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REGULAR ARTICLE

Substituent effects on chiral resolutions of derivatized 1-phenylalkylamines by heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin GC stationary phase

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Abstract

Chiral resolutions of trifluoroacetyl-derivatized 1-phenylalkylamines with different type and position of substituent were investigated by capillary gas chromatography by using heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin diluted in OV-1701 as a chiral stationary phase. The influence of column temperature on retention and enantioselectivity was examined. All enantiomers of *meta*-substituted analytes as well as fluoro-substituted analytes could be resolved. Temperature had a favorable influence on enantioselectivity for small amines with substituents at the *ortho*-position. The type of substituent at the stereogenic center of amines also had a crucial effect as the ethyl group led to poor enantioseparation. Among all analytes studied, trifluoroacetyl-derivatized 1-(2′-fluorophenyl)ethylamine exhibited baseline resolution with the shortest analysis time.

KEYWORDS

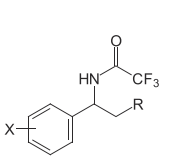
amines, capillary gas chromatography, chiral separation, cyclodextrin derivative, trifluoroacetyl derivative

1 | INTRODUCTION

Accurate and efficient methods for determination of enantiomeric purity are of importance for many fields such as synthetic chemistry, pharmaceutical, agrochemical, flavor, and fragrance. New types of chiral selectors have been continuously introduced and explored to offer more alternatives for chromatographic and electrophoretic separations.[1,2] Nonetheless, cyclodextrin (CD) derivatives are still among the most widely used chiral stationary phases in gas chromatography (GC) for the resolution of volatile and thermally stable chiral compounds. Typically, the type, position, and degree of substitution on the glucopyranose units as well as the size of CD ring can greatly influence the enantioselectivity derivatized CDs offer.[3-5] Various β-CD derivatives with bulky 6-*O*-*tert*-butyldimethylsilyl substituents are among the most useful chiral selectors, providing good enantioselectivity for diverse groups of chiral analytes as well as high column efficiency even at low temperatures.[6-9] Even though a number of new CD derivatives have been developed and proven to be versatile, the understanding of the influence of analyte structure on chiral separation for each CD derivative by GC is thus far insufficient and limited to a certain groups of analytes and CD derivatives.[10-15] Consequently, the selection of appropriate CD derivative for the separation of new chiral analytes is still challenging. Therefore, more studies on the relationship of analyte structures and enantioselectivity offered by existing CD derivatives are still essential and might be beneficial for the enantioseparation of new compounds.

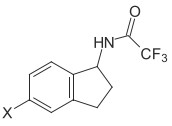
Optically active amines and derivatives are valuable core structures in pharmaceuticals and bioactive compounds.[16,17] In addition, they are used as chiral

resolving agents, chiral catalysts, and chiral auxiliaries in asymmetric syntheses.[18-20] In this work, the retention and enantioselectivity of trifluoroacetyl-derivatized 1-phenylalkylamines were investigated by GC at different temperatures by using the known heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-*β*-CD (or MTBCD)[21] as a chiral selector. 1-Phenylethylamine (PE) and its 18 derivatives were synthesized to systematically explore the effect of type and position of substitution on the aromatic ring. Furthermore, the influence of substituent type at the stereogenic center was studied by comparing the results to those from a series of *para*-substituted 1-phenylpropylamines (PPs) and a series of 5′-substituted 1-aminoindanes (AIs).



compound **1**: R = H; X = H
compound **8**: R = CH_3; X = H

	R = H			R = CH_3
X	*ortho* -	*meta* -	*para* -	*para* -
F	**o2**	**m2**	**p2**	**p9**
Cl	**o3**	**m3**	**p3**	**p10**
Br	**o4**	**m4**	**p4**	**p11**
CF_3	**o5**	**m5**	**p5**	**p12**
CH_3	**o6**	**m6**	**p6**	**p13**
OCH_3	**o7**	**m7**	**p7**	**p14**



