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Computational analysis of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one and its enantiomeric separation

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ABSTRACT: A theoretical analysis of the primary photochemical products of irradiation of α-tropolone methyl ether is presented. Through this analysis, the fact that only two of the four possible stereoisomers of the product are experimentally observed may be explained. We also present a computational scheme for identifying the enantiomers separated by chiral gas chromatography. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: tropolone; α-tropolone methyl ether; semiempirical calculations; chiral separation; 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one; β-cyclodextrin

INTRODUCTION

Driven by the pharmaceutical industry, more than six billion US dollars of enantiomerically isolated chemicals are produced and sold each year worldwide.[1] Separating an enantiomer from its racemic mixture on a production scale, however, is a challenging task. Furthermore, if a specific enantiomer is desired, but the synthesis produces a racemic mixture, the theoretical maximum yield is only 50%. Producing enantiomers asymmetrically in the first place would eliminate both the necessity for a complicated and costly separation procedure and wasteful production of unwanted enantiomers. Toward this end, some headway has been made with synthesis by asymmetric photochemistry. Chiral compounds have been prepared asymmetrically in solution,[2] in the crystalline state[3] and confined in host–guest assemblies,[4] especially chiral modified zeolites.[5–7] In the last procedure, tropolone ethers included within a chirally modified zeolite, upon irradiation with UV photons, yield a preponderance of one of the product enantiomers. This remarkable achievement has profound implications for chiral synthesis, but it is accompanied by a curious result: in the synthesis of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (MBH) from α-tropolone methyl ether (αTME) by asymmetric photochemistry, of four possible product stereoisomers, only two are observed. The overall reaction is shown schematically in Fig. 1, and may be abbreviated as

$$\alpha\text{TME} \xrightarrow{h\nu} \text{MBH} \qquad (1)$$

Furthermore, in an issue of practical importance, when the enantiomeric excess in the products is observed by chiral gas chromatography, it is not known which stereoisomer is more strongly retained on the chromatographic stationary phase, and therefore the order in which they elute is unknown. The implication is that while it is possible to employ chiral gas chromatography to observe that the enantiomers are produced asymmetrically, further steps are necessary to identify the dominant enantiomer.

In this paper, we present a theoretical analysis of the primary photochemical products of reaction (1) and of their separation by chiral gas chromatography. Through this analysis, the absence of two of the four possible stereoisomers of the product may be explained. We also address the problem of identifying the stereoisomers separated by β-cyclodextrin chiral gas chromatography.

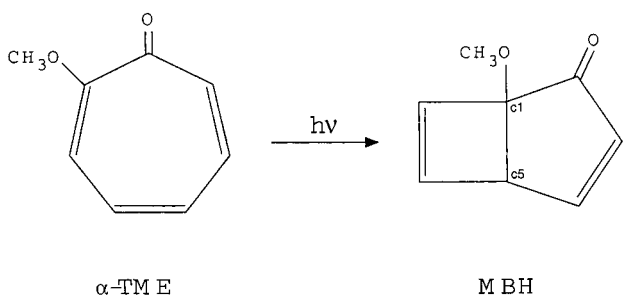

Figure 1. Photolysis of α-tropolone methyl ether (αTME) to yield 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (MBH). The two chiral centers in MBH are marked c1 and c5

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THEORETICAL METHODS

Electronic structure calculations were carried out for the stereoisomers of MBH and the interaction of MBH with β-cyclodextrin (βCD).

Structural optimizations of the stereoisomers of MBH were computed at the semiempirical, (AM1[8] and PM3[9]) and Hartree–Fock self-consistent field (HFSCF) levels of theory.[10] Preliminary HFSCF calculations were carried out with a small split valence 6–31G(d) basis set.[11] For the final HFSCF calculations, the electronic wavefunction was expanded in a triple-zeta-valence Gaussian basis with polarization functions [6–311G(d)].[12] Minimum energy molecular conformations were confirmed by the absence of imaginary normal mode frequencies. Earlier calculations at the HFSCF/6–311G(d) level of theory resulted in good accuracy for conformational structures and energetics of similar unsaturated organic systems.[13,14] In order to investigate the possible role of correlation, configuration interaction calculations for MBH were carried out based on geometry-optimized HF/6–31G(d) reference configurations. The core (1s) orbitals were frozen. Single and double excitations of valence electrons into the lowest 16 virtual orbitals were considered. All calculations were carried out with the GAMESS suite of codes.[10]

Equilibrium populations of the isomers of MBH were computed from Boltzmann populations at 295 K given by

$$f_j = \frac{g_j \exp(-\frac{\varepsilon_j}{kT})}{\sum_i g_i \exp(-\frac{\varepsilon_i}{kT})} \qquad (2)$$

where g_j is the degeneracy of the jth isomer and the sum runs over all isomers i. The total energies ε_i for the isomers were computed at the HF/6–311G(d) level.

