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CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOMERS

II. THIN-LAYER CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOMERIC 1,2-DISUBSTITUTED 1,2-DIARYLETHANES

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SUMMARY

Another 15 pairs of diastereomeric 1,2-disubstituted 1,2-diarylethanes have been separated by thin-layer chromatography on silica gel using solvent systems with and without secondary solvent effects. The results obtained, together with those from a previous study, indicate a correlation of $R_{F(erythro)} > R_{F(threo)}$ for 50 of the 52 diastereomeric pairs studied. Qualitative analysis by means of the Snyder's theory has been used to specify the scope and limitation of this correlation for diastereomers of the type studied.

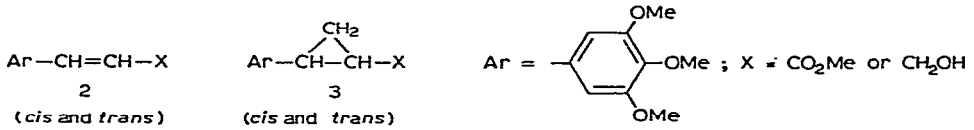
INTRODUCTION

In our first paper of this series[1] we reported the correlation $R_{F(erythro)} > R_{F(threo)}$ obtained by thin-layer chromatography (TLC) on silica gel of 37 diastereomeric pairs of 1,2-disubstituted 1,2-diarylethanes of the type 1. On the basis of general considerations, this result was attributed to two-point, and less sterically hindered, adsorption of only the *threo*-isomers. It was suggested that the correlation could be used for the assignment of the relative configurations of newly synthesized diastereomers of the type 1.

Ar—CH(X)—CH(Y)—Ar′ (1; *erythro* and *threo*) — X and Y = NH_2, OH, CO_2H or their derivatives; Ar and Ar′ = Ph or alkoxyphenyl

Cooper[2] studied the TLC on silica gel of four *cis–trans* pairs of the related compounds 2 and 3; in contrast to our study, a definite correlation was not found. This is not surprising as there is no reason to expect the same TLC separation order for diastereomers which differ in their molecular geometry as do 1, 2 and 3, and as do 2 and 3. Moreover the effective volumes of the strongly adsorbing groups are different, namely X and Y *versus* Ar and X in these two studies. Subsequent papers have

appeared[3–6] which deal with the TLC behaviour of other acyclic diastereomeric compounds.



The present paper reports the TLC behaviour of another 15 diastereomeric pairs of the type 1 having known relative configurations; some of the compounds have not been prepared before. An attempt is made to specify the scope and limitation of the relation $R_{F(erythro)} > R_{F(threo)}$ with diastereomers of the type 1.

EXPERIMENTAL

Silica gel DG (Riedel de Haen, Hannover, G.F.R.) was used for TLC. Coating of the plates, application of the samples and visualization of the zones was performed as previously[1]. Layers of 0.5-mm thickness were used. No preliminary saturation of the tank with vapours of the solvent system was carried out.

The following compounds were synthesized.

Methyl threo- and erythro-3-dimethylamino-2-(3,4-methylenedioxyphenyl)-3-phenylpropionates (3 and 4).* 80% (*ca.* 50% higher yield than obtained in ref. 7) of 3, m.p. 151–152° (hexane), and 52% of 4, m.p. 148–149°, were obtained by N-methylation[8] of methyl *threo-* and *erythro*-3-amino-2-(3,4-methylenedioxyphenyl)-3-phenylpropionates[9].

threo- and erythro-3-Dimethylamino-2-(3,4-methylenedioxyphenyl)-3-phenyl-1-propanols (13 and 14). Lithium aluminium hydride reduction of 3 readily afforded 13, m.p. 90–91° (hexane–ethyl acetate). Similar treatment of 4 gave 14, m.p. 123–124° (ethanol). IR spectra in 10^{-3} *M* carbon tetrachloride solution showed that the extent of intramolecular hydrogen bonding of the type OH...N (3150–3500 cm^{-1}) is greater in 13 than in 14, and hydrogen bonding of the type OH...Ar (3595 cm^{-1}) is present only in 14. No bands attributable to free OH groups were observed.

