

## **Solving multi-site conformational problems with total lineshape analysis of NMR spectral multiplets**

Sergei V. Zubkov, Sergei S. Golotvin, Vyacheslav A. Chertkov\*

Moscow State University, Department of Chemistry, NMR Laboratory

### **Abstract**

Most line fitting algorithms of high resolution NMR spectral multiplets fail to reach the true solution without an exceptionally good starting parameter set. A practical approach to this problem was suggested by Stephenson and Binsch (1980) but it allowed little control over the convergence process, was computationally difficult and so far has not become widespread. We present a more natural algorithm for reaching the global solution. Smoothing of the error functional is reached by multiplying the FID in question by a simple exponential decay function, thus increasing the line width. Obviously, there always exists a line width big enough to eliminate all local minima; and consecutive decrease in broadening factor does not move the global minimum, which solves the convergence problem. Successful analysis of practical multi-site conformational problems as well as a series of rigorous numerical tests prove the efficiency of our approach.

As an example of a complicated conformational problem we chose to study the classical pseudorotation in cyclopentanes. Precise analysis of complex NMR spectra gave more detailed picture of pseudorotation in series of *trans*-1,2-disubstituted cyclopentanes which fit well with the theoretical prediction of the pseudorotation potential curve. Another interesting example we encountered was the conformational analysis of a tetrasubstituted cyclohexane derivative for which, unexpectedly, the most stable conformation was found to be a twist-boat.

\* Corresponding author. NMR laboratory, Department of Chemistry, Moscow State University, 119899, Moscow, Russia, Tel. +7 095 939-5378, Fax +7 095 932-8846, e-mail chertkov@org.chem.msu.ru

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## 1. Total lineshape analysis

Most line fitting algorithms fail to reach the true solution without an exceptionally good starting parameter set, due to many narrow and deep local minima on the hypersurface of the error functional. A practical solution for this problem was suggested by Stephenson and Binsch [1] as early as 1980; a smoothing transformation was applied to the functional, providing a way to iteratively approach the solution. This transformation allows little control over the convergence process, is computationally difficult, and is not widely used. In this work we present a more natural algorithm for reaching the global solution. Smoothing of the error functional is reached by multiplying the FID in question by a simple exponential decay function, thus increasing the line width. Obviously, there always exists a line width big enough to eliminate all local minima, and decrease in broadening factor will not move the global minimum.

Stephenson and Binsch suggested a set of rigorous tests used to determine the “strength” of NMR lineshape spectrum analysis procedures. These consist of four different tightly-coupled ABCD systems, and for each of these systems the procedure should reach the true solution using as starting sets the parameters corresponding to each of the other three systems. Our procedure VALISA, which implements sequentially decreasing broadening of a spectrum using least-squares approach based on Heinzer’s NMRCON [2], managed to solve each of these 12 test successfully. Eight of them were solved within one grand-cycle. For comparison, the original Stephenson and Binsch’s DAVINS solved 10 tests, and only 4 of them required just one grand-cycle. We have successfully used VALISA for many complicated problems, two of which are presented in this work.

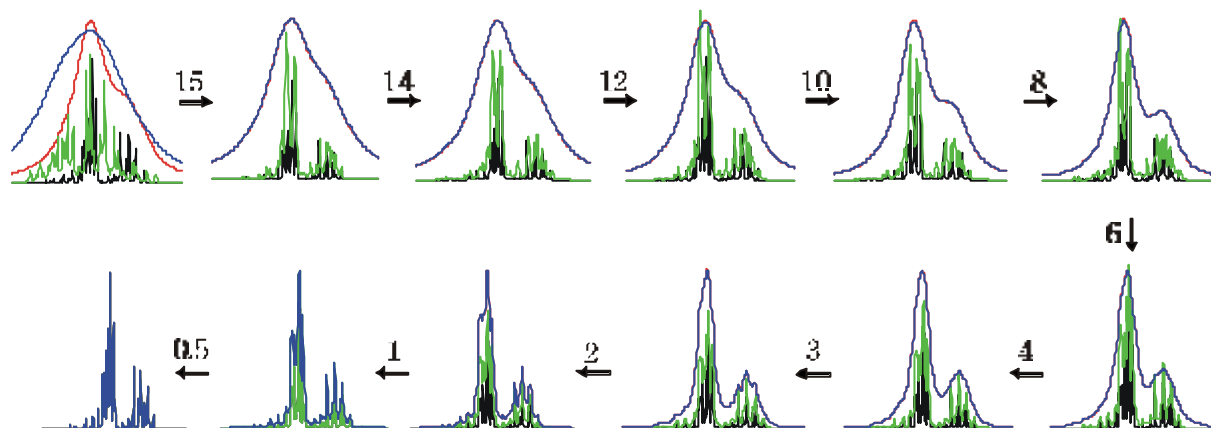


Fig1. VALISA iterations for one of the test systems. Black – target spectrum, green – spectrum, corresponding to the current parameter set, red – broadened target spectrum, blue – broadened current parameter set.