Previous success in treating inclusion phenomena with semiempirical methods[15–17] suggested that treating the βCD–MBH complexes semiempirically would be a judicious approximation. Semiempirical methods, like *ab initio* methods, are based on an inherently quantum-mechanical description of the electronic structure, but are efficient enough for practical calculations on systems of this size. We chose the AM1 semiempirical model.[8] The scope of it parameterization covers all of the elements in the present system, and it is one of the most reliable semiempirical methods.[18] Unlike some other semiempirical methods, AM1 has been found to be qualitatively acceptable for intermolecular hydrogen bonding,[19] the dominant interaction between host and guest here. While routine computations of molecular recognition involving a receptor the size of βCD are intractable with *ab initio* methods, to validate our semiempirical calculations we have also carried out computations for the complexation of MBH by βCD at the HFSCF level of theory with the 3–21G(d) basis set.[20] Glendening *et al.*[21] reported that despite its many shortcomings, HFSCF theory with a small split valence basis set is valuable for predicting qualitative trends in molecular recognition systems, our goal here.

Conformational searching was carried out to determine the optimum binding of MBH by βCD. First an optimized stereoisomer of MBH was placed within the cavity of βCD (structure from Ref. 22) and oriented so that the inertial axes of the MBH were coincident with those of βCD. We refer to these axes as *x, y* and *z*, with *z* being approximately perpendicular to the plane of the βCD ring and passing through its center. Based on this starting structure a systematic search was carried out, selecting *all possible combinations* of the following four parameters to generate trial structures:

1. translation of MBH by ± 2 Å along the *z* axis (two possible choices of *z* translation);
2. rotation of MBH about the *z* axis in 45° steps (eight possible choices of *z* rotation);
3. rotation of MBH about the *y* axis in 120° steps. (three possible choices of *y* rotation);
4. rotation of MBH about the *x* axis in 120° steps. (three possible choices of *x* rotation).

Based on this scheme, 144 unique trial structures were generated for each of the two dominant stereoisomer complexes. Next, all 288 structures were fully optimized (including both guest and host) at the AM1[8] level of theory. We will refer to the results of this systematic search as data set I.

While βCD, rigorously speaking, is a low-symmetry molecule, its construction from seven identical sugar molecules to form a torus means that a small molecule included within the βCD cavity should feel an interaction potential with approximate seven-fold rotational symmetry (this property is clearly evident in Fig. 2). In conformational searching, therefore, if two trial struc-

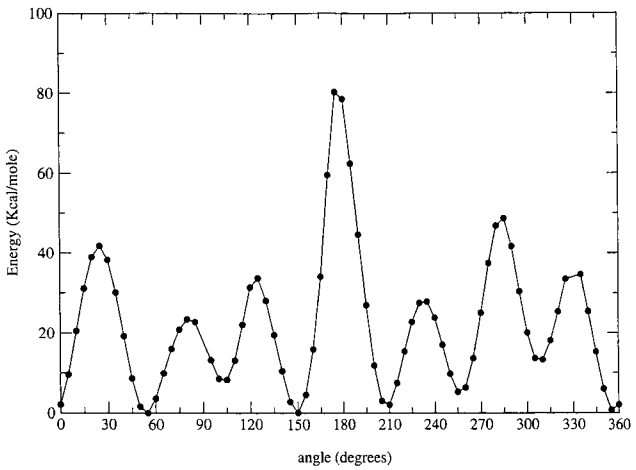

Figure 2. Potential energy curve for rotation of MBH within the βCD cavity. Note the approximate sevenfold hindered rotation

tures differ in orientation about the z axis by more than 360/7°, they should optimize into different basins of attraction. For this reason, searching about the z axis in eight steps of 45° was deemed sufficient for exhaustive searching about the z axis.

