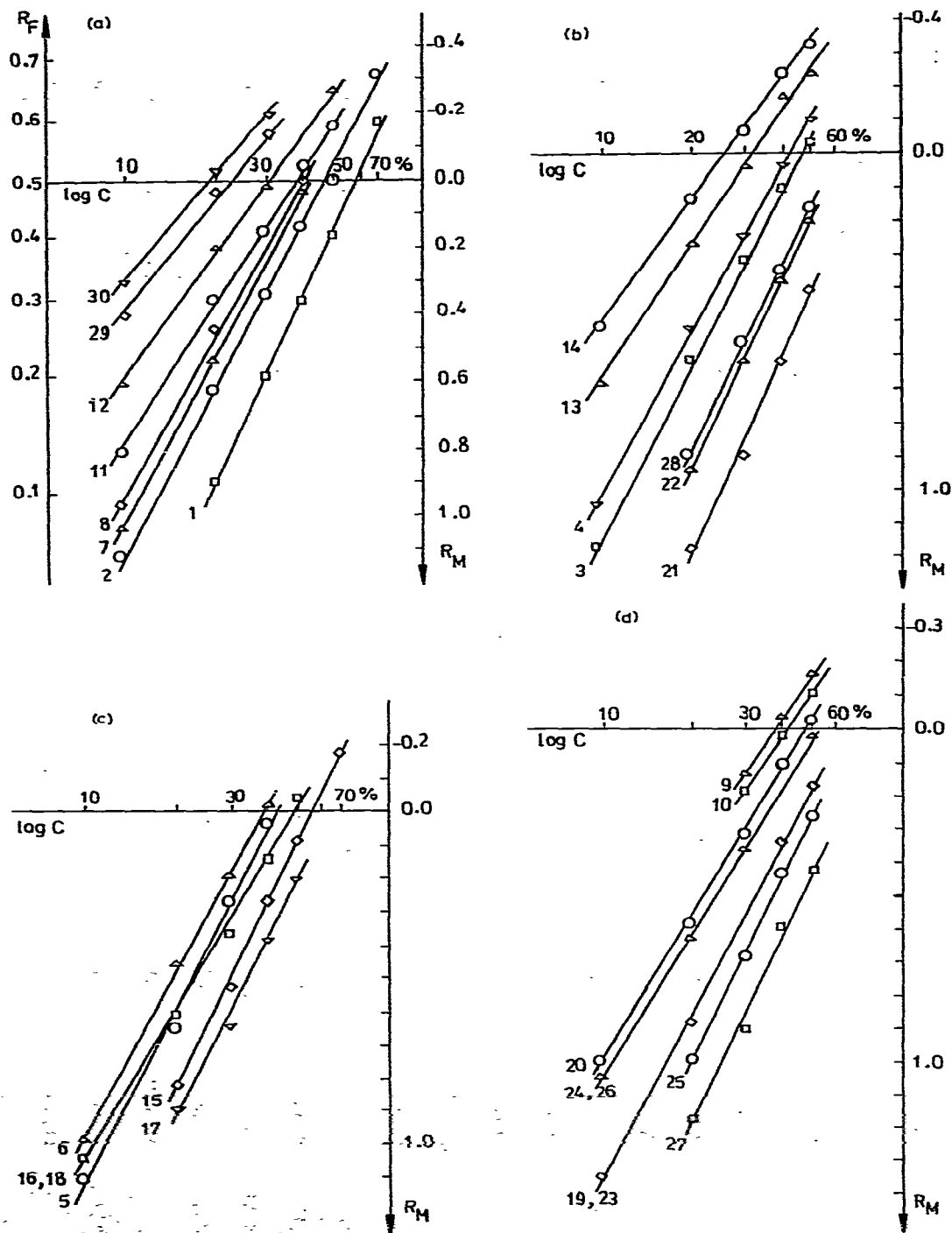
Fig. 1. Plots of R_M versus log C (% of diethyl ether) for compounds 1–30 (see formula in Table II). Diluent: heptane.

TABLE II.

R_F VALUES AND ABSOLUTE VALUES OF THE SLOPES (n) OF R_M VERSUS LOG C PLOTS* FOR COMPOUNDS OF THE TYPE Ar-CH(X)-CH(Y)-Ar'