Diastereomeric methyl 3-(N-methylacetamido)- and 3-(N-methylbenzamido)-2,3-diphenylpropionates (17 and 18, 19 and 20). These compounds were obtained in 48–75% yield from the diastereomeric methyl 3-methylamino-2,3-diphenylpropionates[10] and acetic anhydride or benzoyl chloride–pyridine. The melting points of the products after recrystallization from ethanol were: 147–148° (17), 175–175.5° (18), 161–162° (19) and 146–147° (20).

threo- and erythro-3-(N-Methylacetamido)-2,3-diphenyl-1-propanols (21 and 22) and threo- and erythro-1-acetoxy-3-(N-methylacetamido)-2,3-diphenylpropanes (25 and 26). 28% of 21, m.p. 173–174° (hexane–diethyl ether), and 63% of 25, m.p. 151–152°, were obtained from *threo*-3-methylamino-2,3-diphenyl-1-propanol[11] and acetic anhydride after column chromatography of the crude product on silica gel. Analogously, 19% of 22, m.p. 165–166°, and 47% of 26, m.p. 159–159.5°, were synthesized from *erythro*-3-methylamino-2,3-diphenyl-1-propanol[11]. IR spectra of the amido-alcohols 21 and 22 in 10^{-3} *M* carbon tetrachloride solution are similar to those[11] of

* The numbering of the compounds follows that in Tables II and III.

23 and 24 and show the presence of an intramolecular hydrogen bond of the type OH...O=C–N with the formation of an eight-membered ring only in the *threo*-isomer 21 (intense maximum at 3440 cm^{-1}).

threo- and erythro-3-(N-Methylacetamido)-2,3-diphenylpropionic acids (27 and 28). 860 mg of 17 and 20 ml of 10% ethanolic potassium hydroxide were heated under reflux for 15 min. Column chromatography of the crude product on silica gel gave 13% of 27, m.p. 251.5–252° (hexane–diethyl ether), 17% of 28, m.p. 248–249°, and 37% of a mixture of the isomeric α-phenylcinnamic acids.

threo- and erythro-3-(N-Methylbenzamido)-2,3-diphenylpropionic acids (29 and 30). As in the above preparation, 10% of 29, m.p. 210–211°, and 22% of 30, m.p. 223–224°, were obtained from 19.

The relative configurations of the amidoacids 27–30 were assigned by their conversion using diazomethane into amidoesters, which were compared with 17–20 by mixed m.p. The newly synthesized compounds were identified by their IR spectra and elemental analyses. The experiment analysis figures were in good agreement with the calculated values.

The diastereomeric hydroxyesters[12] 7 and 8 in 10^{-3} *M* carbon tetrachloride solution showed a small amount of intramolecular hydrogen bonding of the type OH...O=C–OMe (a slight increase in intensity in the 3500 cm^{-1} region without a definite maximum) and large amount, especially in 8, of hydrogen bonding of the type OH...Ar (3590 cm^{-1}).

THEORY

Basic theory[13–19] has not treated the TLC behaviour of aliphatic diastereomers. Some aspects of Snyder's theory of linear adsorption chromatography are given here.

The basic equation which expresses the TLC behaviour of non-ionic organic compounds on silica gel as a function of the solute structure and experimental conditions is as follows (see the equations of refs. 13 and 14):

$$R'_M = \log \frac{V_a W}{V^0} + \alpha \left[\sum^{i} Q_i^0 + \sum^{i} \sum^{j} q_{ij}^0 - f'(Q_k^0) \sum^{i \neq k} Q_i^0 - \varepsilon^0 \sum^{i} a_i' \right] + \Delta_{eas} \qquad (1)$$

In this form, eqn. 1 has been applied by Vernin[20] to a large number of thiazoles. R'_M is related to the parameter R_F by the well-known equation:

$$R'_M = \log \left(\frac{1}{\xi R_F} - 1 \right) \qquad (2)$$

where ξ is a constant depending on the chromatographic conditions.

