RSC Advances



View Article Online

View Journal | View Issue

PAPER



Cite this: RSC Adv., 2015, 5, 2988

Received 5th November 2014 Accepted 3rd December 2014

DOI: 10.1039/c4ra13928c

www.rsc.org/advances

Introduction

A comprehensive examination of the selfdisproportionation of enantiomers (SDE) of chiral amides *via* achiral, laboratory-routine, gravitydriven column chromatography⁺

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This work explores the self-disproportionation of enantiomers (SDE) of chiral amides *via* achiral, gravitydriven column chromatography as typically used in laboratory settings. The major findings of this work are: (1) the remarkable persistence and high magnitude of the SDE for the analytes under a variety of conditions, including polar solvents and different achiral stationary phases and (2) the notable generality of the SDE phenomenon as it occurs for a wide range of chiral amide substrates and even for a broad range of starting ee. This last aspect is unusual and not commonly observed. The key conclusion of this work is that it judiciously conveys the predictability of the SDE for chiral amides under the routine conditions of achiral chromatography. These results are consequently of concern for practitioners in the area of catalytic asymmetric synthesis involving chiral amides as intermediates or products and the inferents need to be taken extremely seriously by workers in the field.

The self-disproportionation of enantiomers $(SDE)^1$ describes any process under achiral conditions which transforms a nonracemic sample of a chiral compound into fractions containing varying – enriched and depleted – proportions of the enantiomers in comparison with the enantiomeric composition of the starting sample.² Since the initial observations of SDE *via* sublimation³ and achiral chromatography,⁴ numerous papers have reported this phenomenon to occur *via* sublimation,⁵ achiral chromatography,⁶ and even by distillation.^{6a,7} In addition to the general SDE reviews,^{8,9} there are also two specific reviews^{10,11} on the phenomenon *via* achiral chromatography. The underlying premise is that dimeric homo- or heterochiral associations or other higher-order aggregates are responsible for the phenomenon.^{2,12,13} By far and away the majority of cases appear to involve intermolecular interactions forming homoand heterochiral associates based on hydrogen bonding,^{8,11,12,14} but other cases based on π -stacking^{4,15} or dipole–dipole interactions^{16,17} have been noted. Of particular note, it has been shown that optical purification based on the SDE phenomenon for some compounds can rival conventional recrystallization in performance and practical application.^{6c,d}

It is worth noting the predictions resulting from mathematical modeling¹⁸ that have been made for the SDE phenomenon in idealized cases where only a single intermolecular interaction is present and only one structural entity is formed, e.g. dimer formation. Firstly, baseline separation between the first eluting component (e.g. the excess enantiomer) and the second eluting component is not possible. Secondly, due to being unable to attain baseline separation and the asymptotic convergence of the first eluting component, it is not possible to separate out all of the first eluting component from the sample (*i.e.*, for example, obtaining all of the excess enantiomer from the racemic portion if the excess enantiomer is the first eluting component). In practical terms though, it is possible to obtain a large proportion of it. Thirdly, it is not possible at all to obtain the second eluting component completely free of the first eluting component due to the asymptotic convergence of the first eluting component, though in practice this can be inconsequential since the level of "contamination" becomes negligible as the content of the first eluting component converges to zero. However, it is possible in theory to obtain fractions

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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra13928c

containing the first eluting component completely free of the second eluting component, and this is not wholly dependent on a high starting ee value.

As part of our ongoing investigation into the processes and interactions leading to SDE *via* chromatography,¹⁷ in this study we examine a set of amides in a similar detailed fashion to the previous study by the adjustment of various parameters, *e.g.* solvent polarity changes, other chromatographic parameters, samples of varying initial ee, and varying structure of the analyte, to gauge the sensitivity of the SDE to the prevailing conditions. The previous study¹⁷ was concerned with the behavior of methyl *n*-pentyl sulfoxide (MPS) (and as an extension, to chiral sulfoxides generally), a compound whose intermolecular interactions are based on dipole–dipole interactions. By contrast, the intermolecular interactions of the amides examined here are based on the more commonly ascribed hydrogen bonding.

In a previous examination^{6d} of chiral amides, we were able to demonstrate a very high magnitude for the SDE by medium pressure liquid chromatography (MPLC). Considering that chiral amides are one of the most prevalent classes of organic intermediates, it is of vital importance to know if a sizeable SDE could also readily occur under the routine conditions of achiral chromatography as chiral amides are some of the most commonly used intermediates in asymmetric synthesis and are usually purified by achiral column chromatography as part of common laboratory practice. Thus, if a sizeable magnitude of the SDE is indeed observed under routine laboratory chromatography, this should be brought to the attention of workers in the field and the appropriate precautions enacted in handling research samples and, in particular, to avoid possible erroneous interpretation of the results of catalytic asymmetric reactions. This question has high scientific interest with regards to the generality and understanding of the SDE phenomenon as well as inferences for its predictability.

