# Physical Chemistry

## VALISA: a new procedure for total lineshape analysis of NMR spectra. Conformational analysis of *trans*-1,2-dibromocyclopentane

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A new strategy of total lineshape analysis of the multiplet structure of NMR spectra was proposed and a VALISA program was developed to implement the computational procedure. Evaluation of the new technique taking a solution of several test problems and the complete analysis of the $^1$H NMR spectrum of *trans*-1,2-dibromocyclopentane as examples showed its high efficiency. Using a complete set of vicinal spin-spin coupling constants, detailed conformational analysis of this molecule was carried out and a more correct model for the description of conformational interconversions of the five-membered cycles was proposed. Conformational behavior of *trans*-1,2-dibromocyclopentane molecule can be reasonably described assuming large-amplitude molecular vibrations along a sector of the pseudorotation path, containing mostly diequatorial conformations.

**Key words:** analysis of high-resolution NMR spectra, total lineshape analysis, conformational analysis of cyclopentanes, pseudorotation.

Recently, some new techniques for automated extraction of information from complex NMR spectra have been proposed (see Ref. 1). They are based on the use of multipulse sequences and multidimensional Fourier transform. However, most of these methods are efficient only when analyzing the first-order nuclear spin systems (for the definition of this concept, see Ref. 2). Nevertheless, higher-order effects can manifest themselves even when using NMR spectrometers with high and ultrahigh magnetic fields and studying relatively small molecules. Interpreting such spectra is a classical example of the inverse spectral problem (determination of the chemical shifts and spin-spin coupling constants from experimental spectra[3]). Exact solution of this problem requires the use of iterative procedures with step-by-step control, which includes calculations of the theoretical spectrum (using the current set of spectral parameters), its comparison with the experimental spectrum, and the corresponding changes in the set of parameters based on the results of comparison.

In the case of NMR spectroscopy, such iterative procedures can be implemented using two principal approaches, namely, the approach by Castellano and Bothner-By[4] and the total lineshape analysis.[5] The fundamental differ-

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ence between them concerns the method of processing the spectral data and comparing the calculated and experimental spectra. The method proposed by Castellano and Bothner-By includes separation of the frequencies, $f_i$, of all observed transitions from the experimental spectrum and their assignment to theoretical transitions $\psi_i$ (assignment stage). In the course of the iterative procedure the parameters of this method are changed in such a way that the residual functional be minimum

$$\chi^2_{\text{LAOCOON}}(\bar{p}) = \sum_{i=1}^{N}(f_i - \psi_i(\bar{p}))^2, \qquad (1)$$

where $N$ is the number of the allowed transitions and $\bar{p}$ is the vector of parameters which includes the chemical shifts, $\nu_i$, and the spin-spin coupling constants, $J_{ij}$.

This approach is applicable to the vast majority of relatively well resolved NMR spectra with a simple multiplet structure. Indeed, the procedures based on the classical LAOCOON program[4] are successfully used at present, since they are known to be reliable and provide fast convergence. However, this technique has some drawbacks. First, the assignment of the frequencies to particular theoretical transitions is too labor-consuming and requires skills in the art. Recently,[6] considerable advances have been made in solving this problem using a pattern recognition formalism. Second, deconvolution results in a small set of numerical data. When using functional (1), a considerable body of information is lost prior to starting the iterative process. This concerns, in particular, the cross-correlations of the estimates of the frequencies and amplitudes of the spectral components obtained after deconvolution (off-diagonal elements of the covariation matrix). Our experience suggests that these values are of great importance for correct description of poorly resolved multiplets. This loss can to some extent be compensated by using different weighting factors for different spectral lines or, generally, using the integral transforms.[7—10] Though this approach extends the capabilities of analysis, the fact that some parameters have no physical meaning hampers statistical estimation of the results obtained.

