Enantiomeric Enrichments *via* the Self-Disproportionation of Enantiomers (SDE) by Achiral, Gravity-Driven Column Chromatography: a Case Study Using *N*-(1-Phenylethyl)acetamide for Optimizing the Enantiomerically Pure Yield and Magnitude of the SDE

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This work explores the self-disproportionation of enantiomers (SDE) *via* achiral, gravity-driven column chromatography as typically used in laboratory settings for the purpose of enantiomeric enrichment using *N*-(1-phenylethyl)acetamide (PEA) as a case study. The major finding of this work is the very large magnitude of the SDE for PEA across a variety of conditions and broad range of starting ee values, thereby facilitating a simple, reliable, and predictable means of obtaining enantiomerically pure samples. For example, starting with a sample of PEA of ee as low as 28%, a single column run yielded an enantiomerically pure sample (> 99.9% ee) from the first fractions and a significantly enantiomerically depleted sample (< 17% ee) from the final fractions. An assessment of SDE *via* achiral, gravity-driven column chromatography was also rendered with regard to the differing objectives that workers might target – a large magnitude of the SDE, obtaining an optimum sample of desired ee, or preparative-scale separation of the excess enantiomer. Overall, it can be considered that the SDE phenomenon *via* achiral, gravity-driven column chromatography – readily applicable in the usual laboratory settings – is a simple and convenient method for enantiomeric enrichment with a high degree of proficiency. Advantages of SDE *via* achiral, gravity-driven column chromatography over conventional fractional recrystallization for the enantiomeric enrichment of amides/amines, and applicable also to many other classes of compounds as well, are discussed.

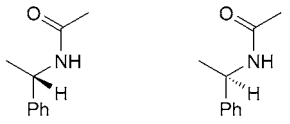
Introduction. – The self-disproportionation of enantiomers (SDE)[1]) [1] describes any process under achiral conditions which transforms a nonracemic sample of a chiral compound into fractions containing varying – enriched and depleted – proportions of

[1]) The applied terminology has been much discussed and debated and is used herein as recommended by *Klika* and *Soloshonok* [1].

the enantiomers in comparison with the enantiomeric composition of the original sample [2]. Since the initial observations of SDE *via* sublimation [3] 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 general reviews [8][9] on the SDE phenomenon, there are also two specific reviews [10][11] focused on achiral chromatography. The acronym ESDAC (enantiomer self-disproportionation over achiral chromatography) is sometimes used for the SDE phenomenon when referring explicitly to SDE *via* chromatography [12–14]. The underlying premise for the process in effect is that the transient formation of dimeric homo- or heterochiral associations or other higher-order aggregates are responsible for the phenomenon [2][12][15]. While the vast majority of cases appear to involve the formation of homo- and heterochiral associates based on H-bonding [8][11][12][16], other cases based on π-stacking [4][17] or dipole–dipole interactions [18][19] have also been described. Of note, it has been shown that enantiomeric enrichment based on the SDE phenomenon can rival conventional recrystallization in performance and practical application for some compounds [6a][6c][6d].

It is worth reiterating [19][20] the predictions resulting from mathematical modeling [14][21] 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 (*e.g.*, the racemic portion) is not possible. Secondly, due to the lack of baseline separation and the asymptotic convergence of the first eluting component, it is not possible to isolate completely the first eluting component, *i.e.*, obtain all of the excess enantiomer from the racemic portion if the excess enantiomer is the first eluting component, but it is possible nevertheless 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, along with the second component, converges to zero. However, it is possible to obtain fractions containing the first eluting component completely free of the second eluting component, and this is not wholly dependent on a high starting ee value [19]. It is also worth noting that there are large deviations from this idealized behavior in many real-world examples.