Ar	Ar'	X	Y	Configuration	Compound No.	R_F Heptane–diethyl ether (2:1)**	Heptane–acetone (5:1)**	Methylene chloride–diethyl ether (95:5)	Methylene chloride	n
Phenyl	Phenyl	OH	COOCH₃	threo	1***	0.32	0.30	0.50	0.21	2.0
				erythro	2***	0.46	0.36	0.69	0.39	1.8
Phenyl	Phenyl	OH	COO-iso-propyl	threo	3	0.48	0.38	0.62	0.29	1.7
				erythro	4	0.53	0.41	0.70	0.39	1.6
Phenyl	Phenyl	OH	COO-n-butyl	threo	5	0.51	0.41	0.66	0.32	1.8
				erythro	6	0.56	0.42	0.73	0.42	1.7
Phenyl	Phenyl	OH	COO-iso-butyl	threo	7	0.54	0.42	0.66	0.33	1.7
				erythro	8	0.59	0.42	0.73	0.42	1.7
Phenyl	Phenyl	OH	COO-tert-butyl	threo	9	0.56	0.46	0.69	0.36	1.4
				erythro	10	0.53	0.42	0.69	0.36	1.4
Phenyl	Phenyl	OCOCH₃	COO-iso-propyl	threo	11	0.59	0.49	0.80	0.58	1.4
				erythro	12	0.68	0.56	0.85	0.65	1.4
Phenyl	Phenyl	OCOCH₃	COO-tert-butyl	threo	13	0.66	0.54	0.83	0.62	1.4
				erythro	14	0.72	0.59	0.88	0.68	1.3
2-ClC₆H₄	Phenyl	OH	COOCH₃	threo	15	0.34	0.29	0.58	0.31	1.9
				erythra	16	0.49	0.33	0.73	0.48	1.6
4-ClC₆H₄	Phenyl	OH	COOCH₃	threo	17	0.36	0.26	0.53	0.26	1.9
				erythro	18	0.51	0.33	0.74	0.48	1.6
4-CH₃C₆H₄	Phenyl	OH	COOCH₃	threo	19	0.39	0.27	0.49	0.21	1.8
				erythro	20	0.49	0.34	0.70	0.39	1.6
4-CH₃OC₆H₄	Phenyl	OH	COOCF₃	threo	21	0.23	0.18	0.38	0.14	2.0
				erythro	22	0.34	0.23	0.56	0.24	1.9
α-Naphthyl	Phenyl	OH	COOCH₃	threo	23	0.37	0.26	0.59	0.29	1.8
				erythro	24	0.49	0.31	0.74	0.48	1.6
4-BrC₆H₄	Phenyl	OH	COOCH₃	threo	25	0.32	0.26	0.49	0.23	1.8
				erythro	26	0.50	0.33	0.73	0.48	1.6
4-CH₃OC₆H₄	Phenyl	OH	COOCH₃	threo	27	0.23	0.19	0.36	0.13	2.0
				erythro	28	0.36	0.24	0.58	0.27	1.9
Phenyl	Phenyl	NHPh	COO-tert-butyl	threo	29	0.78	0.54	0.94	0.88	1.2
				erythro	30	0.82	0.54	0.94	0.88	1.2

* See Experimental section and Fig. 1a–d.

** Developed twice.

*** R_F values of 1–2 with heptane–diethyl ether (1:1) (see ref. 24).

following physical meaning: electronic and steric effects; localization effects, reflecting the number of the adsorbing groups; solute area effects; and so-called secondary effects. When the same adsorbent is used, as in our cases, the latter effects are only secondary solvent ones which arise from the specific solvent–solute and solvent–adsorbent interactions. Using methylene chloride, which is free from significant solvent effects, instead of solvent systems which exhibit such effects, the relation $R_{F(erythro)} > R_{F(threo)}$ was again established. This shows that the secondary solvent effects are of no importance in deciding the retention order. Adsorption by the same group(s) within any two isomers was derived on the basis of Soczewiński's method. Hence, the localization and the solute areas of the diastereoisomers under adsorption seem to be identical, and thus the corresponding effects are not important for the retention order. The *erythro*-isomer of a diastereoisomeric pair of type 1 (see compounds 1–2 of ref. 27) is a stronger base; however, it is again adsorbed less than the *threo*-isomer. Thus, it is clear that electronic effects are not decisive factors. Consequently, steric effects remain and determine the relationship $R_{F(erythro)} > R_{F(threo)}$ in the cases studied.

This conclusion is equal to the widely used concept (*e.g.* see refs. 2,3,5–8,24 and 46) for interpretation of chromatographic behaviour of diastereoisomers which is derived on the basis of conformational analysis[47] without taking into account details of the retention mechanism. However, bearing in mind the other factors mentioned above, concerning the adsorption mechanism, this makes the treatment more reliable and is of great importance in some cases of inversion[25]*.

The groups X and Y seem to be more strongly adsorbing, and with smaller effective volumes, than the groups Ar and Ar′ in any compound studied (see Table 10-2 of ref. 29 and ref. 49). Having also in mind the values of n[27,28], the two cases presented in Fig. 2a and b should be chosen for interpretation of the order $R_{F(erythro)} > R_{F(threo)}$. It can be seen that the adsorbing groups are less sterically hindered in the *threo*-isomers (case a). The adsorbing group in case b, for instance Y, significantly more adsorbing than X, is in nearly the same environment (between X and H). However, the conformation of the *threo*-isomers has less interaction between the bulky groups.