The second classical approach called the total lineshape analysis is *a priori* free from all drawbacks inherent in the above-mentioned methods. The experimental and theoretical spectrum are compared using the entire frequency range and the residual functional has the form

$$\chi^2_{\text{lineshape}}(\bar{p}) = \sum_{f}(y^{\text{exp}}(f) - y^{\text{calc}}(f;\bar{p}))^2, \qquad (2)$$

where the vector of parameters, $\bar{p}$, also includes the lineshape parameters (halfwidth $L$ and the amplitude scale factor $S$). In this case, no line assignment is required and the spectrum can be processed in fully automated mode. Of course, there have also been a number of problems, which hindered the extension of this approach for a rather long time. In particular, convergence is complicated by noise, impurity signals, and by distortions of the base line, phase, and some other lineshape parameters. In addition, the hypersurface of the $\chi^2$ functional of a typical NMR spectrum exhibits numerous narrow and deep local minima, which strongly hampers the search for a global minimum.

In this case, the convergence problem appears to be the most important, since the procedure for total lineshape analysis requires the choice of a highly accurate initial approximation (in other words, one should *a priori* know the desired values of the spectral parameters to be found). Stephenson and Binsch[5] proposed a satisfactory method of attacking this problem and practically implemented it in two programs, DAVINS[5] and DAISY.[11a] They employed a free matrix transformation of the total spectral contour represented as a vector, which smoothes the hypersurface of the functional to be minimized in such a manner that ideally we get only one, global, minimum (strictly speaking, it can differ from true minimum). If the iterative procedure finds this minimum, the transformation is repeated using the matrix with reduced off-diagonal elements and smaller smoothing factor, so that the new global minimum is slightly shifted from the preceding one. Iterations are repeated until a unity transformation matrix is obtained and the global minimum of the transformed functional matches the true minimum. One sequence of the iterative cycles is called a grand cycle.[5]

Such a roundabout procedure, which is methodologically similar to the use of integral transforms, does allow one to find a solution for a large number of spectra irrespective of the choice of the initial approximation for the vector $\bar{p}$. Nevertheless, the choice of the matrix elements involved in the transformation remains a nontrivial problem. In addition, execution of the sequence of iterative cycles is still too labor-consuming for most applications and provides no possibility of visual control of the convergence process. These reasons seem to be responsible for little use of the algorithm by Stephenson and Binsch.

We developed and evaluated a new procedure for solving the convergence problem in the total lineshape analysis of high-resolution NMR spectra. The technique uses a convolution with a Lorentzian line of prescribed width as the smoothing transformation. In essence, this is a standard procedure leading to uniform broadening of all spectral lines, which is often used in NMR spectroscopy for improving the signal-to-noise ratio (see Ref. 1). At a sufficiently large broadening, one can always get a spectrum with one or several flattened maxima that will correspond to minima of the $\chi^2$ functional. Variation of the line broadening has no effect on the position of minimum, and theoretically (in the absence of noise) one could find a correct solution at this step. However, the global minimum can be so flat that the numerical algorithms stop before reaching it. Then, a new iterative cycle is per-

formed with a less broadened spectrum (and less flattened global minimum of the $\chi^2$ functional) and so forth until the initial non-broadened spectrum is considered. This approach seems to be more attractive, since it uses a transformation with clearer physical meaning, which allows visual control of the convergence process, well-substantiated choice of the parameters to be varied, and estimation of adequacy of the solution thus obtained. Evaluation revealed improved convergence and performance of the new procedure (often, obtaining a correct solution requires execution of a small number of the grand cycles).

A representative example of problems that need exact total lineshape analysis of NMR spectra is the conformational analysis of cyclic hydrocarbons (in particular, five-membered cycles). Modern formalism of conformational analysis of these compounds is based on the study by Cremer and Pople[12] who proposed a concept of pseudorotation. NMR spectroscopy provides a unique possibility of experimental determination of the molecular geometry in solutions. Valuable information can be extracted from the $^3J_{H,H}$ vicinal constants, which are related to the H—C—C—H torsion angles ($\varphi$) by relationships similar to the Karplus equation.[13] Therefore, measurements of the spin-spin coupling constants allows determination of the averaged conformational state of a particular molecule. In this case, completeness of spectral analysis is of crucial importance, since each new coupling constant allows one to consider a larger number of conformations. By analogy with cyclohexane derivatives, most of earlier studies used a simplified two-conformation model for analysis of the five-membered cycles (see, *e.g.*, Refs. 14 and 15). With an efficient method of processing the NMR spectra in hand we performed conformational analysis of the *trans*-1,2-dibromocyclopentane molecule taking into account all significant conformations according to the model by Cremer and Pople[12] and compared our results with those obtained using the simplest two-conformation approach.