Six additional searches were also carried out. Employing the same starting structure as above, trial structures were generated as follows:

1. the MBH was rotated about the z axis in 10° steps from − 175 to 175° (36 structures);
2. the MBH was rotated about the y axis in 10° steps from − 175 to 175° (36 structures);
3. the MBH was translated along the z axis by (−4, 0, +4) Å and subsequently rotated about the z axis in 30° steps (36 structures);
4. the MBH was translated along the z axis by (−4, 0, +4) Å and subsequently rotated about the y axis in 30° steps (36 structures);
5. the MBH was translated along the z axis by (−4, 0, +4) Å and subsequently rotated about the x axis in 30° steps (36 structures);
6. the z axis of MBH was skewed with respect to the z axis of βCD by 30° and the MBH was subsequently rotated in 10° steps about the z inertial axis of the complex (36 structures).

These additional searches produced 216 trial structures for each of the dominant stereoisomer complexes. Each structure was then fully optimized at the AM1 level. The results of these six searches, plus data set I, were combined and duplicate structures eliminated. We will refer to this combined and sorted data as the full data set. Statistical analysis was carried out on both data set I and the full data set.

As shown in the Appendix, the difference in retention time for two enantiomers on the gas chromatographic (GC) column is given by

$$\Delta\tau = \left(\tau_A - \frac{L}{u}\right)(\mathrm{e}^{-\Delta\Delta G/RT} - 1) \tag{3}$$

where τ_A is the retention time of enantiomer A, $\Delta\Delta G$ is the difference between the free energies of complexation for the two enantiomers in question, L is the column length, u is the velocity of the mobile phase, T is the absolute temperature and R is the gas law constant. To estimate $\Delta\Delta G$, we start with

$$\Delta G = \Delta H - T\Delta S \tag{4}$$

from which it follows that

$$\begin{aligned}\Delta\Delta G &= \Delta G_B - \Delta G_A \\ &= (\Delta H_B - T\Delta S_B) - (\Delta H_A - T\Delta S_A)\end{aligned} \tag{5}$$

where the subscripts A and B denote the thermodynamic quantities for the reactions exchanging enantiomer A or B between the βCD and the mobile phase (MP):

$$\beta\mathrm{CD} + \mathrm{MP/A} \longrightarrow \beta\mathrm{CD/A} + \mathrm{MP} \tag{6}$$

and

$$\beta\mathrm{CD} + \mathrm{MP/B} \longrightarrow \beta\mathrm{CD/B} + \mathrm{MP} \tag{7}$$

respectively. Based on the chemical and structural similarity of A and B, and of their respective complexes, we assume that $\Delta S_A \approx \Delta S_B$, so that

$$\Delta\Delta G \approx \Delta\Delta H = \Delta H_B - \Delta H_A \tag{8}$$

$\Delta\Delta H$ is simply the change in enthalpy for the reaction

$$\beta\mathrm{CD/A} + \mathrm{MP/B} \longrightarrow \beta\mathrm{CD/B} + \mathrm{MP/A} \tag{9}$$

The change in enthalpy for reaction (9) was computed with,

$$\Delta E = \sum E_p - \sum E_r \approx \Delta\Delta H \tag{10}$$

where $\sum E_p$ is the sum of the total energies of the product molecules and $\sum E_r$ is the sum of the total energies of the reactant molecules. Since $E(\mathrm{MP/A}) = E(\mathrm{MP/B})$ owing to the achirality of the mobile phase, ΔH for reaction (9) and therefore $\Delta\Delta G$ are reasonably approximated by the difference in total energies for βCD/B and βCD/A.

There are at least three advantages of formulating the problem in terms of Eqn. (9) (a guest exchange reaction[23]). First, it reduces the total number of molecular calculations required from that required if the complexations are treated separately as in Eqns (6) and (7). Second, as shown above, it focuses on the more easily computed enthalpic contributions to the free energy. Most importantly, however, it improves the chances of obtaining a reliable result. Computing intermolecular interaction energies is a notoriously difficult computational task. One is faced with the problem of determining a small difference between two numbers that are themselves very large in magnitude, $\sum E_r$ and $\sum E_p$. Consequently, small percentage errors in the reactant and product energies can translate into huge errors in the difference. In reaction (9) the reactants and products are chemically very similar. Any errors in computing the reactant and product energies should therefore be comparable and approximately self-canceling. Specifically, when quantum chemical calculations are carried out with an atom-centered basis for associated and dissociated species and the energies compared, the energy of the associated species is artificially lowered relative to the dissociated system owing to basis set superposition effects. Under the present scheme, comparisons are only drawn between associated species. This is akin to comparing structural isomers of a single molecule, which is free from significant basis set superposition error.