As part of our ongoing, comprehensive investigation into the processes and interactions leading to SDE *via* achiral, gravity-driven column chromatography [19][20], we had examined [20] a set of amides in detail with respect to various parameters, *e.g.*, amide structure, sample ee, eluent polarity, and other chromatographic parameters such as column geometry, ratio of analyte to stationary phase, type of stationary phase and pore size, *etc.*, to gauge the sensitivity of the SDE phenomenon to the prevailing conditions. As a result, we were able to demonstrate the generality and persistence of the SDE phenomenon for the examined compounds. Since chiral amides are one of the most prevalent classes of organic compounds and are some of the most commonly used intermediates in asymmetric synthesis (and duly, also amines), it was of considerable importance to prove that a sizeable, and therefore concerning, magnitude of the SDE (Δee values, defined as the difference in ee between the fractions of lowest



(*S*)-PEA (*R*)-PEA

Fig. 1. *Structures of (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide* (PEA)

and highest ee, ostensibly the first and final fractions) can readily occur [20] under the routine conditions of achiral chromatography as chiral amides are usually purified using this technique as part of common laboratory practice. In addition to noting the generality of the SDE phenomenon *via* achiral, gravity-driven column chromatography for a range of chiral amides, we also demonstrated [20] that it was expressed over a broad range of starting ee values.

Having previously examined the SDE phenomenon with regard to various aspects, we herein focus on *N*-(1-phenylethyl)acetamide (PEA, *Fig. 1*) as a case study to ascertain the conditions for obtaining a high yield of enantiomerically pure samples and how this relates to just enantiomeric purity *per se*.

The aims of the present work are thus to *i*) gain a deeper appreciation of the SDE phenomenon *via* achiral, gravity-driven column chromatography and ascertain the requirements for obtaining a large Δee value, *ii*) ascertain the requirements for obtaining fractions of high enantiomeric purity, and *iii*) ascertain the requirements for obtaining a high, amounting to preparative scale, yield of enantiomerically pure sample. Counter to intuitive expectations, these objectives are not necessarily mutually inclusive.

Results and Discussion. – This present investigation of the SDE phenomenon *via* achiral, gravity-driven column chromatography utilized *N*-(1-phenylethyl)acetamide (PEA), synthesized from (1-phenylethyl)amine by acetylation with AcCl, and centered on examining a range of PEA samples of varying ee under assorted conditions. Samples were constituted from the (*R*)- and (*S*)-enantiomers of PEA that had each been prepared separately from enantiomerically pure samples of (*R*)- and (*S*)-*N*-(1-phenylethyl)acetamide, respectively, with the ee of the resulting PEA mixtures determined by chiral HPLC analysis. Altogether, thirteen gravity-driven column chromatographic runs were performed with the details of each presented in the *Table*. Gravity-driven chromatography columns were eluted with target flows of 3–5 min/10 ml, amounting to total elution times ranging from 4–11 h. The first aliquots collected (denoted as 'early') were 10 ml in volume, followed by 50-ml volumes (denoted as 'middle'), then finally by 100-ml volumes (denoted as 'final'). As noted previously [19], it is important for reproducibility and application transfer to other systems to describe the chromatographic conditions adequately with respect to flow rates, elution times and volumes, *etc.*, as the SDE process is heavily dependent on such parameters, probably more than otherwise, since the dynamic equilibrium between free molecules and homo- and heterochiral dimers is strongly influenced by the prevailing conditions.

Using ^{t}BuOMe/cyclohexane 2:1 as eluent, chromatography of half-a-dozen samples of PEA over achiral silica gel were performed for a range of sample ee

Table. *SDE by Achiral, Gravity-Driven Column Chromatography*[a]) *of* N-*(1-Phenylethyl)acetamide* (PEA)