## Experimental

$^1$H NMR spectra of degassed 2 *M* solutions of *trans*-1,2-dibromocyclopentane in $C_6D_6$, $CD_3CN$, and $CCl_4$ were recorded on a Varian VXR-400 spectrometer (operating frequency is 400 MHz for $^1$H nuclei) at 303 K. Slight experimental distortions of the base line were eliminated using a previously developed algorithm.[16] The model $^1$H NMR spectrum of pyridine was calculated for a Lorentzian line with a halfwidth of 0.32 Hz. The level of white noise added was 2.5%, 10%, and 40% of the peak amplitude of the most intense signal. The digital resolution was 0.04 Hz per point.

*trans*-1,2-Dibromocyclopentane was synthesized by bromination of cyclopentene in $CCl_4$ solution in the cold. After addition of a necessary amount of bromine the solvent was removed and the product was distilled. The yield was 66.5%, b.p. 95—97 °C (35 Torr) (*cf.* Ref. 11b: b.p. 74 °C (17 Torr)).

Calculations using the VALISA program were carried out on a PC with a Pentium® MMX® CPU operated at a frequency of 250 MHz. Typical computing time of one grand cycle was ~0.8 s for pyridine (spin system AA´BB´C, 3000 points in the spectrum, and 11 varied parameters) and ~5 min for dibromocyclopentane (spin system AA´BB´CC´DD´, 20000 points in the spectrum, and 22 varied parameters).

Theoretical spin-spin coupling constants were calculated using Eq. (3) and a home-made Newkarpl program. The geometries and energies of the theoretically possible conformations of *trans*-1,2-dibromocyclopentane molecule were calculated using the Gaussian 94W [17] program suite.

## Results and Discussion

**Program complex VALISA.** Using the above-mentioned new strategy of total lineshape analysis, we developed a VALISA (VAriable LIne Shape Analysis) program complex. The array of input data includes the digitized unbroadened spectrum, description of the spin system (number of spins, information on the chemical and magnetic equivalence of the nuclei, initial approximation for the chemical shifts and spin-spin coupling constants), description of strategy (sequence of line broadenings and parameters to be varied), and some additional parameters (in particular, convergence control parameters, the maximum number of iterations, the operating frequency of the spectrometer, *etc.*). Following the prescribed strategy, the VALISA program convolves the spectrum with the reference line of a given width and executes a search for a minimum of the $\chi^2$ functional.

In each grand cycle, the minimization procedure uses the Levenberg—Marquardt modification of the Newton—Raphson gradient method, which acts under conditions of strongly correlated spectral parameters. Earlier, this method has proved itself in the analysis of NMR spectra. It is employed both in the classical total lineshape analysis program NMRCON[18] and modern program complex PERCHit[19] developed for spectral analysis using the integral transforms. In addition, the damping parameter controlling the correlation elimination mechanism is reduced in each iteration step within the same grand cycle following the procedure developed for the NMRCON program. If the next step leads to an increase in the $\chi^2$ value, the program uses a procedure for linear search for a minimum by the golden section along the direction of the gradient.[20]

After finding the best approximation to the minimum at a given line broadening the width of the reference line is changed, the initial spectrum is convoluted with the new reference line, and the iterative procedure is executed again.

**Convergence problem.** Stephenson and Binsch proposed a number of tests for evaluating the efficiency of the total lineshape analysis algorithms.[21] In particular, the program should find correct values of the chemical shifts

**Table 1.** Chemical shifts ($\Delta\nu$/Hz) and spin-spin coupling constants ($J$/Hz) of the test systems of the ABCD type

| Number of test system | $\Delta\nu_1$ | $\Delta\nu_2$ | $\Delta\nu_3$ | $\Delta\nu_4$ | $J_{1,2}$ | $J_{1,3}$ | $J_{1,4}$ | $J_{2,3}$ | $J_{2,4}$ | $J_{3,4}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12 | 22 | 22 | 33 | 6 | 2 | 3 | 1 | 6 | 7 |
| 2 | 27 | 21 | 15 | 20 | 8 | 4 | 11 | 4 | 7 | 6 |
| 3 | 37 | 11 | 28 | 10 | 3 | 11 | 7 | 7 | 3 | 2 |
| 4 | 20 | 22 | 27 | 35 | 4 | 9 | 2 | 5 | 3 | 2 |