Table 1. Stereoisomers of MBH: calculated relative total energies (kcal mol^{-1}) and 295 K Boltzmann populations for each of the four possible stereoisomers of MBH

Isomer	AM1	PM3	HF/6–31G(d)	HF/6–311G(d)[a]	CI(sd) @ HF/6–31G(d)	Population (%)
$MBH_{R,R}$	54	53	56	56	52	~ 0
$MBH_{R,S}$	0.0	0.0	0.0	0.0	0.0	50
$MBH_{S,R}$	0.0	0.0	0.0	0.0	0.0	50
$MBH_{S,S}$	54	53	56	56	52	~ 0

[a] Recommended values.

RESULTS AND DISCUSSION

Irradiation of αTME initiates a sequence of photochemical processes, the first of which produces MBH.[24] The structures of αTME and MBH are shown in Fig. 1. Note in particular that MBH contains two chiral centers, implying that there are, in principle, four possible stereoisomers. Given that the ether linkage is attached to C-1 in MBH, the two chiral carbon atoms are C-1 and C-5. The four possible stereoisomers are therefore denoted $MBH_{R,R}$, $MBH_{R,S}$, $MBH_{S,R}$ and $MBH_{S,S}$, where we have indicated the chirality of the two chiral centers $MBH_{1,5}$. The mixed-chirality species result from *cis* ring fusion and the $MBH_{R,R}$ and $MBH_{S,S}$ forms from *trans* ring fusion.

Curiously, when MBH is synthesized by asymmetric photochemistry from αTME, only two of the four possible product stereoisomers are observed. We carried out full structural optimizations on each of these four possible stereoisomers of MBH, the results of which are reported in Table 1. Note that $MBH_{R,R}$ and $MBH_{S,S}$ are very much higher in energy than $MBH_{R,S}$ and $MBH_{S,R}$, with computations at several levels of theory giving consistent results. (This result is solidly reinforced by any attempt to construct either of the two high-energy stereoisomers with a simple model kit. The *trans*-fused $MBH_{R,R}$ and $MBH_{S,S}$ forms are severely strained.) From this result, it is immediately clear that the 295 K populations of the $MBH_{R,R}$ and $MBH_{S,S}$ isomers are essentially zero.

Given the high energy of the UV photons employed in the photochemical reaction, there exists the possibility of a non-equilibrium distribution of the products. This possibility may be excluded by combining the present calculational results with published experimental results.[5] The four possible stereoisomers of MBH represent two enantiomeric pairs, one pair much higher in energy than the other. In an achiral synthetic environment, enantiomers must be produced in a racemic mixture. The observation of only two products by chiral GC, even when the synthesis is achiral, means that the two observed products must be an enantiomeric pair. A non-equilibrium distribution of the two enantiomeric pairs is possible, but it is implausible that the high-energy pair is produced exclusively. In fact, frontier molecular orbital symmetry arguments actually favor *cis* ring closing, and therefore the low-energy pair. It follows that the observed pair is $MBH_{R,S}$ and $MBH_{S,R}$.

The above analysis establishes that the observed products of irradiation of αTME are the enantiomeric pair $MBH_{R,S}$ and $MBH_{S,R}$, but a second practical issue arises in the separation of these enantiomers by βCD chiral GC. It is not known which enantiomer is more strongly retained on the column and therefore the later to elute. Typically, the elution products are simply labeled A and B in the order of elution and not further assigned.[5]

Since βCD is chiral, the two enantiomers $MBH_{R,S}$ and $MBH_{S,R}$ will interact with it differently. We carried out a computational analysis of the complexation of $MBH_{R,S}$ and $MBH_{S,R}$ by βCD in order to compare their relative strengths of complexation. Figure 3 shows a histogram of conformational energies for the two complexes based on the full data set. It is clear that $MBH_{R,S}$ can achieve a low-energy structure with greater probability. The computations predict that

$$E(\beta\text{CD/MBH}_{R,S}) - E(\beta\text{CD/MBH}_{S,R}) = \Delta E \approx -1.0\{-1.2\} \text{ kcal mol}^{-1} < 0 \quad (11)$$

(1 kcal = 4.184 kJ), where we report the results at the AM1 level of theory based on Boltzmann average energies from the full data set {data set I}, respectively. For validation, the total energy was recomputed for the lowest energy conformation of each complex at the HFSCF/3–21 G(d) level of theory using the AM1