X	5'-substituted
H	**15**
F	**16**
Cl	**17**
Br	**18**
CH_3	**19**
OCH_3	**20**

FIGURE 1 Structures of the trifluoroacetyl derivatives of nineteen 1-phenylethylamines, seven 1-phenylpropylamines, and six 1-aminoindanes

2 | MATERIALS AND METHODS

2.1 | Preparation of amines and trifluoroacetyl derivatives

1-Phenylethylamine was purchased from Fluka (Switzerland). Other chiral amines were synthesized from corresponding acetophenones, propiophenones, and 1-indanones via reductive amination.[22] All other chemicals, reagents, and solvents were purchased from various suppliers and used as received. ^{1}H and ^{13}C-NMR spectra of all synthesized amines were recorded on a Bruker AV-400 spectrometer by using $CDCl_3$ as a solvent.

The ketone (~0.7 g, 5 mmol) and titanium(IV) isopropoxide (3 mL, 2 equiv) were dissolved and stirred in isopropanol (25 mL), while being purged with gaseous ammonia for 5 to 7 hours at room temperature. Sodium borohydride (0.4 g, 1.5 equiv) was added, and the reaction mixture was stirred at room temperature for another 2 hours. Ammonium hydroxide (2 M, 25 mL) was added to quench the reaction, and the resulting precipitate was filtered off. The filtrate was extracted with dichloromethane (2 × 25 mL). The combined organic layer was then extracted with hydrochloric acid (2 M, 30 mL). The acidic aqueous extract was treated with sodium hydroxide (1 M) to raise the pH to 10 to 12 and extracted again with dichloromethane (2 × 25mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated to obtain the corresponding pure amine. (^{1}H and ^{13}C NMR spectral information of all synthesized amines is provided in the supporting information.)

All amines were derivatized into trifluoroacetyl (TFA) derivatives. Each amine analyte (20 μL) was dissolved in dichloromethane (1 mL) followed by the addition of trifluoroacetic anhydride (50 μL). The mixture was allowed to react at room temperature for 30 minutes. The solvent and excess reagent were removed by purging with nitrogen. The residue was redissolved in dichloromethane for GC analyses. The structures of all 32 TFA amines used in this study are shown in Figure 1.

2.2 | GC analyses

All GC analyses were performed on an Agilent 6890 series gas chromatograph (Agilent Technologies, USA) equipped with a split/splitless injector and a flame ionization detector. Both injector and detector temperatures were maintained at 250°C. Hydrogen was used as a carrier gas at an average linear velocity of 50 cm second^{-1}. A 15 m, 0.25 mm ID deactivated fused silica capillary column (Agilent Technologies) was coated with a 0.25-μm-thick film of 30% MTBCD in OV-1701 (Supelco, USA) by a static method. Column characteristics were evaluated by the Grob test.[23] Column efficiency over the temperature range of 90 to 220°C was determined with *n*-alkanes and found to be 3600 to 4100 plates m^{-1} ($k' > 7$). All analyses were performed isothermally, in duplicate, every 10°C in the temperature range of 90 to 190°C.

3 | RESULTS AND DISCUSSION

Because separation temperature is one of the most influential operating variables in GC, all analytes were analyzed isothermally at different temperatures and the effect of temperature on the retention factor (k') of the analytes resulting from the interactions between the analytes and the stationary phase was evaluated in the enthalpy change (ΔH) and entropy change (ΔS) values according to:

$$\ln k' = -\frac{\Delta H}{RT} + \frac{\Delta S}{R} - \ln \beta \quad (1)$$

where R is the universal gas constant (1.987 cal mol^{-1} K^{-1}) and β is the volume ratio of mobile phase to stationary phase.