## 2. Conformational analysis of cyclopentane

Conformation state of cyclopentane derivatives, according to Cremer and Pople [3] is described by two puckering coordinates: angle of pseudorotation  $\phi$ , which corresponds to the position of the most displaced part of the ring, and ring puckering  $q$  which measures how far the ring is distorted from a flat pentagon. In terms of these coordinates, a cyclopentane ring travels along a circle, passing on its way each of 20 symmetrical conformations – ten twist-forms and ten envelopes (see fig 2).

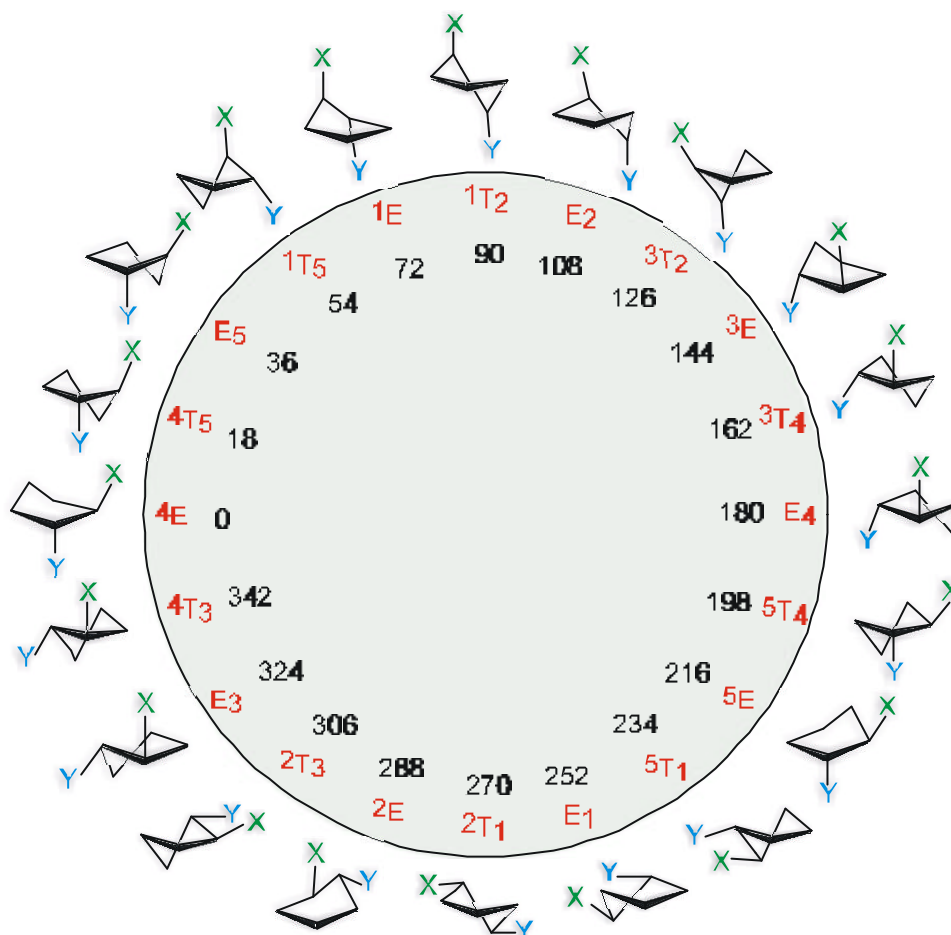


Fig 2. Pseudorotation in *trans*-1,2-disubstituted cyclopentanes.

There are no energy barriers for pseudorotation in non-substituted cyclopentane. In substituted derivatives this degeneration is removed; some positions on the pseudorotation circle are preferred. As an example for which the general behavior is known, we have chosen *trans*-1,2-disubstituted cyclopentanes. Here the most stable (and, usually, the only two discussed) conformations are the symmetrical twist forms <sup>1</sup>T<sub>2</sub> and <sup>2</sup>T<sub>1</sub>. The *ab initio* calculations with Gaussian 94 [5] in HF/6-31G\* basis set suggest that potential energy changes along the pseudorotation path as shown on fig 3. The two classical forms are located at the bottoms of broad minima. Their relative depths as well as the height of the barrier vary for different substituents.

