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Gas–Liquid Chromatographic Separation of Structurally Related Diastereoisomeric Systems

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Summary Diastereoisomeric amides separate better than esters by g.l.c.; several new types of diastereoisomers are separated for the first time.

The separation of diastereoisomers by gas–liquid chromatography has been studied.[1,2] Such separations have potential use for the resolution of optical isomers, determination of optical purity, and, in certain cases, determination of absolute configurations.

We have been concerned with those underlying structural features of the diastereoisomers which contribute to separation. We have previously postulated that for diastereoisomeric esters, separation results, in part, through differences in steric accessibility of the central ester linkage flanked by the two asymmetric centres for interaction with a polar stationary liquid phase.[1] To examine the effect of the central polar group further, we have chromatographed a series of structurally related diastereoisomers (Table).

Separation data for structurally related diastereoisomeric systems; column: 150 *ft.* × 0·01 *in. stainless steel capillary column*, T = 100°

	Solute	α[a]	$\Delta(\Delta G)$[b] (cal./mole)
1	$R^1CO_2R^1$	1·039	−28
2	$R^1CO{\cdot}NHR^1$	1·088	−62[c]
3	$R^1CO{\cdot}NMeR^1$	1·079	−55
4	$R^1O{\cdot}CO{\cdot}OR^1$	1·045	−32
5	$R^2O{\cdot}CO{\cdot}OR^2$	1·126	−88
6	$R^1O{\cdot}CH_2{\cdot}OR^1$	1·036	−26
7	$R^2O{\cdot}CH_2{\cdot}OR^2$	1·074	−53
8	$R^2O_2C{\cdot}CO_2R^2$	1·000	N.S.[d]

[a] $\alpha = \frac{{}^tR^2 - {}^ta}{{}^tR^1 - {}^ta}$; ${}^tR^1$, ${}^tR^2$ = retention times of 1st and 2nd components, respectively.
${}^ta$ = elution time for non-sorbed component, *i.e.* the air peak.

[b] $\Delta(\Delta G^\circ) = -RT\ln\alpha$. Values reproducible to ±2 cal./mole.

[c] Extrapolated from plot of log α *vs.* $1/T$.

[d] No separation, $\Delta(\Delta G^\circ) < -2$ cal./mole.

In this study, the groups attached to the polar linkage are the same on both sides of the linkage [1,2-dimethylpropyl (R^1) or 1,2,2-trimethylpropyl (R^2)]. These groups contain no polar functions which could complicate the interpretation of the results. Such a controlled structure variation study is not only of value in assessing the influence of the polar linkage, but also in determining the different types of diastereoisomeric systems that are amenable to separation by gas chromatography.

The diastereoisomeric amide, **2**, is better separated than the corresponding ester, **1**. In order to make a valid comparison of **1** and **2**, it was necessary to extrapolate the linear plot of log α *vs.* $1/T$ for the amide down to 100°, the lowest experimental temperature being 130°. However, even at 130°, $\Delta(\Delta G^\circ)$ was larger (*i.e.* −52 cal/mole) for the amide than the ester at 100°. This result is the first direct example to indicate that diastereoisomeric amides separate better than diastereoisomeric esters, at least where there are no other intervening polar effects from substituents attached to the asymmetric centres. In previous work,[3] there were indications that diastereoisomeric amides separated better than esters but the direct comparison was not made. The reason for the difference in $\Delta(\Delta G^\circ)$ for the two isomeric pairs is due in part to the fact that **2** can hydrogen bond to the solvent *via* the proton attached to the nitrogen, whereas **1** cannot. This reasoning is enforced by the fact that the diastereoisomeric pair, **3**, has a lower $\Delta(\Delta G^\circ)$ value than **2**, the essential difference in the two isomer systems being the substitution of a methyl group attached to the nitrogen for the hydrogen atom.

Diastereoisomers **4** and **5**, as well as **6** and **7**, *illustrate the* not surprising result that R^2 produces better separation than R^1. This trend is due to the larger size differential between the groups attached to the asymmetric centre in R^2 relative to R^1.[3] It is next interesting to compare diastereoisomers **1** and **4**. It was previously shown[2] that the distance between the two asymmetric centres played an important role on separation, with a decrease in separation as the centres were moved apart. However, in **4**, there is little difference in $\Delta(\Delta G^\circ)$ from **1**, even though the distance between the optical centres is further apart in the former diastereoisomer. This result is probably due to the enhanced conformational immobility of the groups attached to the asymmetric centre when that centre is attached to the ethereal oxygen rather than directly to the carbonyl group.[1] Also, the ethereal oxygens themselves must contribute to the separation. This conclusion can be seen by a comparison of **4** and **6** or **5** and **7**. Substitution of a methylene group for the carbonyl drops the $\Delta(\Delta G^\circ)$ values, as expected, since the carbonyl must play a role in causing free energy differences for the diastereoisomers; however, the fact that diastereoisomers **6** and **7** separate at all indicates strongly that the ethereal oxygens contribute to separation as well. The carbonic esters, as in diastereoisomers **4** and **5**, are particularly useful for preparative scale resolution of enantiomeric alcohols, due to their ease of synthesis and subsequent hydrolysis. Westley and Halpern[4] have also recently separated diastereoisomeric carbonic esters on an analytical scale, using different groupings attached to the ethereal oxygens than those studied here. Finally, diastereoisomer **8** is non-separable. Apparently the distance between the two asymmetric centres is becoming too far apart to achieve separation.

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