The physical meanings of the individual terms in eqn. 1 (which are dimensionless) are as follows. $\log(V_a W/V^0)$ expresses the correlation between R_M and the quantities of the adsorbent (W), of the solvent system (V^0) and a parameter of the adsorbent (V_a). $\alpha \sum^{i} Q_i^0$ is the sum of the free energies of adsorption of all of the groups i of the solute on a particular adsorbent, *i.e.*, the solute free energy of adsorption relative

to that of *n*-pentane. $\alpha \Sigma \overset{j}{\Sigma} q^0_{ij}$ is a measure of the change in the free energy of adsorption due to electronic and steric interactions within the groups *i* and *j* in the solute molecule being adsorbed. $-\alpha f'(Q^0_k) \overset{i\neq k}{\Sigma} Q^0_i$ is a measure of the decrease in the solute free energy of adsorption due to delocalization of the groups *i*, with the exception of the most strongly adsorbed group *k*. The latter is localized, *i.e.*, it is orientated for maximum overlap with an active site of the adsorbent. For instance, in Fig. 1 the groups X and Y are localized in cases a and b, whereas in case c the group X is localized and Y is delocalized.

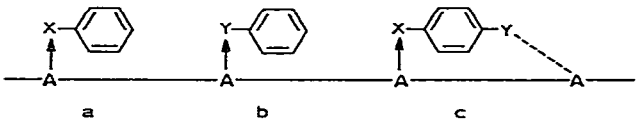


Fig. 1. Origin of the sample localization.

$-\alpha \varepsilon^0 \overset{i}{\Sigma} a'_i$ takes into consideration the work required to displace the solvent from the surface of the adsorbent; it is proportional to the area ($\overset{i}{\Sigma} a'_i$) over which the solvent is displaced. Δ_{eas} is a correction term for "secondary adsorption effects" of the solvent, adsorbent and solute which are not covered by the other terms of the equation. In this study, only secondary solvent effects are expected since the same adsorbent is used throughout and the solutes have the same skeleton, 1,2-disubstituted 1,2-diarylethane. Here, $\Delta_{eas} \neq 0$ when the solvent can interact with the solute through hydrogen or complex bonds, or when the solvent molecules are capable of localization together with those of the sample. The latter case can occur when the solvent also possesses a strongly adsorbed group. All of the terms of eqn. 1, with the exception of the first, express the effective (nett) free energy of adsorption of the solute. Here the terms $-\alpha \varepsilon^0 \overset{i}{\Sigma} a'_i$ and Δ_{eas} are substracted from the free energy of adsorption (the sum of the second, third and fourth terms).

When applied to a diastereomeric pair under definite TLC conditions, eqn. 1 simplifies* to eqn. 3:

$$R'_{M(erythro)} - R'_{M(threo)} = \Delta R'_M =$$

$$= \underbrace{\alpha \Delta \overset{i}{\Sigma} \overset{j}{\Sigma} q^0_{ij}}_{\text{I}} \underbrace{- \alpha \Delta \left[f'(Q^0_k) \overset{i\neq k}{\Sigma} Q^0_i \right]}_{\text{II}} \underbrace{- \alpha \varepsilon^0 \Delta \overset{i}{\Sigma} a'_i}_{\text{III}} \underbrace{+ \Delta \Delta_{eas}}_{\text{IV}} \qquad (3)$$

The operator Δ in eqn. 3 expresses the difference between the values of the given

* $\Delta \log (V_n W / V^0) = 0$ since the experimental conditions for the two isomers are the same; $\alpha \Delta \Sigma Q^0_i = 0$ because the coefficient α for a particular silica gel is a constant, and the diastereomeric compounds have the same solute groups *i* (and Q^0_i values).

TABLE I

RELATIVE FREE ENERGIES OF ADSORPTION OF SOME GROUPS ON SILICA GEL
Data from Table 10-2 of ref. 14.

Group i	Q_i^0
X (Y)	
Primary amine, R–NH_2	8.00
Tertiary amine, R_3N	5.8
Alcohol, R–OH	5.60
Ester, R–CO_2Me	5.27
Amide, R–$CONH_2$	9.6
Ar (Ar')	
Aromatic carbon atom	0.25
Ether, Ar–OMe	1.83

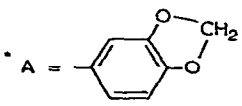
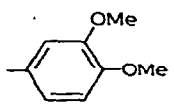
parameter for the two compounds of the diastereomeric pair. Term I of eqn. 3 is attributable to electronic and steric effects, term II is to localization effects, term III to area effects and term IV to secondary solvent effects. These four terms are of importance whether a given *threo*-isomer has a higher or lower R'_M value than the corresponding *erythro*-isomer.