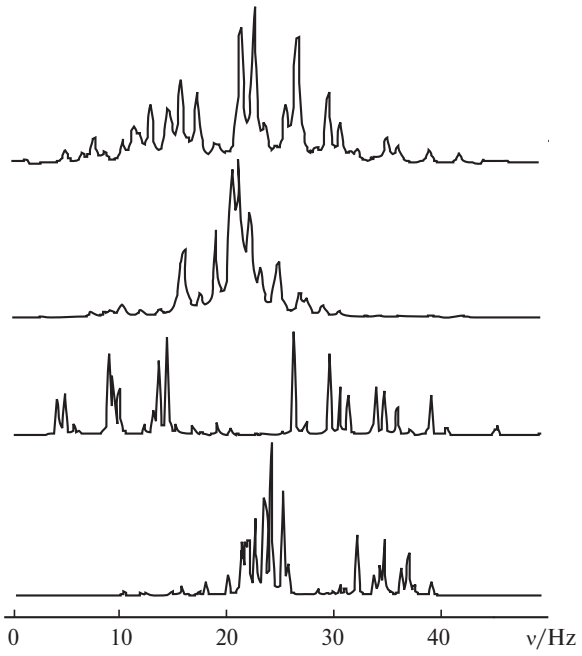



**Fig. 1.** NMR spectra of test systems of the ABCD type in the spectral region from 0 to 50 Hz.

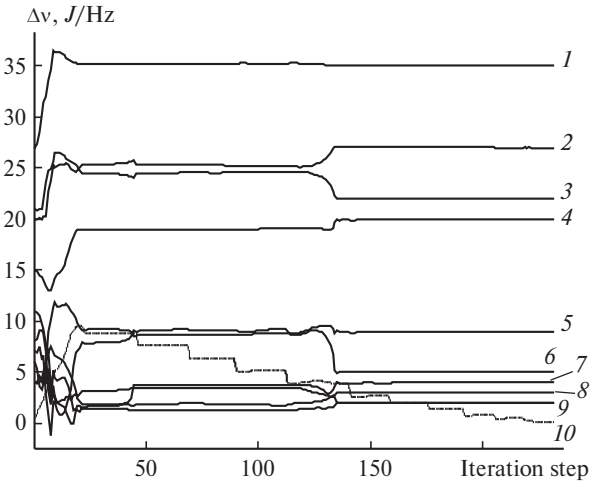



**Fig. 2.** Variations of parameters in different stages of solution of the test system 4 using the parameters of the test system 2 taken as initial approximation: $\Delta\nu_4$ (*1*), $\Delta\nu_3$ (*2*), $\Delta\nu_2$ (*3*), $\Delta\nu_1$ (*4*), $J_{1,3}$ (*5*), $J_{2,3}$ (*6*), $J_{1,2}$ (*7*), $J_{2,4}$ (*8*), $J_{3,4} = J_{1,4}$ (*9*), and $L$ (*10*).

and spin-spin coupling constants in four different, strongly coupled ABCD systems (see Fig. 1 and the parameters in Table 1) by sequentially using the parameters of each of the other three test systems as initial approximation. As can be seen in the typical plot of changes in the spectral parameters (Fig. 2), our algorithm finds the global minimum in the stage where the linewidth becomes comparable with the smallest spin-spin coupling constants. Until then the changes in small coupling constants have little effect on the functional (2), so they can vary over a rather wide range. Indeed, the spin-spin coupling constants vary nearly randomly at a broadening of 10 Hz (see Fig. 2).

The results obtained using the VALISA program are listed in Table 2. The figures in this Table represent the numbers of the grand cycles required to find the correct solution. As can be seen in Table 2, the VALISA system solved all the twelve tests, eight of them being solved after execution of one grand cycle. For comparison, the procedure by Stephenson and Binsch[20] solved a total of ten tests and only three of them required one grand cycle. We believe that combining the new approach proposed in this work and modern optimization methods allows one to exclude this class of problems from the "hard-to-solve" category.