In this work, we systematically examined various conditions for the gravity-driven column chromatography of a set of chiral amides with the variance of a number of parameters other than the substrate structure. Often, it is the case that only a small range of ee values lead to a high Δ ee, and therefore potentially to the obtainment of enantiomerically pure fractions.² Consequently, it has mistakenly been believed that a high initial ee was therefore required to obtain an enantiomerically pure fraction, but we demonstrate herein that this need not be the case. Furthermore, quite interestingly, we show that the dependency on initial ee for these compounds was much reduced and high ee values for the first eluting fraction were obtained for a wide range of samples of varying initial ee.

Results and discussion

The structures of the amides examined in this work are presented in Fig. 1. We initiated our study using compound 1 in the test experiments to see if the SDE can be observed under routine laboratory-run, gravity-driven chromatography. For this test we used arbitrary conditions derived from our previous experience with the SDE study of chiral sulfoxides.¹⁷ The first test run fully





realized our worries; thus, compound **1**, of 72.3% ee, when subjected to routine column chromatography yielded initial fractions highly enriched in the excess enantiomer (>93% ee) while the final fractions were alternatively drastically depleted in the excess enantiomer (<45% ee). One may agree that this experiment underscores the scientific significance of this study and its general importance for organic chemistry and asymmetric synthesis. Currently, there is not yet an established protocol regarding the conduct of a systematic SDE study, but what is clear is that it is needed to (1) determine how the SDE phenomenon depends on the chromatographic conditions, thereby allowing chemists some degree of control over it, and (2) ascertain its generality for chiral amides in terms of predictability and the precautions required for dealing with this class of chiral organic compounds.

With these considerations in mind, we decided to examine the effect of solvent polarity whereby the ratio of hexane to ethyl acetate was varied. It was assumed^{8,11,12,14} that a more polar eluent might disrupt the homo- and heterochiral interactions during the chromatography and therefore quench the SDE phenomenon. With this aim, we conducted a series of experiments varying the ratio of hexane to ethyl acetate from 5:3 to 5:6. Analysis of the collected fractions for each chromatographic run showed that the early eluting fractions were quite uniformly enantiomerically enriched in comparison to the starting sample while the later eluting fractions were correspondingly enantiomerically depleted (Fig. 2).

The first striking observation was that the magnitude of the SDE (Δee , defined as the difference between the first and final fractions) was effectively impervious to the solvent changes, a result which is highly unexpected and contrary to previous observations. As mentioned above, it has so far been a basic rationale that with higher solvent polarity, the breakup of associates can be anticipated leading to a muting of the SDE phenomenon. Although elution is considerably accelerated with an increase in the content of the ethyl acetate, the ee of the initial fraction remains high in all cases, indeed, inexplicably it is even highest in the chromatographic run using the most polar of the eluent mixes. A second point of note is that, e.g. in the chromatographic run using hexane to ethyl acetate in a ratio of 5 : 3, the ee does not drop continuously and both the second and the twelfth fractions exhibit a rise in the ee relative to the preceding fraction. These aberrations have previously been



Fig. 2 The effect of solvent polarity on the SDE of compound 1 using a sample of 72.3% ee. The ratio of hexane to ethyl acetate is indicated for each run. For each run, 50 mg of compound 1 per 6.3 g of silica gel were used (60 Å pore size, $40-63 \mu m$ particle size) on a column 20 mm in diameter and length 45 mm. Each collected fraction consisted of 10 mL of eluent.

described¹⁷ as "kinks" and allude to the complex nature of the processes leading to the SDE phenomenon or to drastic changes in the local concentrations, a point discussed in detail further on.

As a result of these measurements, for all subsequent chromatographic runs, it was considered judicious to use an equal ratio of hexane to ethyl acetate (5:5) as the eluent.

In our next set of experiments, the first examination of varying the chromatographic conditions was to increase the amount of compound 1 loaded onto the column from 50 mg to 100 mg whilst keeping all other parameters constant (run b, Fig. 3). The result was that an almost identical elution profile was obtained. Since the SDE phenomenon is dependent on the



Fig. 3 The effect of other chromatographic parameters on the SDE of compound 1 using a sample of 72.3% ee. For each run, the ratio of hexane to ethyl acetate was 5 : 5. Runs: (a) 50 mg of compound 1 per 6.3 g of silica gel were used (60 Å pore size, $40-63 \mu m$ particle size) on a column 20 mm in diameter and length 45 mm (*i.e.* the same conditions as in Fig. 2); (b) 100 mg of compound 1 was applied to the column under otherwise identical conditions; (c) 12.6 g of silica gel was used under otherwise identical conditions (resulting in a column length of 90 mm); (d) silica gel of $60-200 \mu m$ particle size was used under otherwise identical conditions; and (e) aluminum oxide (neutral, grade I) was used instead of silica gel under otherwise identical conditions. Each collected fraction consisted of 10 mL of eluent.

formation of analyte associates, increasing the amount of the analyte can favor the formation of the required associates. Since substantial changes were not observed, it can be assumed that the optimum concentration of the analyte has been reached and above this level no further improvement will be forthcoming. Very high concentrations might even lead to a decrease in the magnitude of the SDE, though this has never been observed and it has always been the case that either the Δ ee increased, or, as in this instance, essentially the same Δ ee was obtained.