Run	Eluent (ratio)	Flow rate[b])	Total elution time	Sample wt.	No. of collected aliquots[c])			Elution volume	ee [%]			SDE mag.	Yield of enantiomerically pure sample[d])			Opt.[e])
					Early	Middle	Final									
		[min/10 ml]	[h]	[mg]	10 ml	50 ml	100 ml	[ml]	Sample start	First fraction	Last fraction[f])	Δee	> 95% ee	> 99% ee	> 99.9% ee	
1	^{t}BuOMe/cyclohexane (2 : 1)	5.0	10.8	200.8	15	5	3	700	90.4	99.9	57.4	42.5	95.9	80.3	58.2	1st
2	^{t}BuOMe/cyclohexane (2 : 1)	5.0	9.3	199.2	15	5	2	600	78.9	99.9	56.6	43.3	49.8	24.0	9.2	1st
3	^{t}BuOMe/cyclohexane (2 : 1)	5.5	8.8	175.2	15	5	2	600	70.0	99.9	45.4	54.5	21.3	8.7	3.6	1st
4	^{t}BuOMe/cyclohexane (2 : 1)	5.0	9.6	196.8	15	5	2	600	50.2	99.9	25.8	74.1	13.8	10.1	7.4	both
5	^{t}BuOMe/cyclohexane (2 : 1)	5.0	10.0	200.9	15	5	2	600	27.6	99.9	16.2	83.7	2.2	1.6	1.4	both
6	^{t}BuOMe/cyclohexane (2 : 1)	5.0	10.8	207.0	15	5	3	700	13.8	45.2	3.8	41.4	–	–	–	2nd
7	Et_2O/cyclohexane (4 : 1)	4.4	9.4	187.5	15	5	2	600	69.9	99.9	49.2	50.7	11.9	5.8	4.5	1st
8	Et_2O/cyclohexane (4 : 1)	4.4	8.1	208.0	15	5	2	600	47.6	99.9	20.6	79.3	8.8	5.7	3.4	both
9	Et_2O/cyclohexane (4 : 1)	4.4	7.8	205.5	15	5	2	600	29.6	99.9	13.4	86.5	2.3	0.8	0.6	both
10	Et_2O/cyclohexane (4 : 1)[g])	3.0	4.8	197.9	15	7	–	500	69.4	99.9	34.4	65.5	1.3	0.4	0.3	both
11	AcOEt/cyclohexane (1 : 1)	2.5	3.6	230.6	10	6	1	500	70.2	99.8	55.4	44.4	0.8	0.6	0.3	1st
12	AcOEt/hexane (1 : 1)	2.5	4.0	201.0	10	6	1	500	69.6	88.8	46.2	42.6	–	–	–	–
13	CH_2Cl_2/AcOEt (10 : 1)	3.4	5.0	168.0	10	6	–	400	71.6	91.2	62.4	28.8	–	–	–	–

[a]) Ratio of PEA to silica gel (230–400 mesh), *ca.* 1 mmol:30 g unless otherwise stated. [b]) Targeted flow rate, particularly for early fractions. [c]) The first aliquots collected (early) were 10 ml in volume, followed by 50-ml volumes (middle), then finally by 100-ml volumes (final); thus for run *1*, 15 × 10 ml aliquots were first collected, then 5 × 50 ml aliquots were collected, and then finally 3 × 100 ml was collected to give a total elution volume of 700 ml. [d]) Yield of combined fractions and part thereof. [e]) Optimal for the obtaining of just a best sample of the desired ee, either the racemate or the enantiomer, as either the first eluting or the second eluting component. [f]) The ee of the last fraction or of the fraction with the lowest ee. [g]) Ratio of PEA to silica gel, *ca.* 1 mmol : 20 g.

values, from 13.8–90.4% (runs *1–6*, *Table*). A graphical representation of the chromatographic profile for run *4* is depicted in *Fig. 2*. The profile of run *4* is considered to represent a typical elution profile akin to that of an idealized system. Although the occurrence of the SDE phenomenon does depend to a degree on the starting ee of a sample, previous investigations have implied [2][22] that, to simply obtain a sample with high enantiomeric purity using SDE *via* chromatography, it was necessary to utilize a sample of high ee, but this need not be the case. Nevertheless, it may be the case in some instances that only a small range of ee values lead to a large Δee value 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, a strong dependency on sample ee was not evident and in all cases, a large Δee value resulted (41.4–83.7%), and, except for run *6* where a sample of 13.8% ee was used, an enantiomerically pure sample (> 99.9% ee) of PEA was always obtained in the early fractions. This latter aspect is generally considered unusual but may, in fact, be a much more common occurrence as demonstrated, in line with theory, here for samples of only modest ee (< 28%). Thus, the results confirm previous observations [20] that SDE *via* achiral, gravity-driven column chromatography does neither require a high ee of the starting sample nor is it necessarily restricted to a limited range of ee values to attain a large resultant Δee value or to attain an enantiomerically pure sample.