**Stability problem.** To evaluate the solution stability in the presence of typical disturbing factors, we chose a strongly coupled, five-spin AA´BB´C system, which corresponded to the $^1$H NMR spectrum of pyridine. This is a well-known test developed for the LAOCOON program.[4] It was also used in evaluating the efficiency of the

**Table 2.** Number of the grand cycles necessary for execution of the tests taken from Ref. 21 by the VALISA (I, this work) and DAVINS programs (II, see Ref. 21)

| Number of target test system | Number of initial test system | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | | | | II | | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 1 | * | 1 | 2 | 1 | * | — | 2 | 1 |
| 2 | 2 | * | 3 | 2 | 2 | * | 2 | 1 |
| 3 | 1 | 1 | * | 1 | 1 | 2 | * | 2 |
| 4 | 1 | 1 | 1 | * | 2 | 4 | — | * |

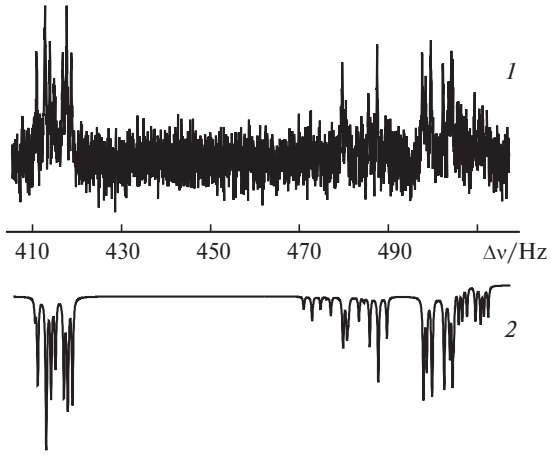
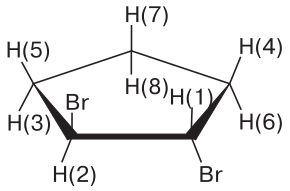



**Fig. 3.** $^1$H NMR spectrum of pyridine with the highest noise level (*1*) and solution obtained by the VALISA program (*2*).

PAREMUS program complex.[6] In the case of the VALISA program white noise was added to the spectrum under study, while the initial approximation was the same as that used in Ref. 4. The level of white noise added was 2.5, 10, and 40% of the amplitude of the most intense signal. The halfwidth of each spectral line was 0.36 Hz and an additional line broadening of 3, 1, and 0.5 Hz was used during the iterative process. The results obtained are presented in Table 3. As can be seen in Fig. 3, even at very high level of noise in the spectrum the iterative process overcomes numerous noise-induced local minima and finds a rather correct solution. This is possible owing to substantial improvement of the effective signal-to-noise ratio in the intermediate (broadened) spectra at the cost of a loss of resolution. In fact, the broadening procedure used by the program complex VALISA represents a commonly accepted noise reduction technique that is used in routine NMR spectroscopy in those cases when a small additional broadening of spectral components causes no loss of information on the multiplicity of the system under study.




**Conformational analysis of cyclopentane derivatives.** In the case of cyclic hydrocarbons typical $^1$H NMR spectra exhibit strongly overlapped complex multiplets while obtaining information on the torsion angles requires knowledge of exact values of as many vicinal spin-spin coupling constants as possible. For instance, the $^1$H NMR spectrum of *trans*-1,2-dibromocyclopentane (Fig. 4) exhibits a total of nearly 300 discernible lines grouped into four multiplets from the H(1) and H(2), H(3) and H(4), H(5) and H(6), and H(7) and H(8) protons (Fig. 4). Using the total lineshape analysis procedure with the three-step additional broadening of 0.5, 0.2, and 0.1 Hz, we obtained the estimates of all conceivable chemical shifts and proton—proton spin-spin coupling constants for this compound. We compared these values with the vicinal spin-spin coupling constants corresponding to theoretically possible conformations and calculated from the torsion angles ($\psi$) using the generalized Karplus equation

$$^3J_{H,H} = P_1\cos^2\psi + P_2\cos\psi + P_3 + \Sigma\Delta\chi_i\{P_4 + P_5\cos^2(\xi_i\psi + |\Delta\chi_i|)\}, \quad (3)$$

where $\Delta\chi_i$ is the electronegativity difference between the substituent (bromine) and hydrogen, $\xi_i$ is the sign corresponding to the relative orientation of the substituent, and $P_i$ ($i$ = 1, 2, ..., 5) are the empirical constants dependent on the number of non-proton substituents.[23]