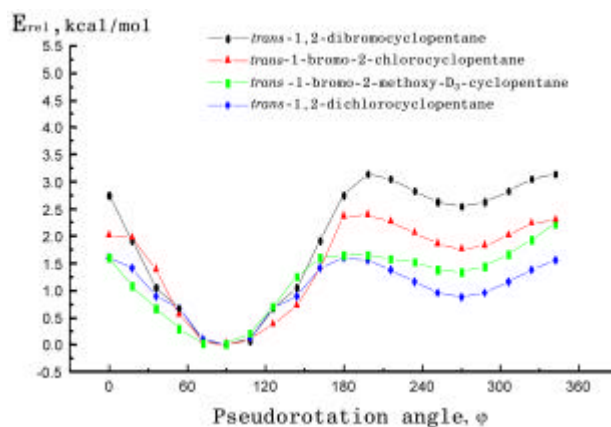


Fig 3. Pseudorotation energy for disubstituted cyclopentanes.

*Trans*-1,2-dichlorocyclopentane, *trans*-1,2-dibromocyclopentane, *trans*-1-bromo-2-chlorocyclopentane and *trans*-1-bromo-2-methoxycyclopentane were studied in CD<sub>3</sub>CN, C<sub>6</sub>D<sub>6</sub> and CCl<sub>4</sub>. For the dichlorocyclopentane every spectrum was broadened by 5, 3, 1, 0.5, and 0.3Hz and a line shape fitting was performed, giving approximations for all coupling constants. The trial parameter set was taken from the dibromocyclopentane calculations performed earlier in our group using alternative spectral analysis application PAREMUS [8]. Thirteen vicinal coupling constants, found in each case, were then used to define the shares of each of the 11 conformations (for dichloride and dibromide) or 20 conformations (for non-symmetrical derivatives) in the conformational state. In the latter two cases, the least-squares analysis was run independently for ten twists and ten envelopes and rerun several times to give the best fitting conformations set.

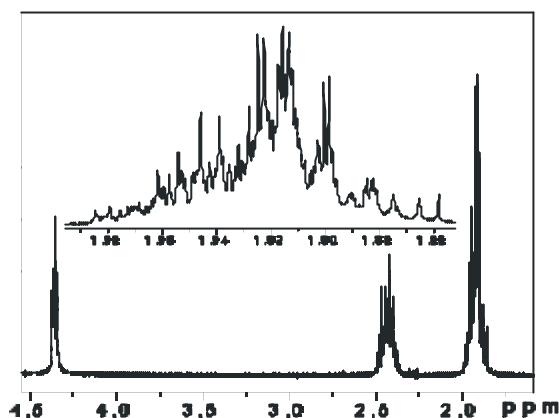


Figure 4. <sup>1</sup>H NMR spectrum of *trans*-1,2-dichlorocyclopentane (303K, 2M degassed solution in CD<sub>3</sub>CN, VXR-400)