An observable trend in runs *1–6* is that while runs *1–3* are appropriate for obtaining samples highly enriched in the first eluting component, *i.e.*, the excess enantiomer in this instance, runs *4* and *5* are also useful for obtaining samples highly 'enriched' in the second eluting component, *i.e.*, the racemic portion in this instance, while run *6* is useful only for obtaining a sample highly 'enriched' in the second-eluting, racemic portion. It is also conceivable, albeit likely to be only occasional, that

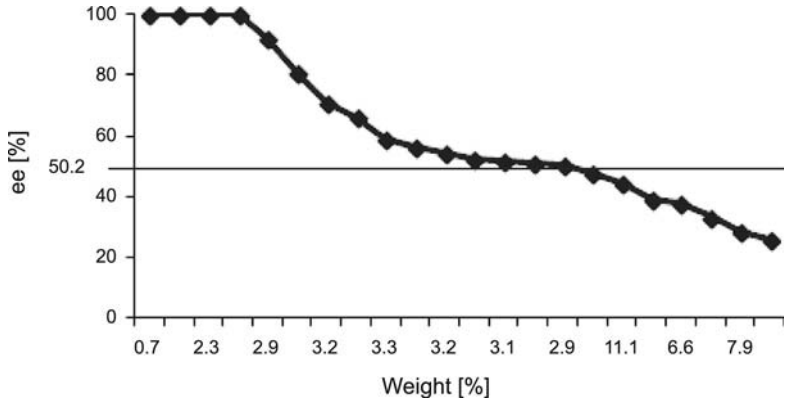


Fig. 2. *Graphical representation of chromatography run* 4 (see *Table*) *showing the % ee of each fraction* vs. *the weight percent of each fraction.* The starting ee (50.2%) is indicated. Run *4* represents a typical elution profile akin to that of an idealized system. *t*BuOMe/cyclohexane (2 : 1) was used as eluent and the ratio of PEA to silica gel was *ca.* 1 mmol : 30 g. The column flow rate was targeted to 5.0 min/10 ml and altogether 22 fractions were collected consisting of 15 × 10 ml early aliquots, 5 × 50 ml middle aliquots, and then two final aliquots of 100 ml to give a total elution volume of 600 ml.

circumstances can arise where the racemic portion as well as the excess enantiomer, or even the former *in lieu* of the latter, is desired. Thus, perceivable, and competing, objectives could be for obtaining the first, the second, or even both components depending on elution order and/or the desired component.

Further consideration of the graphical representations for runs *1*–*6* reveals that they are not ideal and aberrant SDE behavior can be observed in that the ee did not always fall smoothly during the course of the chromatography, as is predicted by mathematical modeling [14][21] assuming a single intermolecular interaction and the formation of only one type of transitory aggregate structure [11][12]. Even rises in ee are evident in some of the graphical representations, particularly for runs *2*, *3*, and *5*. A graphical representation of the chromatographic profile for run *2* is depicted in *Fig. 3*. These latter aberrations have previously been described [19] as 'kinks' and allude to the complex nature of the processes leading to the SDE phenomenon or to drastic changes in the local concentrations as well as the shortfall of describing the system in simple terms such as the formation only of homo- and heterochiral dimers based on a single interaction. Such kinks have been observed to occur at the front end of the elution profile [6b][17][19][23], but they may also occur in the middle [19] as well as the tail [19] and even occur multiple times during the course of the elution [19]. By far, the most dramatic example, so extreme in fact it has been dubbed [13] 'double ESDAC', was observed during the chromatography of spirobrassinins [24]. 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 [13][25], with some legitimacy, to account for the dramatic behavior of the spirobrassinins [24]. For PEA, only the intermolecular H-bonding-based interactions are considered to be sufficiently effectual for SDE purposes, thus leaving oligomer formation by default as the cause of the anomalous behavior observed in this instance.