The second examination involved increasing the amount of silica gel to attain a column length double that initially used (run c, Fig. 3). SDE *via* chromatography differs fundamentally from the usual chromatography of analytes in that in the latter case, resolution improves indefinitely with increasing column length, albeit with an ever-decreasing gain in resolution and at the cost of ever-increasing broader peaks. Since SDE *via* chromatography is dependent on analyte–analyte interactions, dilution from passage along a column only serves to reduce these interactions and hence the phenomenon reaches a limit in terms of performance. In this case, as also observed previously,¹⁷ this limit is easily attained as the run with a longer column failed to improve or alter the magnitude of the SDE to a significant extent after taking into account the extended elution profile due to the longer column length engaged.

The third examination involved using silica gel of larger particle size, 60-200 µm rather than 40-63 µm (run d, Fig. 3). Again, discernible differences amenable to meaningful interpretation were not observed. This was a surprising result, and in contrast to previous observations17 it must be noted, as the chromatographic performance is usually dependent on the particle size of the stationary phase - which may have as much to do with reduced inherent chromatographic capability of the stationary phase as it does with a change in system dimensions relevant to SDE via chromatography - but it indicates that for SDE via chromatography, the formation of analyte associates is probably as much dependent on the solution phase as it is on the adsorbed phase. The initial thinking was that a larger grain size would provide larger interstitial volumes, which in turn can result in a reduced concentration of the analyte in these voids, thus affecting the magnitude of the SDE result. However, since the previous run (run b) indicated that the system is already at a high optimum in terms of concentration for this particular substrate and its intermolecular interactions, it may be that a relatively small alteration resulting from interstitial volume changes would not be sufficient to result in discernible effects. The dependency on the chromatographic performance of the system can also be very much substrate dependent as well as on the type of interactions involved; in the previous study¹⁷ with sulfoxides, the compound's intermolecular interactions are based on dipole-dipole interactions.

The final examination involved using aluminum oxide instead of silica as the stationary phase (run e, Fig. 3). Here the magnitude of the SDE was markedly reduced in comparison to the results obtained with silica gel, though still notable none-theless. But the result, given that the magnitude of the SDE was effectively impervious to all other parameter changes, lends credence to the premise of Klika *et al.*¹⁹ whereby it was asserted

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that the SDE phenomenon is not just a question of a preference between homo- and heterochiral dimers, but the relative stability of these homo- and heterochiral dimers as the environment changes, *e.g.* from solution in the eluent in the interstitial spaces to the pores of the stationary phase. That is, a perturbation in aggregation behavior between the free molecules and the homo- and heterochiral dimers can arise from the different environments of the different stationary phases in use. The observed change in SDE behavior of compound **1** upon changing the stationary phase from silica gel to aluminum oxide supports this assertion.

As before, it is noted that there is a substantial kink in the early part of the elution profile for aluminum oxide. Such kinks occasionally occur at the front end of the elution profile,6b,15,17,20 but may also occur in the middle¹⁷ (vide infra) as well as the tail¹⁷ (vide supra) and even occur multiple times during the course of the elution.¹⁷ By far the most dramatic example, so extreme in fact it has been considered¹⁹ a double SDE via chromatography event, was observed during the chromatography of spirobrassinins.²¹ Such aberrant behavior or any deviation from ideal indicates that the system is far from a simple and idealized one that can be described by one intermolecular interaction and one type of transitory structure such as dimers. Thus oligomer formation, in addition to dimer formation, or alternative binding modes must be occurring whenever aberrant behavior is observed. The latter explanation has been proposed, 19,22 with some legitimacy, to account for the dramatic behavior of the spirobrassinins.²¹ Thus it is clear that the graphical representations are not ideal with respect to mathematical modeling assuming a single intermolecular interaction and the formation of only one type of transitory aggregate structure11,12 and/or the differential formation of the dimers under the various environments of the chromatography.