Experimental free energies of adsorption (Q_i^0) of the groups of interest are given in Table I. The higher the Q_i^0 value, the stronger is the adsorption of the group *i*.

TABLE II

R_F VALUES OF THE DIASTEREOMERIC PAIRS OF Ar–CH(X)–CH(Y)–Ar'

Chromatogram No.	*Ar**	*Ar'***	*X*	*Y*	*Configuration*	*Ref.*	*Compound No.*	R_F	*Solvent system*
1	A	A	NHMe	CO_2Me	*threo*	8	1	0.29	Benzene–diethyl ether
					erythro		2	0.52	(1:1)
2	Ph	A	NMe_2	CO_2Me	*threo*		3	0.76	Benzene–diethyl ether
					erythro		4	0.83	(1:1)
3	A	A	NMe_2	CO_2Me	*threo*	8	5	0.39	Heptane–benzene–
					erythro		6	0.48	diethyl ether (2:5:5)
4	Ph	B	OH	CO_2Me	*threo*	12	7	0.36	Hexane–acetone (4:1)**
					erythro		8	0.41	
5	B	Ph	NH_2	CH_2OH	*threo*	9	9	0.14	Diethyl ether–methanol
					erythro		10	0.41	(17:3)
6	Ph	A	NH_2	CH_2OH	*threo*	9	11	0.35	Diethyl ether–methanol
					erythro		12	0.74	(17:3)
7	Ph	A	NMe_2	CH_2OH	*threo*		13	0.23	Diethyl ether
					erythro		14	0.38	
8	Ph	A	OH	CH_2OH	*threo*	12	15	0.46	Chloroform–diethyl ether–ethyl acetate–
					erythro		16	0.51	acetic acid (10:10:2:0.3)

* A =  ; B = 

** Developed four times.

TABLE III

R_F VALUES OF THE DIASTEREOMERIC PAIRS OF Ph–CH[N(Me)Z]–CH(Y)–Ph

Chromatogram No.	*Z*	*Y*	*Configuration*	*Compound No.*	R_F	*Solvent system*
9	Ac	CO_2Me	*threo*	17	0.13	Heptane–diethyl ether (1:2)
			erythro	18	0.26	
10				17	0.17	Carbon tetrachloride–methanol (10:1)
				18	0.25	
11	Bz	CO_2Me	*threo*	19	0.48	Heptane–diethyl ether (1:1)*
			erythro	20	0.55	
12				19	0.31	Hexane–diethyl ether–methanol (15:10:1)**
				20	0.35	
13	Ac	CH_2OH	*threo*	21	0.21	Hexane–diethyl ether–acetone (5:5:3)
			erythro	22	0.30	
14				21	0.11	Hexane–diethyl ether–methanol (10:10:1)
				22	0.18	
15				21	0.31	Benzene–acetic acid (10:1)
				22	0.40	
16	Bz	CH_2OH	*threo*	23	0.51	Benzene–diethyl ether (1:2)**
			erythro	24	0.58	
17			(ref. 11)	23	0.33	Benzene–methanol (10:1)
				24	0.26	
18				23	0.51	Benzene–ethanol (10:1)
				24	0.46	
19				23	0.47	Benzene–acetic acid (10:1)
				24	0.41	
20	Ac	CH_2OAc	*threo*	25	0.40	Hexane–diethyl ether–acetone (5:5:3)
			erythro	26	0.49	
21				25	0.61	Benzene–methanol (10:1)*
				26	0.71	
22	Ac	CO_2H	*threo*	27	0.03	Ethyl acetate*
			erythro	28	0.14	
23				27	0.18	Benzene–methanol (10:1)*
				28	0.25	
24				27	0.05	Chloroform–diethyl ether–acetone–methanol (10:7:1:4)**
				28	0.13	
25				27	0.39	Benzene–acetic acid (10:1)
				28	0.54	
26				27	0.15	Benzene–methanol–acetic acid (20:1:1)
				28	0.22	
27	Bz	CO_2H	*threo*	29	0.08	Ethyl acetate*,***
			erythro	30	0.16	
28				29	0.31	Benzene–methanol (10:1)
				30	0.20	
29				29	0.58	Benzene–acetic acid (10:1)
				30	0.64	

* Developed twice.
** Developing distance, 18 cm.
*** Developing distance, 16 cm.