Plots of ln k' versus $1/T$ for both the less and the more retained enantiomers of all analytes were linear with $R^2 > 0.998$. The $-\Delta H$ and $-\Delta S$ values of the more retained enantiomers varied in the range of 13.6 to 17.8 kcal mol^{-1} and 19.8 to 26.9 cal mol^{-1} K^{-1}, respectively, as shown in Figure 2. Both type and position of the substituents of the analytes influenced retention: In most cases, analytes with electron withdrawing groups (—Cl, —Br, and —CF_3) had slightly higher $-\Delta H$ and $-\Delta S$ values than those with electron donating groups (—CH_3 and —OCH_3) in the same position. For a series of 1-PEs, most *ortho*-substituted amines had lower $-\Delta H$ and $-\Delta S$ values than their corresponding *meta*- and *para*-substituted amines. While 1-AIs showed mostly higher $-\Delta H$ and $-\Delta S$ values than those of *para*-substituted 1-PEs and *para*-substituted 1-PPs of the same type of the substituents.

The influence of temperature on the enantioselectivity (α) of analytes resulting from the difference in the interactions between the two enantiomers and the stationary phase was assessed in the $\Delta\Delta H$ and $\Delta\Delta S$ values according to

$$\ln \alpha = -\frac{\Delta\Delta H}{RT} + \frac{\Delta\Delta S}{R} \quad (2)$$

When enantioseparation occurred, the difference of $-\Delta H$ values ($-\Delta\Delta H$ value) and the difference of $-\Delta S$ values ($-\Delta\Delta$S value) for the two enantiomers could be obtained. The plot of $-\Delta\Delta H$ versus $-\Delta\Delta S$ of all 32 TFA-derivatized amines gave good correlation ($R^2 = 0.999$) as shown in Figure 3, suggesting that all analytes probably interact with the stationary phase in a similar fashion. Figure 4 shows the $-\Delta\Delta H$ values of the TFA derivative of 1-PE (**1**) and its 18 structural analogs with different substituents both in type and position on the aromatic ring. Their $-\Delta\Delta H$ values varied from 0 to 0.48 kcal mol^{-1}. It was noticed that amines with halogen substitution had higher $-\Delta\Delta H$ values than with other types of substituents, suggesting a stronger influence of temperature on enantioselectivities. The $-\Delta\Delta H$ values for the enantiomers of **5** that have trifluoromethyl groups, a stronger electron

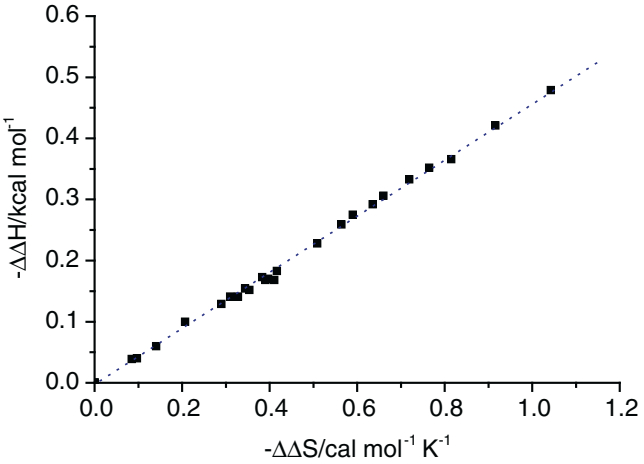


FIGURE 3 Plot of $-\Delta\Delta H$ versus $-\Delta\Delta S$ for all 32 trifluoroacetyl-derivatized amines analyzed on the MTBCD column