Let us return to the chromatographic behaviour of the compounds of the present study. Diethyl ether and acetone in the solvent systems used can form hydrogen bonds with the OH groups of the hydroxyesters 1–10 and 15–28 while with methylene chloride such a possibility is negligible. Table II shows that retention of the compounds does not change with the presence or absence of a solvent with secondary solvent effects. The values of n (see Table II) within any diastereoisomeric pair are nearly equal. Hence, the electronic and steric effects only should be responsible for the relative retentions. The hydroxyesters 1–10 and 15–28, including those in Table I, possess intramolecular hydrogen bonds; electronic effects should therefore be discussed. The hydroxyesters, excluding for the moment 9–10, the acetoxyesters 11–14 and the anilinoesters 29–30 have the same retention, $R_{F(erythro)} > R_{F(threo)}$. It should be borne in mind that 11–14 and 29–30 are free from intramolecular hydrogen bonding.

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* The retention order of diastereoisomers in LSC is often treated in analogous manner, as in the case of gas–liquid chromatography (GLC)[45]. However, the main mechanism in GLC is "dissolution of the solute in the bulk of the liquid film"[46] complicated by some types of adsorption[48]. Thus such an analogy requires caution.
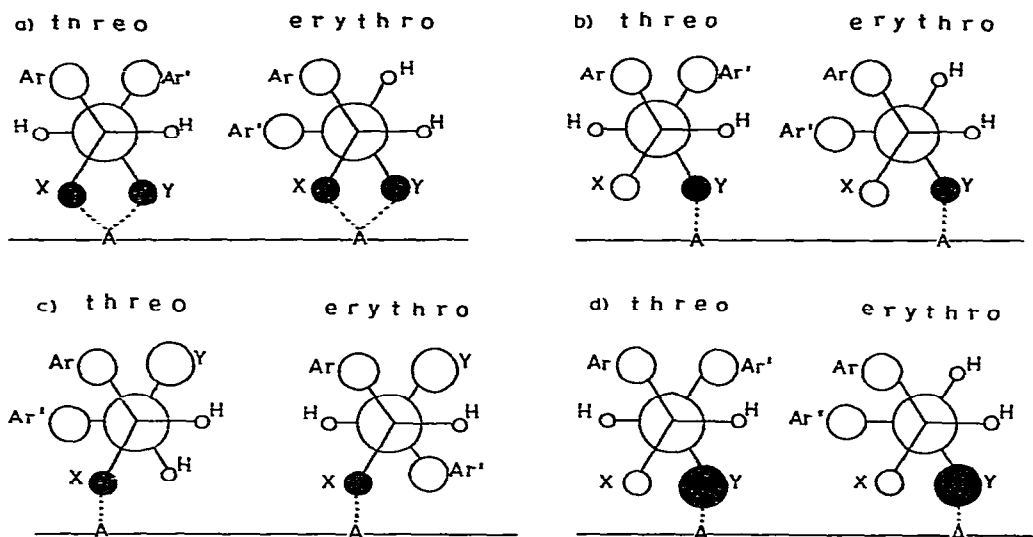
Fig. 2. Illustrative representation of the adsorption patterns for diastereoisomeric compounds of type 1. The full circle denotes the strongest adsorbing group/s of the molecule. A = Active site comprising the different types of the adsorbent surface hydroxyl groups; see p. 157 of ref. 29. (a) Two-point adsorption with X and Y; $R_{F(erythro)} > R_{F(threo)}$. (b) One-point adsorption with Y (or with X via conformations where X is between H and Y, not presented); $R_{F(erythro)} > R_{F(threo)}$. (c) One-point adsorption with X; $R_{F(threo)} > R_{F(erythro)}$. (d) One-point adsorption with Y; $R_{F(erythro)} > R_{F(threo)}$. In (a) and (b) X and Y are smaller than Ar and Ar'; in (c) and (d) X is smaller and Y bulkier than Ar and Ar'.

This means that the electronic effects are of no decisive importance; physically it can be rationalized by the previously adopted concept of cleavage of the intramolecular hydrogen bonds under the action of the adsorbent[24-26,28]. Such a cleavage seems possible only when the distance between the intramolecularly bonded groups of the solute is similar to that between the hydroxyl groups of the active site of the adsorbent (see the interpretation of TLC behaviour for compounds 23-24 in ref. 25). The hydrogen bonding in 1 and 9 and in 2 and 10 is similar, which indicates that the electronic effects in 9-10 can also be neglected. Thus, the steric effects will be discussed below.