These values refer to the case when the group i is localized, electronic and steric interactions of the groups with the solute molecule being absent and the strength (ε^0) of the solvent system (n-pentane) being assumed to be equal to zero.

RESULTS AND DISCUSSION

The main results of the TLC separations on silica gel of the diastereomers of type 1 are shown in Tables II and III. Table III indicates the behaviour of several diastereomeric amido compounds in the different solvent systems. The column of references concerns the assignment of the relative configurations.

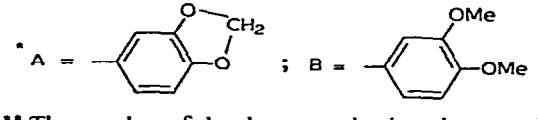
Secondary solvent effects such as hydrogen-bond formation with the solutes and/or simultaneous localization of the solvent and the solute can be assumed whenever the solvents diethyl ether, ethyl acetate, acetone, ethanol, ammonia and acetic acid occur in the solvent systems in Tables II and III. In Table IV are shown the results of the TLC on silica gel of several diastereomers of the type 1 developed with

TABLE IV

R_F VALUES OF SEVERAL DIASTEREOMERIC PAIRS OF Ar–CH(X)–CH(Y)–Ar′ WITH METHYLENE CHLORIDE

Methylene chloride is probably free from secondary solvent effects (see above); it was purified from mixtures of higher ε^0 values by column chromatography on alumina. The numbering of the chromatograms continues that of Tables II and III.

Chromatogram No.	*Ar*	*Ar′***	*X*	*Y*	*Configuration*	*Compound No.*	R_F**
30	Ph	Ph	NMe_2	CO_2Me	*threo*	31[1]	0.00 (1–5)
					erythro	32[1]	0.00 (1–5)
31	Ph	Ph	OH	CO_2Me	*threo*	33[1]	0.18
					erythro	34[1]	0.35
32	Ph	A	OH	CO_2Me	*threo*	35[1]	0.11
					erythro	36[1]	0.21
33	Ph	B	OH	CO_2Me	*threo*	7	0.20 (4)
					erythro	8	0.20 (4)
34	Ph	Ph	N(Me)Ac	CO_2Me	*threo*	17	0.05 (3)
					erythro	18	0.10 (3)
35	Ph	Ph	N(Me)Bz	CO_2Me	*threo*	19	0.18 (3)
					erythro	20	0.18 (3)
36	Ph	Ph	CH_2OH	CH_2CH_2OH	*threo*	37[1]	0.03 (3)***
					erythro	38[1]	0.06 (3)***
37	Ph	A	OH	CH_2OH	*threo*	15	0.12 (5)
					erythro	16	0.18 (5)
38	Ph	Ph	N(Me)Ac	CH_2OH	*threo*	21	0.02 (5)
					erythro	22	0.02 (5)
39	Ph	Ph	N(Me)Bz	CH_2OH	*threo*	23	0.13 (4)
					erythro	24	0.08 (4)



** The number of developments is given in parentheses.

*** The diastereomers were well separated when the samples were applied in 1-cm lines at the start.

methylene chloride which is to a first approximation free from secondary effects. (The correction term Δ_{eas} is considered to be equal to zero in the case of the TLC on silica gel of some phenols in chloroform, see p. 220 of ref. 14.) The diastereomeric compounds 31–38 in Table IV were chromatographed previously[1] with solvents possessing secondary effects. A separation of the diastereomers was achieved in only part of the chromatograms.