The molecule of a substituted cyclopentane can adopt a total of twenty classical conformations (Fig. 5) that can undergo interconversions during pseudorotation.[12] In the case of unsubstituted cyclopentane they correspond to two symmetrical conformations, namely, the twist and

**Table 3.** Spectral parameters ($\Delta\nu$, $J$/Hz) used as initial approximation and the results of analysis of simulated $^1$H NMR spectrum of pyridine

| Parameters | Initial values | *S/N* | | | True values |
|---|---|---|---|---|---|
| | | 0.025 | 0.1 | 0.4 | |
| $\Delta\nu_1 = \Delta\nu_5$ | 516.0 | 516.5055(4) | 516.506(2) | 516.499(5) | 516.506 |
| $\Delta\nu_2 = \Delta\nu_4$ | 427.0 | 427.4345(5) | 427.433(2) | 427.429(7) | 427.435 |
| $\Delta\nu_3$ | 450.0 | 450.1466(9) | 450.153(4) | 450.12(1) | 450.148 |
| $J_{1,2} = J_{4,5}$ | 5.0 | 4.9507(6) | 4.948(3) | 4.960(9) | 4.950 |
| $J_{1,3} = J_{3,5}$ | 2.0 | 1.82422(7) | 1.825(3) | 1.83(1) | 1.824 |
| $J_{1,4} = J_{2,5}$ | 1.0 | 1.0193(7) | 1.017(3) | 1.02(1) | 1.019 |
| $J_{1,5}$ | −0.1 | −0.0418(4) | −0.04(2) | −0.04(5) | −0.043 |
| $J_{2,3} = J_{3,4}$ | 8.0 | 7.6277(9) | 7.631(4) | 7.63(1) | 7.627 |
| $J_{2,4}$ | 1.5 | 1.4680(2) | 1.466(7) | 1.49(2) | 1.466 |

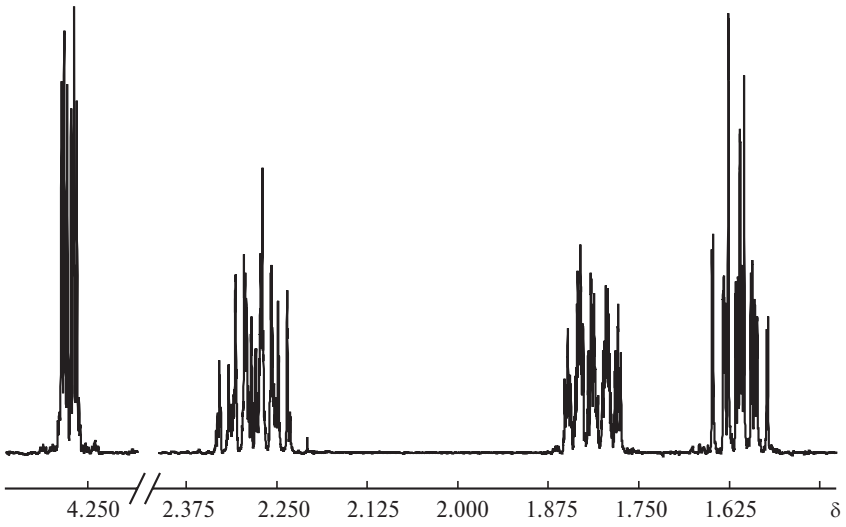



**Fig. 4.** $^1$H NMR spectrum of 2 *M* solution of *trans*-1,2-dibromocyclopentane in $CD_3CN$.

envelope conformations with $C_2$ and $C_S$ symmetry, respectively. We performed conformational analysis of the *trans*-1,2-dibromocyclopentane molecule. Symmetry considerations allowed reduction of the number of different molecular conformations down to eleven. These are five envelope conformations, namely, $^1E(\varphi = 72)$, $E_5(\varphi = 36)$, $^4E(\varphi = 0)$, $E_3(\varphi = 324)$, $^2E(\varphi = 288)$ and six twist conformations, namely, $^1T_2(\varphi = 90)$, $^1T_5(\varphi = 54)$,