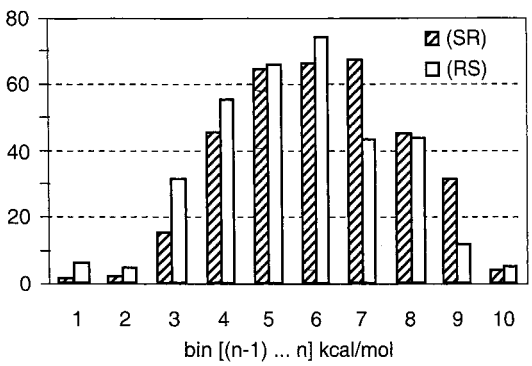

Figure 3. Histogram of conformational energies for βCD–$MBH_{R,S}$ and βCD–$MBH_{S,R}$. Energies are relative to the lowest energy structure found, in kcal mol^{-1}. Vertical axis is number of structures.

optimized structures. At this level of theory $\Delta E = -1.4$ kcal mol^{-1}. From these results, it is predicted that A = $MBH_{S,R}$ and B = $MBH_{R,S}$, i.e. the latter is more strongly retained on the βCD column and elutes last, a conclusion that awaits experimental verification. While there is a large uncertainty in such a small predicted energy difference, we require only the sign of the difference to identify which species is more strongly retained. As noted above, we do not anticipate quantitative reliability in the computed $\Delta\Delta G$, but using measured differences in retention time (V. Ramamurthy personal communication) in the rough approximation technique outlined in the Appendix, $\Delta\Delta G \approx -10$ kcal mol^{-1}, which is of similar magnitude to our values.

The computational scheme outlined here, by design, relies on cancellation of errors and therefore falls short of a definitive prediction of the elution order. The overall reliability of the technique could be greatly enhanced by employing a more advanced electronic structure method in the calculation of the total energies of the complexed species, thereby decreasing the absolute errors. Since the semiempirical Hamiltonian used here (AM1) is probably the most reliable one for hydrogen bonding interactions, any more reliable electronic structure method would almost certainly be a first principles one. Given the necessity for extensive sampling of trial structures of each complex, and the considerable size of the molecules involved, the computational demands of applying the present scheme with a first-principles technique would be prohibitive, and are likely to remain so for some time.

CONCLUSIONS

Of the four possible stereoisomers of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (MBH), only two have been experimentally observed as photoproducts from the irradiation of α-tropolone methyl ether. We have carried out electronic structure calculations for the stereoisomers MBH, and their interaction with β-cyclodextrin (βCD). From these calculations, it is found that two of the four stereoisomers are very high-energy forms (severely strained), and therefore have no appreciable population.

Since βCD is chiral, the free energy of complexation of MBH by βCD differs for the two low-energy stereoisomers of MBH, the enantiomeric pair $MBH_{S,R}$ and $MBH_{R,S}$. This difference in binding strength is the basis for the difference in retention times in βCD chiral GC. Experimentally it is typical to assign the chromatographic peaks only generically (A and B). A computational scheme for ascertaining the relative strengths of binding, and therefore the order of elution in chiral GC is presented. It is found that $MBH_{R,S}$ is more strongly retained than $MBH_{S,R}$ on the βCD column and therefore the former should elute last. The computational scheme is general and could aid in identifying other enantiomeric pairs separated by chiral GC.

Acknowledgements

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APPENDIX

Although it is obvious that the species with the greatest free energy release upon complexation by βCD will be the most strongly retained on the chromatography column and therefore elute last, it is instructive to consider the relationship between the difference in complexation free energies $\Delta\Delta G$ and the difference in retention times $\Delta\tau$.

We start by denoting the velocity of the mobile phase u and the average velocity of the solute υ. It follows that

$$\upsilon = u(\text{fraction of time a solute molecule is in the mobile phase}) \tag{A1}$$

or

$$\upsilon = u\left(\frac{\text{moles solute in the mobile phase}}{\text{total moles of solute}}\right) \tag{A2}$$

Symbolically we may write

$$\upsilon = u\left(\frac{c_m V_m}{c_m V_m + c_s V_s}\right) \tag{A3}$$

where c_i denote the concentrations of solute in the mobile phase ($i = m$) and stationary phase ($i = s$) respectively, and V_i denote the corresponding volumes. The partition coefficient K, which is simply the equilibrium constant for exchange of the solute between the stationary and mobile phases, Eqns (6) or (7), is given by

$$K = \frac{c_s}{c_m} \tag{A4}$$

Dividing the right-hand side of Eqn. (A3) by $c_m\, V_m$ and substituting with Eqn. (A4), one arrives at the well known form[25]