Although the occurrence of the SDE phenomenon does depend to a degree on the starting ee of a sample, previous investigations have implied^{2,23} that to obtain a sample with high optical purity via SDE it was necessary to utilize a sample of high ee, but this need not be the case. Nevertheless, often it is the case that only a small range of ee values lead to a high Δee and therefore potentially to the obtainment of enantiomerically pure fractions,² this only adding to the mistaken belief that a high initial ee was required to obtain an enantiomerically pure fraction. Here, interestingly, the dependency on initial ee was reduced and high ee values for the first eluting fraction were obtained for a wide range of samples of varying initial ee. The results are portrayed in Fig. 4 for a range of initial ee's, from 12-90%. Essentially, a set of runs spanning >35% initial ee (54-90% initial ee) all provided similar results in terms of high enantiomeric purity for the first eluting fraction. Of note, the largest magnitudes for the Δee , 30–40%, were obtained for initial ee's from 45–72% ee, thus even the Δee spans a considerable range.

Overall though, and truly quite remarkably, regardless of the conditions applied, generally the same robust and unquenchable effect of the SDE phenomenon was observed for compound **1**.

To complete our investigations and demonstrate the robust generality of the SDE phenomenon for these amides, we



Fig. 4 The effect of the sample initial ee on the SDE of compound 1. For each run, the ratio of hexane to ethyl acetate was 5 : 5 under otherwise identical conditions as described in Fig. 1. The initial ee of the sample is indicated for each run. Each collected fraction consisted of 10 mL of eluent.

examined all nine compounds 1-9 displayed in Fig. 1 using similar initial ee's in each case. The results are portrayed in Fig. 5. For compounds 1 and 4–9, the Δ ee values are reasonable to high. For compounds 2 and 3, however, with the two lowest values for Δee , 6.3 and 10.9%, respectively, clearly there must be steric hindrance from the large groups adjacent to the carbonyl impeding the formation of any dimers, hence precluding manifestation of the SDE phenomenon to a high degree. Thus, as long as the substituents do not sterically impede the formation of hydrogen bonding between the amide groups, SDE *via* chromatography appears to be impervious to the substrate structure for this class of compounds. Notable again is that kinks are evident in the elution profiles for some of the compounds under these conditions in both the middle (compounds 2 and 8) and in the tail (compounds 5 and 7) sections of the elution profiles.



Fig. 5 The SDE behavior of the compounds 1–9. For each run, the appropriate ratio of hexane and ethyl acetate was used under otherwise identical conditions as described in Fig. 1 with the compound number indicated for each run. The initial ee's of the samples with the attained Δ ee's in parentheses were: 1, 72.3 (39.9); 2, 69.6 (6.3); 3, 68.7 (10.9); 4, 69.9 (31.2); 5, 72.0 (28.9); 6, 72.5 (24.7); 7, 70.2 (24.5); 8, 72.9 (17.6); and 9, 75.0% (21.8%). Each collected fraction consisted of 10 mL of eluent.

Conclusions

In conclusion, we have described the results of an investigation into the SDE phenomenon via gravity-driven chromatography over achiral silica gel for a set of amides. We demonstrated that it is possible to obtain the compounds in high optical purity under various conditions. Indeed, it was found that the SDE phenomenon for these compounds could be observed under all applied conditions, including for a broad range of starting ee. This latter aspect is unusual and not commonly observed. Most importantly however, SDE via chromatography has a considerable and noticeable effect on the ee of sample by the standard, routine column chromatography conditions that are in use in any research laboratory. These results are consequently of considerable concern for workers in the field of asymmetric synthesis concerned with chiral amides as intermediates if they are unaware of the problem. On the other hand, it is highly probable that optical purification based on the SDE phenomenon represents a simple, convenient, and inexpensive method for the optical purification of this class of compounds with a high degree of proficiency. These results should serve as a warning to organic chemists as the SDE for amides cannot be effectively controlled and occurs under virtually any conditions and for, as we anticipate, virtually any structural type of chiral amide.

The SDE for these chiral amides can be explained by the strong tendency of these compounds to form homo- and heterochiral dimers by hydrogen bonding interactions with the differing chromatographic behavior of the entities the underlying mechanism responsible for the SDE phenomenon. Aberrant SDE behavior, however, was also noted in that the ee did not always fall continuously during the progression of the chromatography, and this was attributed to the complexity of the system at hand which cannot be described in simple terms such as the formation only of homo- and heterochiral dimers based on a single interaction. It is possible that higher-order aggregates might also be involved to explain the deviation of behavior from ideal as well as the premise that it is the perturbation in aggregation behavior between the free molecules and the homo- and heterochiral dimers which can arise from the different environments that is an important factor in the SDE process.

Acknowledgements

The authors gratefully acknowledge financial support from IKERBASQUE, Basque Foundation for Science; the Basque Government (SAIOTEK S-PE13UN098), and Hamari Chemicals (Osaka, Japan).

Notes and references

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