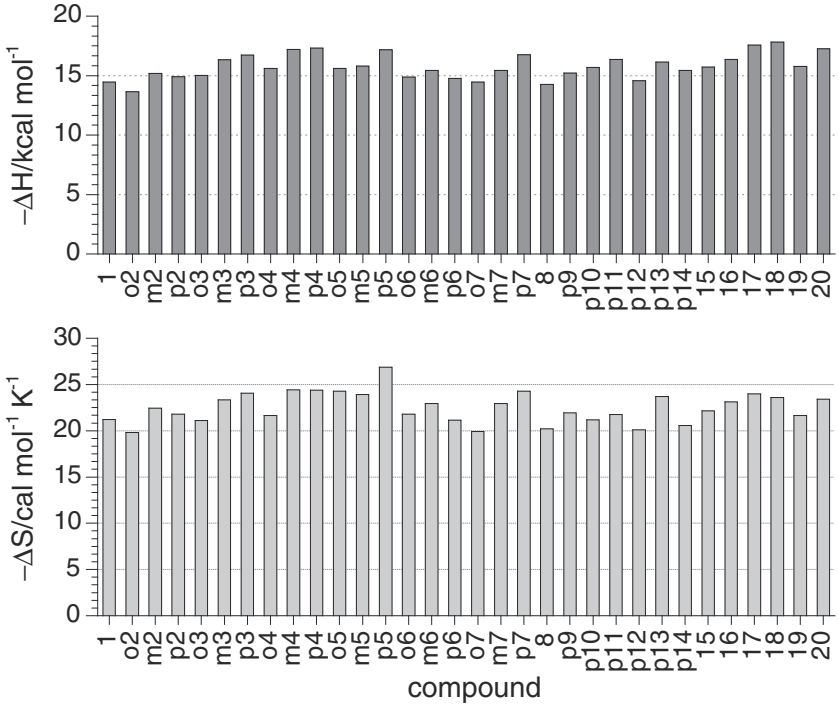


FIGURE 2 $-\Delta H$ and $-\Delta S$ values calculated for the more retained enantiomers of all analytes on the MTBCD column

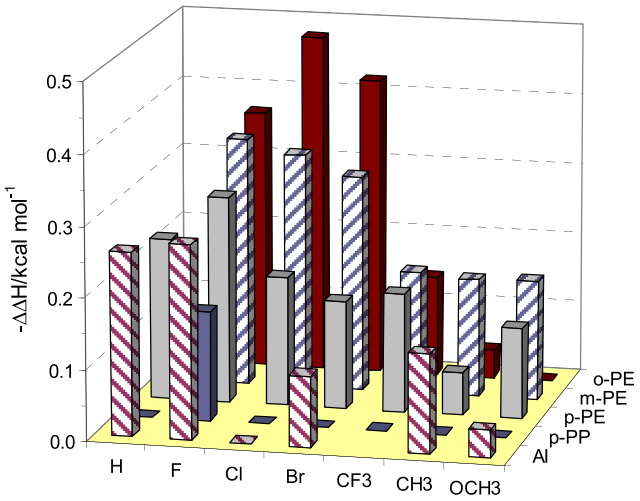


FIGURE 4 $-\Delta\Delta H$ values calculated for the trifluoroacetyl derivatives of all amines having different substituents both in type and substitution position on the MTBCD column

withdrawing substituent than halogen, were surprisingly lower than those of halogen-substituted amines but were in the same range as those of methyl- and methoxy-substituted amines (enantiomers of **6** and **7**, respectively). These results pointed out that large analytes may be too bulky to enter the cavity of MTBCD, thus leading to lower $-\Delta\Delta H$ values. Nonetheless, analytes with substituents of a similar size may not necessarily exhibit the same degree of $-\Delta\Delta H$ values as in the case of the enantiomers of **5** and **6** (trifluoromethyl vs methyl).