Table 1. Conformations of disubstituted cyclopentanes

Solvent	Conformations
<i>trans</i> -1,2-dibromocyclopentane	
CD <sub>3</sub> CN	0.44(6) <sup>1</sup> E+0.39(4) <sup>1</sup> T <sub>5</sub> +0.17(4) <sup>4</sup> T <sub>5</sub>
C <sub>6</sub> D <sub>6</sub>	0.53(6) <sup>1</sup> E+0.42(4) <sup>1</sup> T <sub>5</sub> +0.11(4) <sup>4</sup> T <sub>5</sub>
CCl <sub>4</sub>	0.56(7) <sup>1</sup> E+0.42(5) <sup>1</sup> T <sub>5</sub> +0.07(6) <sup>4</sup> T <sub>5</sub>
<i>trans</i> -1,2-dichlorocyclopentane	
CD <sub>3</sub> CN	0.54(4) <sup>1</sup> E+0.28(4) <sup>4</sup> T <sub>5</sub> +0.18(5) <sup>2</sup> T <sub>1</sub> +0.10(4) <sup>4</sup> T <sub>3</sub>
C <sub>6</sub> D <sub>6</sub>	0.64(5) <sup>1</sup> E+0.33(4) <sup>4</sup> T <sub>5</sub> +0.12(4) <sup>4</sup> T <sub>3</sub>
CCl <sub>4</sub>	0.40(16) <sup>1</sup> E+0.40(18) <sup>1</sup> T <sub>5</sub> +0.24(12)E <sub>5</sub>
<i>trans</i> -1-bromo-2-chlorocyclopentane	
CD <sub>3</sub> CN	0.38(8) <sup>1</sup> E+0.25(8)E <sub>5</sub> +0.13(8) <sup>4</sup> T <sub>5</sub> +0.18(5) <sup>4</sup> E+0.14(4) <sup>2</sup> T <sub>1</sub>
C <sub>6</sub> D <sub>6</sub>	0.28(9) <sup>1</sup> E+0.32(9)E <sub>2</sub> +0.14(10)E <sub>5</sub> +0.18(5) <sup>4</sup> T <sub>5</sub> +0.14(7) <sup>3</sup> T <sub>4</sub>
CCl <sub>4</sub>	0.32(12) <sup>1</sup> E+0.34(12)E <sub>2</sub> +0.17(6) <sup>4</sup> T <sub>5</sub> +0.21(9) <sup>3</sup> T <sub>4</sub>
<i>trans</i> -1-bromo-2-methoxy-D <sub>3</sub> -cyclopentane	
CD <sub>3</sub> CN	0.36(11) <sup>1</sup> E+0.15(13) <sup>1</sup> T <sub>5</sub> +0.17(6) <sup>4</sup> E+0.33(15) <sup>4</sup> T <sub>5</sub> +0.13(4) <sup>2</sup> T <sub>1</sub>
C <sub>6</sub> D <sub>6</sub>	0.55(4) <sup>1</sup> E+0.28(4) <sup>4</sup> T <sub>5</sub> +0.21(4) <sup>3</sup> T <sub>4</sub>
CCl <sub>4</sub>	0.51(5) <sup>1</sup> E+0.30(4) <sup>4</sup> T <sub>5</sub> +0.24(5) <sup>3</sup> T <sub>4</sub>

The largest contributions in the conformational state of all studied cyclopentanes belong to the conformations surrounding the main energy minimum ( $^1E$ ,  $^1T_5$ ,  $E_5$ ). In the most polar of the solvents used,  $CD_3CN$ , a large enough share of the  $^2T_1$  conformation appears in all cases except dibromocyclopentane, which is in perfect agreement with theoretical calculations presented above. Significant contribution from conformations other than  $^1T_2$  and  $^2T_1$  can be explained if one observes that the minima on the pseudorotation path are very broad. Thus the molecule at room temperature will almost never stay at the exact minimum, but rather will oscillate, moving along a sector of the full pseudorotation circle.

### 3. Conformational analysis of cyclohexanes

The conformational space for cyclohexanes is three-dimensional, so the common way of presenting this construction is a sphere called “conformational globe”[4]. The two chair conformations,  $^1C_4$  and  $^4C_1$ , are located at the north and south poles ( $\theta=0,180^\circ$ ), six boat and six twist-boat conformations, alternating, occupy the equatorial plane ( $\theta=90^\circ$ ), and the transitional envelope and half-chair conformations are located at the so-called tropic of Cancer ( $\theta=66.5^\circ$ ) and the tropic of Capricorn ( $\theta=113.5^\circ$ ) (see fig 5). In non-substituted cyclohexane the two global energy minima are positioned at the poles and the other local minimum is distributed around the equator, with the energy barriers located on the tropics.

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Fig 5. Conformational globe for diethyl ester of *trans*-1,2- cyclohexanediol-*trans*-1,2-dicarboxylic acid

In most cases cyclohexanes are described adequately by only two chairs, but substituents can stabilize some of the equatorial conformations by means of H-bonds or other interactions. We encountered diethyl ester of *trans*-1,2- cyclohexanediol-*trans*-1,2-dicarboxylic acid (**I**), which displayed behavior in lactone formation reactions that could only be explained if a boat or twist-boat form of this compound was predominant [6]. Every theoretically possible boat, twist-boat, and chair conformation of this compound was constructed and its geometry optimized using a semi-empirical method AM1. For every optimized conformation a calculation of Cremer and Pople’s puckering coordinates according to [7] was rerun. Figure 6 shows the conformation energies relative to the pseudorotational angle  $\varphi$  (chair forms are represented by horizontal lines). It can be seen from this calculation that some of the twist-boat and boat conformations actually have energy equal or even lower than one of the chair forms.