$$\upsilon = u\left(\frac{1}{1 + \frac{KV_s}{V_m}}\right) \tag{A5}$$

The partition constant may also be expressed in terms of the free energy of complexation of the solute by the stationary phase:

$$K = \mathrm{e}^{-\Delta G/RT} \tag{A6}$$

Employing the subscripts A and B for enantiomers A and B, the fact that the retention time $\tau = L/\upsilon$, where L is the column length, and the average velocity of the solute υ is given by Eqn. (A5), we may write

$$\tau_A = \left(\frac{L}{u}\right)\left(1 + \frac{V_s}{V_m}\mathrm{e}^{-\Delta G_A/RT}\right) \tag{A7}$$

$$\tau_B = \left(\frac{L}{u}\right)\left(1 + \frac{V_s}{V_m}\mathrm{e}^{-\Delta G_B/RT}\right) \tag{A8}$$

It follows that the difference in retention times is given by

$$\Delta\tau = \tau_B - \tau_A = \left(\frac{L}{u}\right)\left(\frac{V_s}{V_m}\right)\left(\mathrm{e}^{-\Delta G_B/RT} - \mathrm{e}^{-\Delta G_A/RT}\right) \tag{A9}$$

We may now write the difference in retention time as a function of the difference in free energies of complexation:

$$\Delta\tau = \left(\frac{L}{u}\right)\left(\frac{V_s}{V_m}\right)\left[\left(\mathrm{e}^{-(\Delta G_A + \Delta\Delta G)/RT}\right) - \mathrm{e}^{-\Delta G_A/RT}\right] \tag{A10}$$

where $\Delta G_B = \Delta G_A + \Delta\Delta G$. Rearranging yields

$$\Delta\tau = \left(\frac{L}{u}\right)\left(\frac{V_s}{V_m}\right)\left(\mathrm{e}^{-\Delta G_A/RT}\right)\left(\mathrm{e}^{-\Delta\Delta G/RT} - 1\right) \tag{A11}$$

$$= \left(\frac{L}{u}\right)\left(\frac{V_s}{V_m}\right)K_A\left(\mathrm{e}^{-\Delta\Delta G/RT} - 1\right) \tag{A12}$$

Employing equations Eqns (A7) and (A8) and recognizing that $K_A = \mathrm{e}^{-\Delta G_A}/RT$, we may write

$$\tau_A = \left(\frac{L}{u}\right)\left(1 + \frac{V_s}{V_m}K_A\right) \tag{A13}$$

This may be rearranged to

$$K_A = \frac{V_m}{V_s}\left(\frac{\tau_A u}{L} - 1\right) \tag{A14}$$

Finally, substitution into Eqn. (A12) yields

$$\Delta\tau = \left(\tau_A - \frac{L}{u}\right)\left(\mathrm{e}^{-\Delta\Delta G/RT} - 1\right) \tag{A15}$$

In the above, the quantity L/u is simply the time required for an unretained species to pass through the column. This is typically small in comparison with solute retention times in GC. One sees then that if there is no difference in free energies of complexation, the A and B species will elute together. If the free energies of complexation differ, Eqn. (A15) gives the difference in retention time as a fraction of the retention time for one of the two species. For $\Delta\Delta G > 0$ the B species will elute first and for $\Delta\Delta G < 0$ the B species will elute last. Note Eqn. (5).

If we assume that $L/u \ll \tau_A$, and that $\Delta\tau \ll \tau_A$, we may write

$$\frac{2\Delta\tau}{(\tau_A + \tau_B)} \approx \frac{\Delta\tau}{\tau_A} \approx \left(\mathrm{e}^{-\Delta\Delta G/RT} - 1\right) \tag{A16}$$

Since $2\Delta\tau/(\tau_A + \tau_B)$ is nothing more than the difference in retention times divided by the average retention time, we have a crude means of estimating $\Delta\Delta G$ from

chromatographic data:

$$\Delta\Delta G \approx -RT \ln\left(\frac{2\Delta\tau}{\tau_A + \tau_B} + 1\right) \qquad \text{(A17)}$$

Equation (A17) is likely to overestimate the magnitude of $\Delta\Delta G$. Gas–condensed-phase equilibria often exhibit a positive deviation from the ideal linear concentration distribution curve, c_s versus c_m.[25] Such a positive deviation increases the effective value of $K = c_s/c_m$. Consequently [by Eqn. (A12)], there is an artificial increase in $\Delta\tau$, leading to an overestimate of the magnitude of $\Delta\Delta G$.