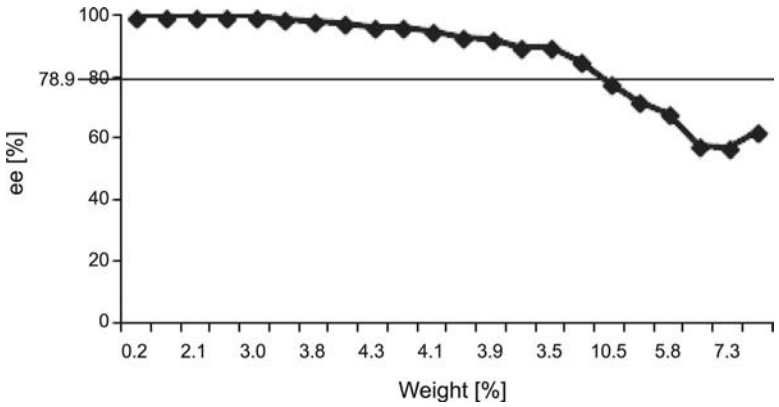


Fig. 3. *Graphical representation of chromatography run* 2 (see *Table*) *showing the % ee of each fraction* vs. *the weight percent of each fraction.* The starting ee (78.9%) is indicated. The pronounced kink towards the end of the run is discussed in the text. *t*BuOMe/Cyclohexane (2 : 1) was used as eluent and the ratio of PEA to silica gel was *ca.* 1 mmol : 30 g. The column flow rate was targeted to 5.0 min/10 ml, and altogether 22 fractions were collected consisting of 15 × 10 ml early aliquots, 5 × 50 ml middle aliquots, and then two final aliquots of 100 ml to give a total elution volume of 600 ml.

Using Et_2O/cyclohexane in a 4 : 1 ratio as eluent, very similar results in comparison to runs *3*–*5*, in terms of Δee values, obtaining an enantiomerically pure sample, and obtaining the second-eluting, racemic portion, were obtained for the three comparable runs (runs *7*–*9*, resp., *Table*) using this solvent with sample ee values in the range 29.6–69.9%. The persistence of the SDE phenomenon for PEA using different eluents is thus notable.

As previously noted [19], the SDE phenomenon is dependent on the ratio of analyte to stationary phase. Reducing the amount of silica gel used for the chromatography at a set sample ee, *viz.*, run *10* relative to run *7*, revealed some surprising results (*Table*). While Δee values, in accord with expectations, increased from 50.7 to 65.5%, and both runs were able to furnish initial fractions containing enantiomerically pure PEA, the amount of enantiomerically pure material that could be obtained from the chromatography, whether of 99.9, 99, or 95% ee, was considerably reduced in the case of run *10*. Run *10* was also more amenable to obtaining both the first and second eluting components in comparison to run *7*. Thus, while a higher concentration of analyte generally favors expression of the SDE phenomenon, sufficient chromatographic exposure is still necessitated, and clearly for run *10*, this is suboptimal. In addition, the kink appearing near the end of the chromatographic run is much more pronounced in run *10* (see *Fig. 4*) in comparison to run *7*, suggesting that, in line with proposed suppositions, kinks are concentration dependent and infer that drastic changes in local concentration leading to the formation of higher aggregates might be responsible for their occurrence. Thus, while a greater analyte to stationary phase ratio may improve overall Δee values, it may not necessarily facilitate improved isolation of a preparative-scale enantiomerically pure sample and, in addition, may exacerbate any aberrant effects that are present.