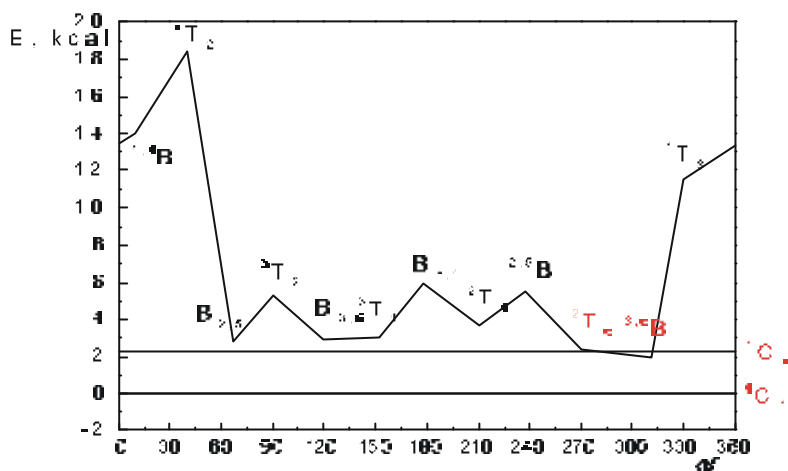


Fig 6. Pseudorotation energy for the compound I

NMR  $^1\text{H}$  spectra (fig. 7) of oxygen-free samples of the compound I were obtained at about RT in a series of  $(\text{CD}_3)_2\text{SO}$ ,  $(\text{CD}_3)_2\text{CO}$ ,  $\text{CDCl}_3$ ,  $\text{C}_6\text{D}_6$ ,  $\text{CCl}_4$ . Every spectrum was analyzed with VALISA program and an approximation for every H-H coupling constant was found, thus providing 10 vicinal coupling constants for use in conformational analysis. In all five cases the best fitting basis of theoretical conformations turned out to be the same; the two chairs and the two conformations on the equatorial plane with the lowest energies (the conformations' names are displayed in red on fig. 3). Since the energies and NMR parameters of these conformations were obtained independently, this further proves our research to be correct.

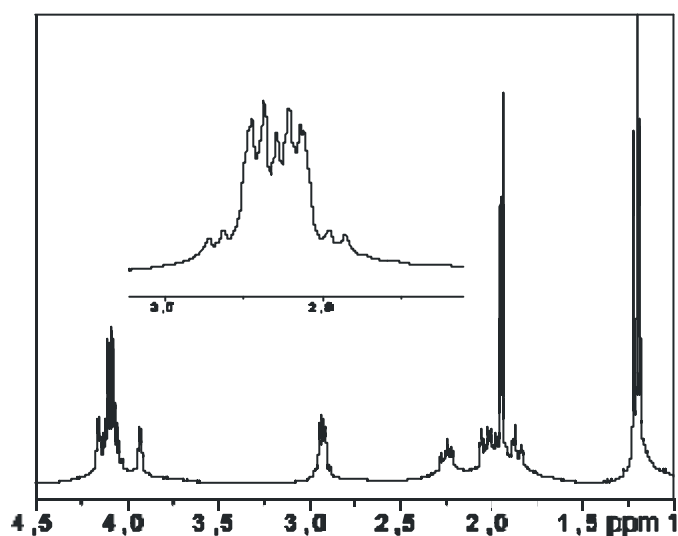


Figure 7. NMR  $^1\text{H}$  spectrum of the compound I

In all solvents, the most significant contribution into the conformational state comes from the twist-boat conformation  $^2\text{T}_6$ , which apparently gains additional stability from two hydrogen bonds between OH and COOEt groups. Actual conformational state mainly consists of a single distorted twist-boat conformation located between  $^2\text{T}_6$  and  $^{3,6}\text{B}$ , and both chairs.

Table 2. Conformations of the compound I

Solvent	$^2\text{T}_6$	$^1\text{C}_4$	$^4\text{C}_1$	$^{3,6}\text{B}$
$(\text{CD}_3)_2\text{SO}$	0.41(14)	0.40(10)	0.00(8)	0.24(14)

(CD <sub>3</sub> ) <sub>2</sub> CO	0.70(18)	0.20(13)	0.13(11)	0.03(18)
CDCl <sub>3</sub>	0.55(13)	0.20(9)	0.20(8)	0.14(13)
C <sub>6</sub> D <sub>6</sub>	0.70(14)	0.23(10)	0.19(8)	0.00(14)
CCl <sub>4</sub>	0.54(15)	0.25(10)	0.27(8)	0.06(15)

#### 4. Conclusions

The new lineshape analysis program VALISA was developed and proved to be an effective tool for numerical evaluation of complex high-resolution multiplet structure.

Precise analysis of complex NMR spectra gave more detailed picture of pseudorotation in cyclopentanes which fits the theoretical prediction of the pseudorotation potential curve.

Unexpectedly, the most stable conformation for a cyclohexane derivative was found to be twist-boat.

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