The conformations preferred in solution are identical to those of the compounds of type 1 studied earlier, namely of type A for the *erythro*-isomers and of type B for the *threo*-isomers (see the formulae below)[8–12,21]. In the compounds studied, on the basis of IR and NMR data (see Experimental section and refs. 9, 11, 12 and 22), there are intramolecular hydrogen bonds. The bonds OH...OH in the diastereomeric diols 15 and 16 and OH...N in the aminoalcohols 9–14 are in six-membered rings, while the bonds OH...OH in the diols 37 and 38 and OH...O=C–N in the *threo*-amidoalcohols 21 and 23 are in eight-membered rings. The extents of OH...OH and OH...N bonding were largest in the *threo*-isomers. These alcohols also possess very weak intramolecular hydrogen bonds of the type OH...Ar. This type of bonding, and the small amount OH...O=C–OMe bonding in the hydroxyesters 7 and 8, is not taken into consideration in the following discussion.

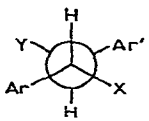
The data in Tables II–IV show the same correlation of $R_{F(erythro)} > R_{F(threo)}$ as previously observed[1]. However, the *erythro–threo* retention sequence of the diastereomeric benzamidoalcohols 23 and 24 and benzamido acids 29 and 30 was dependent on the solvent systems used (see chromatograms 16–19 and 27–29 of Table III and chromatogram 39 of Table IV). These compounds are the first to indicate a limitation of the correlation. The TLC behaviour of the non-ionic compounds 23 and 24 will be discussed in detail.

According to Table I, the following decreasing order of adsorption is expected within any diastereomeric pair studied:

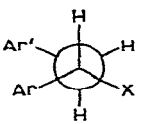
$$X, Y > (RO)_2C_6H_3 > (RO)C_6H_4 > Ph$$

The latter three groups comprise Ar and Ar′ and are probably not adsorbed (see Part III of this series[27]). Thus diastereomers of type 1 will be adsorbed either through the two most strongly adsorbing groups X and Y (two-point adsorption), or through the group which has the higher adsorption energy (one-point adsorption). Under the conditions of adsorption, change in the conformations preferred in solution is possible. The following four patterns of adsorption are the most probable for diastereomers of type 1.

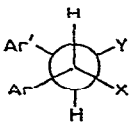
(a) One-point adsorption via conformations A and B (with the group X or Y). This mode of attachment can be postulated for the amino group of the aminoester since $Q^0_{NH_2}$ is 2.73 times greater than $Q^0_{CO_2Me}$.



A (*erythro*)



A′ (*erythro*)



B (*threo*)

(b) One-point adsorption via conformations A′ and B. The driving force for a change in conformation from A to A′ of the *erythro*-isomers may be the tendency to level the steric hindrance of the adsorbing group in the two steric series. (The steric hindrances of group X in conformations A′ and B are equal.)

(c) One-point adsorption of the erythro-isomers via conformation A, and two-point adsorption of the threo-isomers via conformation B. A possibility for realizing two-point attachment is "site chelation" (see p. 315 of ref. 14), *i.e.*, simultaneous localization of the groups X and Y on a single strong adsorbent site probably consisting of two adjacent surface hydroxyl groups. Proximity of the groups X and Y is required, as in the conformation B of the *threo*-isomers. Site chelation is not possible in the *erythreo*-isomers with conformation A and only one of the groups X and Y will be localized.

(d) Two-point adsorption via conformations A′ and B. The conformations of the *erythro*-isomers may change from A to A′ on adsorption in order that site chelation of the groups X and Y can take place. Two-point adsorption is probable for all of the compounds studied. However it can be expected to be present to a greater extent for the hydroxyesters since Q^0_{OH} and $Q^0_{CO_2Me}$ differ only by 0.33.

The possibilities (c) and (d) correspond to those discussed previously[1]. We note that the conclusions regarding the Q^0_i values relating to one-point or two-point adsorption are only approximate since the values are only valid in a particular case (see p. 65). In order to specify the scope and limitations of the relation $R_{F(erythro)} > R_{F(threo)}$ for diastereomers of type 1, one must examine the predictions which can be made from eqn. 3. Here, only a semiempirical approach is possible. This problem will now be discussed in detail for two types of compounds.

Non-ionic diastereomers of type 1 which do not possess intramolecular hydrogen bonds

The diastereomeric compounds which did not possess intramolecular hydrogen bonds, 17 and 18 and 33–36, were chromatographed both with solvent systems exhibiting secondary solvent effects (see Table III and ref. 1) and with a solvent which did not exhibit such effects (see chromatograms 31, 32 and 34 of Table IV). There was no difference in the *erythro–threo* retention sequence. Hence the secondary solvent effects may be neglected.