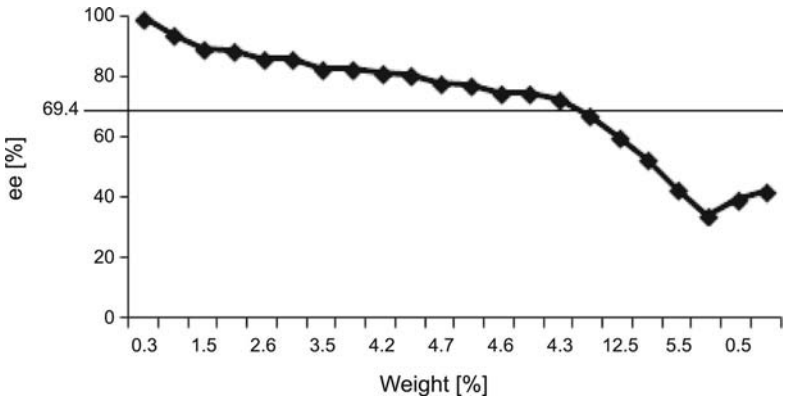


Fig. 4. *Graphical representation of chromatography run* 10 (see *Table*) *showing the % ee of each fraction* vs. *the weight percent of each fraction.* The starting ee (69.4%) is indicated. The kink towards the end of the run is more pronounced in comparison with run *7* where a lesser analyte to stationary phase ratio was used. Et_2O/Cyclohexane (4 : 1) was used as eluent and the ratio of PEA to silica gel was *ca.* 1 mmol : 20 g. The column flow rate was targeted to 3.0 min/10 ml, and altogether 22 fractions were collected consisting of 15 × 10 ml early aliquots and 7 × 50 ml middle aliquots to give a total elution volume of 500 ml.

Runs *11* and *12* tested a general change in solvent by using AcOEt in place of ^{t}BuOMe/Et_2O as the polar component of the eluent, and wherein the SDE phenomenon was found to still persist strongly though the Δee value was reduced (*Table*). The graphical representations for runs *11* and *12* looked very different to previous runs *3* and *7*, and while run *11* was adequate for furnishing an enantiomerically pure sample (but not for the racemic portion), run *12* was good for neither. The amount of enantiomerically pure sample that could be realized in the case of run *11* was also markedly reduced. Clearly, the higher polarity of AcOEt in the eluent system is, not unexpectedly, debilitating for the SDE phenomenon since it is, in this case, based on intermolecular H-bonding. Runs *11* and *12* also compare the result of a subtle change in the eluent, specifically comparing the substitution of cyclohexane (run *11*, *Table*) with hexane (run *12*). Although the differences in terms of Δee values are modest between runs *11* and *12* with the graphical profiles nominally similar, they are noticeable and are in concert with the premise of *Klika et al.* [13] who maintain that the SDE phenomenon is very sensitive to the applied conditions. Thus, while Δee values for runs *11* and *12* were comparable (44.4 and 42.6%, resp.), only run *11* was able to furnish a fraction containing enantiomerically pure PEA.

Even with the use of a very polar eluent system, CH_2Cl_2/AcOEt in a ratio of 10:1 (run *13*, *Table*), the SDE phenomenon was still in effect despite the H-bonding-based mode of intermolecular interaction. However, the Δee value was greatly reduced and the system was unable to furnish a fraction that was enantioenriched or -depleted. Nevertheless, overall the SDE phenomenon for PEA is generally persistent across all of the conditions applied here and previously [20] and is not restricted to a limited range of ee values for the sample applied. Thus, in terms of providing an enantiomerically pure sample of 99.9% ee, all of the chromatographic runs provided such with the exception of runs *6* (ee of the applied sample 13.8%), *12*, and *13* (wherein a highly polar eluent was used). Even run *11* using AcOEt/cyclohexane in a ratio of 1:1 was able to furnish an enantiomerically pure sample. Clearly though, strongly polar eluents are prohibitive towards the SDE phenomenon in this case and to obtain a large Δee value, whether for the purposes of furnishing an enantiomerically pure sample, both enantioenriched or -depleted samples, or a practical amount of an enantiomerically pure sample, ethereal-based eluents, or at least eluents that are not highly polar, are required. However, in terms of isolating the excess enantiomer, chromatographic runs that utilized ^{t}BuOMe as the polar component in the eluent were much more efficient than comparable runs using Et_2O. Indeed, in terms of extraction of the excess enantiomer, the yields relative to the available amount of excess enantiomer correlated strongly with the ee of the original sample. So although large Δee values and the ability to obtain an enantiomerically pure fraction were possible for almost all of the runs conducted here, high yielding extractions of the excess enantiomer at the preparative scale were obtained only for runs conducted with a high ee for the original sample.

Although the SDE for PEA can be explained by the formation of homo- and heterochiral dimers *via* H-bonding with the differing chromatographic behavior of the entities the underlying mechanism responsible for the SDE phenomenon, it has been intimated previously [12] that a large energy differential between the dimer types is not required in principle for observation of SDE *via* achiral chromatography. That is, there

need not be a large, overwhelming, almost exclusive, bias towards the formation of one aggregate type over the other to account for the observations of SDE *via* achiral chromatography. Indeed, it already has been proven that the domination of one dimer type over the other cannot be the sole determining factor, since the elution order – excess enantiomer or racemate first – can be dependent on the very stationary phase in use [19]. That observation substantiates the premise of *Klika et al.* [13] whereby they assert 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 different stationary phases.