The position of substituents on the aromatic ring also played a role in determining the $-\Delta\Delta H$ values for the amines in this study. For all halogen-substituted amines, the $-\Delta\Delta H$ values noticeably decreased in the order of *ortho-* > *meta-* > *para-*. Higher $-\Delta\Delta H$ values are likely due to the steric hindrance created by the *ortho*-substitution close to the stereogenic center. As the column temperature decreased, the interaction between one enantiomer of appropriate conformation and the MTBCD became stronger, while the interaction between the other enantiomer and the MTBCD was obstructed by the steric hindrance. Thus, the enantioselectivity was well improved. Among all amines used in this work, the TFA derivative of 1-(2′-chlorophenyl)ethylamine (**o3**) exhibited the largest $-\Delta\Delta H$ value, indicating that column temperature had the strongest effect on enantioselectivity for **o3**, thus giving a good chance to improve the resolution of its enantiomers. The influence of temperature on the $-\Delta\Delta H$ values of positional isomers of the amines with large substituents (CF_3, CH_3, and OCH_3) was contrary to those with halogen substitution. *Ortho*-substitution with large functional group led to either low $-\Delta\Delta H$ values (**o5** and **o6**) or no separation (**o7**). *Meta*-substitution seemed to provide the highest $-\Delta\Delta H$ values among three substitution positions. The trends in the $-\Delta\Delta H$ values obtained for the TFA derivatives of methyl- and methoxy-substituted 1-PEs (**6** and **7**) did not agree with those reported by using heptakis(2,6-di-*O*-nonyl-3-*O*-TFA)-*β*-CD and heptakis(2,6-di-*O*-pentyl-3-*O*-TFA)-*β*-CD as chiral GC stationary phases[24]: Both of these CD derivatives gave the highest $-\Delta\Delta H$ values for *ortho*-substituted analytes; the MTBCD stationary phase used in this study showed the opposite. It was interesting to observe that the $-\Delta\Delta H$ values of the three positional isomers of trifluoromethyl-substituted amines (**o5**, **m5**, and **p5**) were very similar. Plots on ln α versus $1/T$ for the three isomers of compound **5** suggest that temperature has the same influence on enantioselectivities as the slopes are nearly parallel (Figure 5). *Meta*-substitution with a trifluoromethyl group leads to superior chiral discrimination: The enantioselectivities for **m5** are higher than for **o5** and **p5** at every temperature. Thus, the enantiomers of **m5** could be completely separated in a shorter analysis time.

The effects of substituents at the stereogenic center of analytes were further studied. Replacing the methyl group at the stereogenic center of 1-PE and its *para*-substituted derivatives (p-PE: **1**, **p2**-**p7**) with a larger ethyl group (pPP: **8**, **p9**-**p14**) resulted in a complete loss of enantioseparation for all analytes, except for the TFA derivative of 1-(4′-fluorophenyl)propylamine (**p9**) (Figure 4). The $-\Delta\Delta H$ value of **p9** was approximately half of that of **p2**. The rigidity of analyte structure on enantioseparation was also considered by comparing the $-\Delta\Delta H$ values of *para*-substituted 1-PPs (p-PP: **8**, **p9**-**p11**, **p13**-**p14**) to those of 5′-substituted 1-AIs (**15**-**20**) which contain the same carbon atoms in the molecule. Interestingly, all enantiomers of 1-AI derivatives could be resolved, except for the TFA derivative of 5′-chloro-1-AI

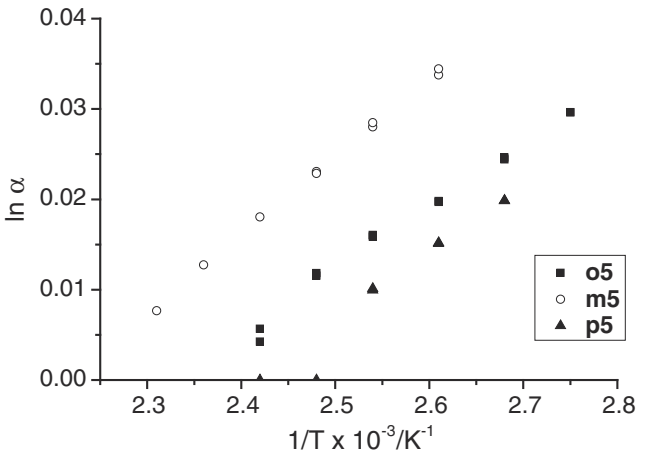


FIGURE 5 ln α versus $1/T$ for the enantiomers of **o5**, **m5**, and **p5** on the MTBCD column

(**17**). For the three series of amines investigated, it was noticed that all enantiomers of fluoro-substituted amines could be resolved. Comparison of the separation of the enantiomers of **p2**, **p9**, and **16** at 140°C is shown in Figure 6. These results point out the significance of the type of substituent at the stereogenic center as well as the type of substituent on the aromatic ring.