When a solvent which did not exhibit secondary effects was used (as in Table IV), the relative retention of the diastereomers depended only on the first three terms, I–III, of eqn. 3. Area effects are not important when the adsorption of the diastereomers occurs through the same number of groups (cases a, b and d) since there is no difference in the relative adsorption area. In case c, comprising adsorption with different numbers of groups, the *threo*-isomer should exhibit a greater adsorption area due to two-point adsorption than the corresponding *erythro*-isomer. According to eqn. 1, the greater the solute area, the greater is the work required to displace the adsorbed solvent, and correspondingly the lower is the solute adsorption energy. Thus if the area effects determine the relative retention of the diastereomers in case c, the correlation of $R_{F(threo)} > R_{F(erythro)}$ is expected. This was not the case in the chromatograms 31, 32 and 34. Consequently, area effects are not responsible for the *erythro–threo* retention sequence.

It is clear that the relative retention of the diastereomers of type 1 which do not possess intramolecular hydrogen bonds is determined by the first two terms, I and

II, of eqn. 3 which give the relative adsorptivity of the diastereomers in the absence of solvent (as assumed previously[1]). Let us consider whether terms I and II place restrictions on the correlation $R_{F(erythro)} > R_{F(threo)}$ other than that the groups X and Y should be more strongly adsorbing than Ar and Ar'. This relation is characteristic for all diastereomers studied, and permits the choice of the adsorption patterns a–d.

With diastereomers, all of the electronic effects are equal except the field effect. The field effect can be neglected for non-ionic compounds which do not have intramolecular hydrogen bonds (*cf.* p. 316 of ref. 14). For these compounds, only steric effects need to be taken into consideration for the term I. The correlation of $R_{F(erythro)} > R_{F(threo)}$ is expected to be valid until the steric hindrance of the adsorbing group(s) in the *erythro*-isomers is greater than in the corresponding *threo*-isomers. This restriction with the conformations A, A' and B of the cases a–d will operate if the groups X and Y have smaller effective volumes than those of the groups Ar and Ar' as in the cases studied[23].

The definition of cases a, b and d excludes a difference in the relative localization of the adsorbing group(s) within the diastereomeric pair, and so localization effects are of no importance here. When adsorption occurs according to pattern c, site chelation in the *threo*-isomers is expected to favour their stronger adsorption (*cf.* Section 11.1.C of ref. 14). It is clear that localization effects do not restrict the correlation of $R_{F(erythro)} > R_{F(threo)}$ for diastereomers of type 1.

Non-ionic diastereomers of type 1 having intramolecular hydrogen bonds

A theoretical prediction of the scope and limitation of the correlation $R_{F(erythro)} > R_{F(threo)}$ for compounds of type 1 possessing intramolecular hydrogen bonds is complicated since the electronic effects cannot be neglected in principle. Moreover, the secondary solvent effects may have a role, as assumed by Drefahl *et al.*[24] in the TLC behaviour of some diastereomeric aminoalcohols. The electronic and secondary solvent effects can sometimes cause inversion of the relative retentions of diastereomers (*cf.* pp. 317 and 318 of ref. 14). We shall use the experimental data to elucidate this problem.

There was no difference in the *erythro–threo* retention sequence for the diols 15 and 16 and 37 and 38 (having OH...OH intramolecular hydrogen bonds) when solvent systems with and without secondary effects were used (see chromatogram 8, Table II; chromatograms 36 and 37, Table IV; and ref. 1). Hence secondary solvent effects are not present in this case. There was also no difference in the separation order of these diastereomeric diols and of diastereomers which do not possess intramolecular hydrogen bonds. This indicates that the presence of OH...OH bonds is not the determining factor, *i.e.*, as in the case of the absence of intramolecular hydrogen bonds, the electronic effects do not exceed the steric effects. This is equivalent to the suggestion made previously[1] for cleavage of the OH...OH bonds during adsorption, namely the energy required for the cleavage is compensated for by the energy gained during adsorption. The restrictions operating on the correlation $R_{F(erythro)} > R_{F(threo)}$ in diastereomers of type 1 having OH...OH bonds should therefore be the same as in the case of compounds which do not possess intramolecular hydrogen bonds.