Since PEA provides such a large Δee value, it represents a good example to test the assertion regarding energy differentials. Thus, quantum-chemical molecular modeling was conducted to confirm the premise using DFT calculations at the M06-2X/tzvp level of theory. This level of theory with respect to both the functional and the basis set was considered adequate to account for the H-bonding present in the constructs [12][26]. In *Fig. 5* are presented the homochiral and heterochiral dimeric associates of PEA wherein it was found that the difference in *Gibbs*' free energies, Δ*G*, was only 0.06 kcal/mol in favor of the heterochiral construct. This negligible value thereby was in full support of the postulation.

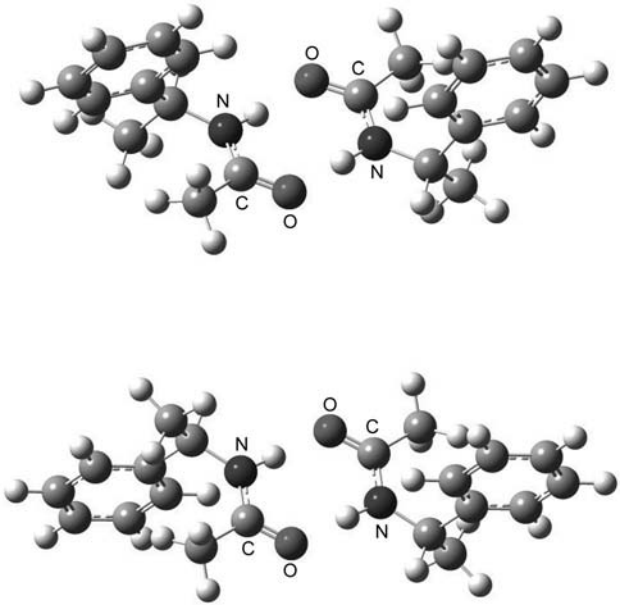


Fig. 5. *The DFT-optimized model structures at the M06-2X/tzvp level of theory of the homochiral* (upper) *and heterochiral* (lower) *dimeric associates of PEA*. The calculated difference in *Gibbs*' free energies, Δ*G*, indicated the heterochiral construct to be favored by 0.06 kcal/mol.

Conclusions. – In this work, we have described the results of an investigation into the SDE phenomenon *via* gravity-driven chromatography over achiral silica gel using *N*-(1-phenylethyl)acetamide (PEA) as a case study. We demonstrated that it is possible to obtain in a practical and useful manner enantiomerically pure PEA starting from a sample of only modest ee. Indeed, it was observed that PEA exhibited the SDE phenomenon under all applied conditions, including a broad range of starting ee values. These results can thus be useful for practical applications to obtain enantiomerically pure samples from a nonracemic sample of a chiral compound. While strongly polar eluents are clearly prohibitive towards the SDE phenomenon in this case and to obtain a large Δee value, whether for the purposes of simply furnishing an enantiomerically pure sample, both enantioenriched or -depleted samples, or a practical amount of an enantiomerically pure sample, ethereal-based eluents, or at least eluents that are not highly polar, are required. However, in terms of isolating the excess enantiomer, chromatographic runs that utilized ^{t}BuOMe as the polar component in the eluent were much more efficient than comparable runs using Et_2O. Indeed, in terms of extraction of the excess enantiomer, the yields relative to the available amount of excess enantiomer correlated strongly with the ee of the original sample. So although large Δee values and the ability to obtain an enantiomerically pure fraction were possible for almost all of the runs conducted here, high yielding extractions of the excess enantiomer at the preparative scale were found only for runs conducted with a high ee for the original sample. Nevertheless, it could well be that enantiomeric enrichment based on the SDE phenomenon *via* gravity-driven chromatography represents a simple, reliable, and predictable method with a high degree of proficiency for this class of compounds.