The TLC behaviour of the hydroxyesters 1-8 and 25-28, showing two-point adsorption ($n > 1.5$) with the functional groups X and Y, can be explained in Fig. 2a as above. The substituents Cl, Br, CH_3 and CH_3O attached to the phenyl groups, as well as the naphthyl group, in these cases are less adsorbing than X and Y (see Table 10-2 of ref. 29). Thus, the former groups are not directly adsorbed; they are delocalized, which leads to a change in the adsorption of the directly attached groups (see p. 270 of ref. 29). The position (*ortho* or *para*) of these low-adsorbing groups, as expected, does not affect the retention order of the diastereoisomers.

The compounds 1-8 differ in the alkyl group of the ester group only. Its effective volume increases in the order Me, *iso*-Pr, *n*-Bu, *iso*-Bu. The above-mentioned two-point adsorption of 1-8 gradually decreases (see Table II) owing to the increasing hindrance of the adsorbing carbonyl oxygen. Substitution of the *iso*-Bu group by the most bulky[40] *tert.*-Bu group results in one-point adsorption (9-10, $n = 1.4$) and inversion of the retention to $R_{F(threo)} > R_{F(erythro)}$. It is clear that the ester group COO-*tert.*-Bu is not a more adsorbing one and the adsorption of 9-10 occurs by means of the hydroxyl group X. In this case the most favourable position of the latter is that between H and Ar', as shown in Fig. 2c, because the effective volume of COO-*tert.*-Bu

(Y) is expected to exceed that of Ar'[49]. The conformation of the *erythro*-isomer shown coincides with the energetically preferred conformation in solution of 10. However, the conformation depicted for the *threo*-isomer differs from the preferred conformation of 9. For this reason *erythro*-10 should be and is more strongly adsorbing than *threo*-9. The inversion of the retention order for the butyl esters 5–10 occurs exclusively with compounds 9–10 which have a tertiary butyl group. Consequently, COO-*n*-Bu and COO-*iso*-Bu groups should be considered as groups possessing a smaller effective volume than Ar'.

In the course of isolation of a series of optically active diastereoisomeric hydroxyesters of type 1, X = OH, Y = COO(−)-menthyl, the retention $R_{F(threo)} > R_{F(erythro)}$ was established[50] on the same silica gel as in the present study. The group COO(−)-menthyl could also be assumed to be bulkier than Ar'. Thus, it becomes clear that 9–10 is not an isolated case and the latter retention is normal when the adsorption occurs as shown in Fig. 2c.

The *tert*.-Bu esters 9–10 and 29–30 differ in the group X only. Comparison of the R_F values of these compounds reveals that the adsorptivity of the anilino group NHPh in 29–30 is considerably smaller than that of the OH group in 9–10. Hence, one-point adsorption of the group COO-*tert*.-Bu is expected and is found for 29–30 (n = 1.2), as shown in Fig. 2d. This group is in the most favourable position in the conformations shown (between X and H), but only the conformation of the *threo*-isomer coincides with the energetically preferred conformation of 29. Thus it is clear why the retention in this case is $R_{F(erythro)} > R_{F(threo)}$. The same pattern of adsorption (case d) is probably responsible for the TLC behaviour of the acetoxyesters 13–14. In this case one-point adsorption ($n < 1.5$) should also occur with the ester group COO-*tert*.-Bu. The lack of adsorption of the acetoxy group X is not so apparent because it has a greater adsorption than the anilino group (*cf.* the R_F values of 13–14 with those of 29–30).

The retention of the diastereoisomeric acetoxyesters of Table I and 11–12 is probably due to adsorption with the ester group Y (COOMe or COO-*iso*-Pr) which is smaller than Ar' (see Fig. 2b). The behaviour of the diastereoisomeric hydroxyacids of Table I could be attributed to adsorption with the strongest adsorbing carboxyl group Y, as shown in Fig. 2b, provided there are no considerable complications by the fact that these compounds are not fully non-ionic ones.

CONCLUSIONS

The results of the present study support the criteria given in refs. 25 and 28 for assessing the relative configurations of the diastereoisomers of type 1 on the basis of the relation $R_{F(erythro)} > R_{F(threo)}$. The principle requirement, in such a case, is that the groups X and Y should be more strongly adsorbing, and with smaller effective volumes, than the groups Ar and Ar', as shown in Fig. 2a and b. The results also provide a further development of the criteria for the case where X is smaller, and Y is bulkier, than Ar and Ar':

(1) Adsorption with Y (see Fig. 2d) results in retention of the order $R_{F(erythro)} > R_{F(threo)}$.

(2) Adsorption with X leads to inversion, as shown in Fig. 2c.

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