The characteristic retention sequence of the benzamidoalcohols 23 and 24, having OH...O=C–N intramolecular hydrogen bonds in the *threo*-isomer 23, is $R_{F(threo)} > R_{F(erythro)}$ (established when secondary solvent effects were absent, see

chromatogram 39 of Table IV). This sequence is opposite to that of the benzamidoesters 19 and 20 which do not possess intramolecular hydrogen bonds (see chromatograms 11 and 12 of Table III). Hence, the OH...O=C–N bonds in 23, *i.e.*, the electronic effects, determine the relative retention of 23 and 24 in chromatogram 39. A study of atomic models reveals that the distance between the oxygen atoms of the N(Me)Bz and CH_2OH groups in conformers having *syn*-CH_2OH group is less than that in the diols 15 and 16 and 37 and 38. Thus the distance between X and Y in the *threo*-isomer 23 probably differs significantly from the distance between two adjacent hydroxyl groups on the adsorbent surface, which does not permit cleavage of OH...O=C–N bonds. In such a case the intramolecularly bonded *threo*-isomer 23 is expected to, and does indeed, exhibit less adsorption than the *erythro*-isomer 24.

The retention sequence of $R_{F(threo)} > R_{F(erythro)}$ was again established for 23 and 24 in chromatograms 17–19 of Table III where the solvent systems were benzene–methanol, benzene–ethanol and benzene–acetic acid (each 10:1). This indicates the absence of significant secondary solvent effects. It is noteworthy that the strong solvents methanol, ethanol and acetic acid are present in low concentration. In chromatogram 17, a second front with $R_F = 0.10$ is visible due to demixing of the solvent system (see p. 213 of ref. 14). The spots due to 23 and 24 occur beyond the second front where methanol is practically absent. The reverse sequence, $R_{F(erythro)} > R_{F(threo)}$, was established for 23 and 24 in chromatogram 16 of Table III when the solvent system was benzene–diethyl ether (1:2), thus confirming the role of the secondary solvent effects. In this case the large amount of diethyl ether used ensures its presence throughout the length of the chromatogram and give rises to the possibility for specific interactions with the benzamidoalcohols. Such interactions are expected to occur to a greater extent with the *erythro*-isomer which does not exhibit intramolecular hydrogen bonding with its hydroxyl group and thus has a lower adsorption compared to the *threo*-isomer, as in chromatogram 16.

A correlation of $R_{F(erythro)} > R_{F(threo)}$ was established for the acetamidoalcohols 21 and 22, where OH...O=C–N bonds are present in the *threo*-isomer 21 (see chromatograms 13–15, Table III). It is not clear whether the above separation order is characteristic or due to secondary solvent effects since in chromatogram 38 of Table IV there was no separation of 21 and 22 with methylene chloride.

A separation of the diastereomeric aminoalcohols studied was not achieved with a solvent free from secondary effects. However, the TLC behaviour of these compounds is probably analogous to that of the diols, because of the expected similarity in the geometry of the OH...OH and OH...N bonds.

CONCLUSIONS

The qualitative analysis of the experimental data by means of Snyder's theory suggests that the correlation of $R_{F(erythro)} > R_{F(threo)}$ on silica gel can be used for the assignment of the relative configurations of other non-ionic diastereomeric compounds of the type I which do not possess intramolecular hydrogen bonds or which have such bonds of the types OH...OH or OH...N. In such cases it should first be ascertained whether the groups X and Y are adsorbed more strongly, and have smaller effective volumes, than the groups Ar and Ar'. To this end, Table 10-2 of ref. 14 and the tabulated data in refs. 25 and 26 can be used. Moreover, the ranges over which

the parameters of these groups vary in the present study and that in ref. 1 is to be borne in mind. The *erythro–threo* retention sequence must be established on silica gel DG or on an adsorbent with the same activity (for precautions against secondary adsorbent effects see p. 140 of ref. 14), and the spots of the two isomers must be above the start line, as in all of the cases studied here.

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