In addition to a high $-\Delta\Delta H$ value for the analyte, a rapid and complete separation of the enantiomers is always desirable. Despite having the highest $-\Delta\Delta H$ value, compound **o3** did not have the shortest analysis time for the separation of its enantiomers at a minimum resolution (Rs) of 1.5. Unexpectedly, the analyte whose enantiomers could be completely resolved in the shortest analysis time on the MTBCD stationary phase is compound **o2**. Although the separation temperature affected both retention and enantioselectivity simultaneously, its influence on both of these factors may be significantly different.

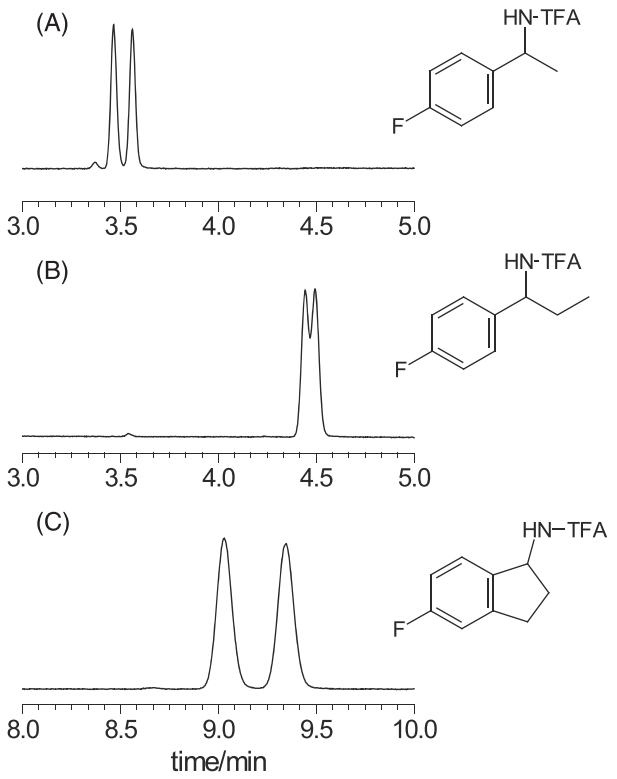


FIGURE 6 Separation of the enantiomers of (A) **p2**, (B) **p9**, and (C) **16** at 140°C on the MTBCD column

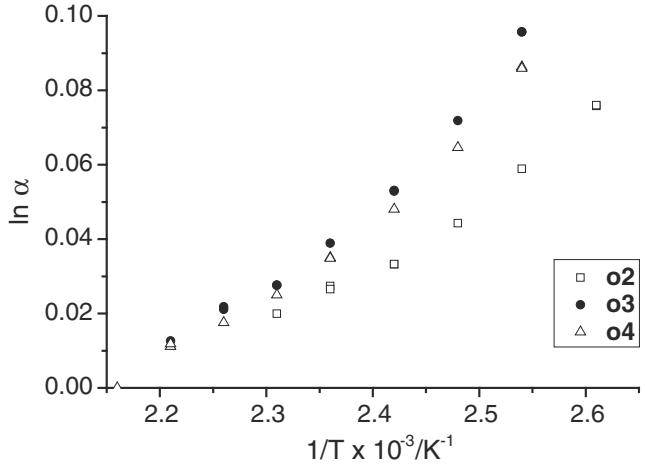


FIGURE 7 ln α versus $1/T$ for the enantiomers of **o2**, **o3**, and **o4** on the MTBCD column