The conventional means to obtain an enantiomerically pure sample from a nonracemic sample of a chiral compound without recourse to, for example, chiral chromatography, is fractional recrystallization. There are, however, some limitations to this time-honored technique. For one, fractional recrystallization becomes increasingly difficult and generally less efficient with a reduction in ee and is limited to ee values above the eutectic point of the system. Secondly, fractional recrystallization is problematic on a practical level with small sample sizes. Finally, there are often problems with controlling the solvent and the amount of the racemic portion that is kept in solution while depositing the excess enantiomer when performing fractional recrystallization. By comparison, the SDE phenomenon *via* chromatography can readily persist to low ee values, small sample sizes are easily handled by chromatography, and with chromatography one can readily select quite easily the amount of the sample to fractionate or to combine fractions accordingly. Thus, in many respects, SDE *via* chromatography represents a complementary, alternative technique to fractional recrystallization for the purposes of extracting the excess enantiomer from a nonracemic sample to obtain an enantiomerically pure sample. Since it is possible to control precisely how much of the sample is collected during chromatography and SDE *via* chromatography performs so well at high ee values, SDE *via* chromatography might even be superior to fractional recrystallization for preparative-scale isolations in particular cases.

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Experimental Part

General. AcCl, (*R*)-, and (*S*)-(1-phenylethyl)amine were purchased from *Aldrich*. Column chromatography solvents, CH_2Cl_2, cyclohexane, hexane, AcOEt, and Et_2O were purchased from *Chempur* (Poland) while ^{t}BuOMe was purchased from *POCh* (Poland); all solvents were used without further purification. HPLC Solvents, hexane and i-PrOH, and silica gel (230–400 mesh) for column chromatography were purchased from *Merck*.

HPLC Chromatographic analysis was performed on a *Varian ProStar* instrument equipped with a UV/VIS detector and a *Vertex Plus Eurocel 01* chiral column (5 μm, 250 × 4.6 mm; *Knauer*, Germany) using hexane/i-PrOH 90:10 as the mobile phase at a flow rate of 0.8 ml/min.

Gravity-driven column chromatography with the various eluents given in the text was performed using a column of diameter 20 mm and height 600 mm. The ratio of PEA to silica gel was 1 mmol:30 g unless otherwise stated. Samples of PEA of various ee were prepared by mixing appropriate amounts of the (*R*)- and (*S*)-enantiomers of PEA and loaded onto the column as a soln. in CH_2Cl_2. Columns were eluted with target flows of 3–5 min/10 ml amounting to total elution times of *ca.* 4–11 h.

DFT Quantum chemical calculations were performed following previous methodology [12][27] using *Gaussian09* [28] (version D.01) and analyzed using *GaussView* [29] (version 4.1.2). Geometry optimization of the structures in the gas phase were performed using the M06-2X hybrid meta density functional [30] with the tzvp basis set in tandem with vibrational analyses and thermochemistry calculations at the same level of theory. Geometry optimization was conducted with tight criteria by invoking the keyword *opt = tight* and fine intervals by invoking the keyword *int = ultrafine*. Vibrational analyses by invoking the keyword *freq = noraman* were conducted to confirm that optimized structures were true minima on the potential energy surface by not providing imaginary frequencies and to obtain the thermodynamic contributions at 298.15 K and 1 atm wherein frequencies were left unscaled.

*(*R*)- and (*S*)-*N*-(1-Phenylethyl)acetamide* (PEA). The (*R*)- and (*S*)-enantiomers of PEA were synthesized according to literature [6d][31]. To a soln. of (*R*)- or (*S*)-(1-phenylethyl)amine (2 g, 16.5 mmol) in anh. THF was added Et_3N (3.5 ml, 24.8 mmol) followed by, after cooling to 0°, AcCl (1.2 ml, 16.5 mmol), and then, the soln. was left to be stirred. After 5 h at r.t., the mixture was poured into an aq. sat. NH_4Cl soln. and extracted with AcOEt (3 × 20 ml). The combined org. extracts were washed with brine, dried ($MgSO_4$), and then evaporated to dryness. The crude product was purified by recrystallization from Et_2O. The physical and spectral data of the products (*R*)- and (*S*)-PEA were consistent with those in [31b].

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