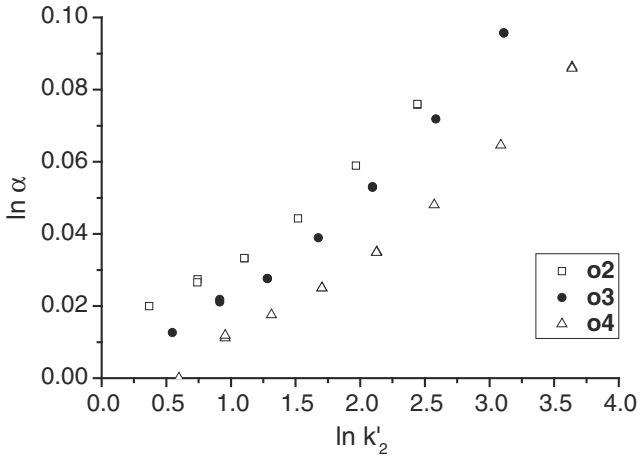


FIGURE 8 ln α versus ln k'_2 for the enantiomers of **o2**, **o3**, and **o4** on the MTBCD column

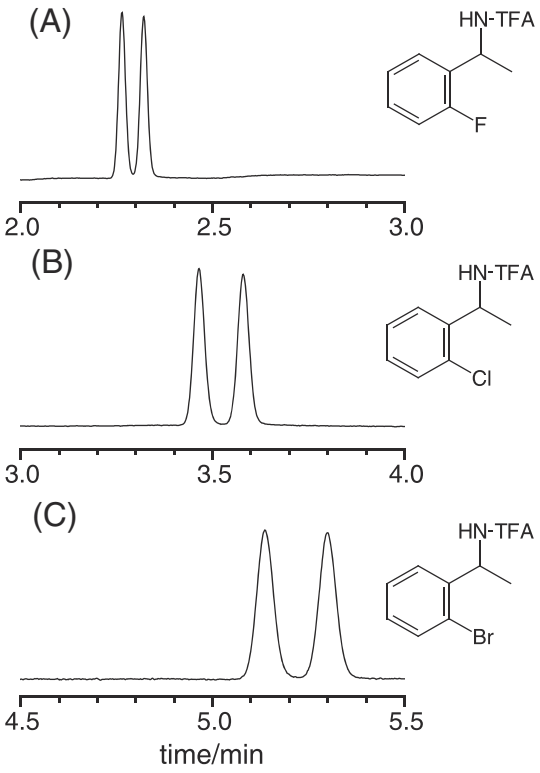


FIGURE 9 Separation of the enantiomers of (A) **o2**, (B) **o3**, and (C) **o4** on the MTBCD at their highest separation temperature with a minimum resolution (Rs) of 1.5

Plots of ln α as a function of $1/T$ and ln k'_2 for analytes with the three largest $-\Delta\Delta H$ values (**o2**, **o3**, and **o4**) are illustrated in Figures 7 and 8, respectively. As shown in Figure 7, enantioselectivities for the three analytes at the same separation temperature were in the order of **o3** > **o4** > **o2**, similar to their $-\Delta\Delta H$ values. Enantioselectivities for the analytes having the same retention value follow a different order: Enantioselectivity is the highest for amine **o2**, followed by **o3** and **o4**, respectively (Figure 8). Temperature had a lesser effect on retention for **o2** as reflected by the lowest $-\Delta H$ and $-\Delta S$ values (Figure 2), but a higher effect on the enantioselectivity. Separation of three racemates with baseline resolution and their analysis times are illustrated in Figure 9.

4 | CONCLUSION

It can be seen that chiral recognition of 1-phenylalkylamine derivatives by the MTBCD stationary phase is governed by several factors simultaneously. The size, polar property, and substitution position of a group on the analyte structure as well as the separation temperature can influence the resolution of the enantiomers for each analyte differently. All enantiomers of analytes with fluoro substitution on the aromatic ring showed good enantioseparation by the MTBCD stationary phase, and they could be completely resolved in a reasonable analysis time. *Meta*-substitution on the aromatic ring seemed to provide adequate enantioseparation regardless of the type of substituent. Small functional groups (such as fluoro, chloro, and bromo) substituted at *ortho*-position of the aromatic ring tend to improve enantioseparation, while a larger ethyl group substituted at the stereogenic center tends to hinder enantioseparation.

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