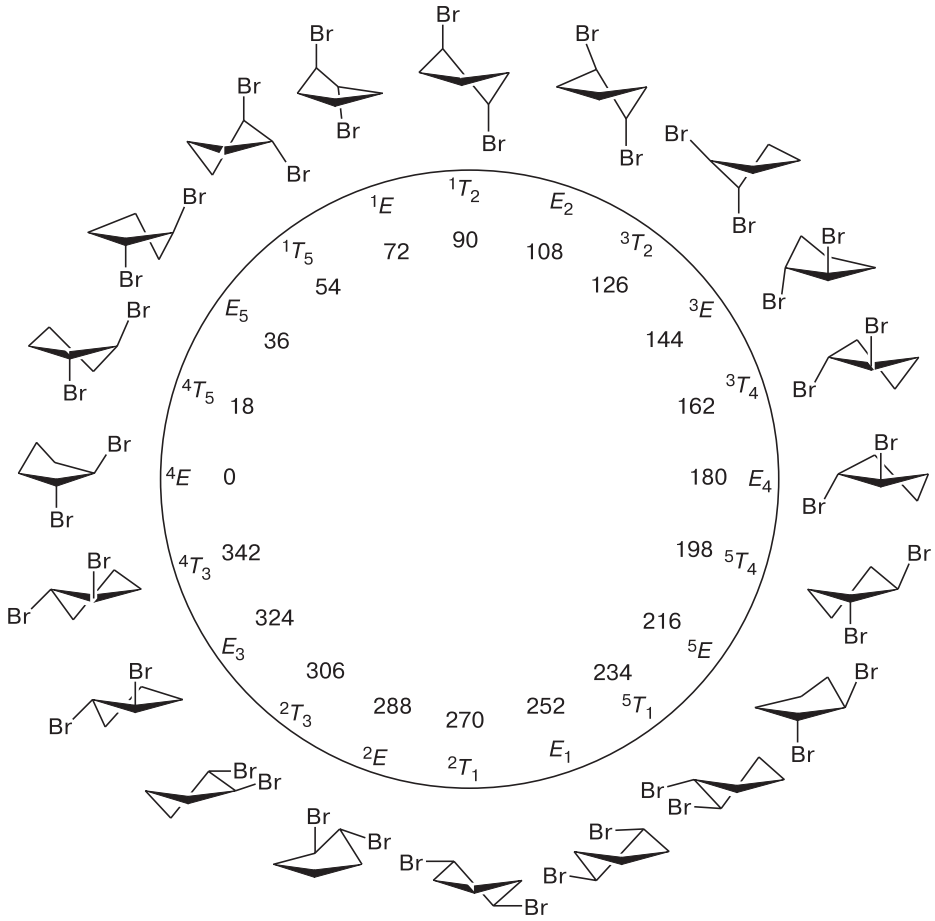



**Fig. 5.** Canonical conformations of disubstituted cyclopentanes. Figures inside the circle denote the phase angles of pseudorotation.

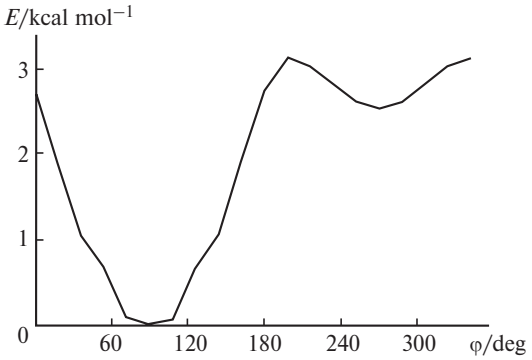



**Fig. 6.** Pseudorotation potential of *trans*-1,2-dibromocyclopentane molecule.

$^4T_5(\varphi = 18)$, $^4T_3(\varphi = 342)$, $^2T_3(\varphi = 306)$, $^2T_1(\varphi = 270)$, where φ is the phase angle of pseudorotation. The fact that the number of different molecular conformations is less than that of the vicinal spin-spin coupling constants (a total of 13) allowed simultaneous consideration of all theoretical conformations, thus excluding the determination of the more or less significant conformations. The geometry of each conformation was optimized by the *ab initio* HF/6-31G* method. The pseudorotation potential of *trans*-1,2-dibromocyclopentane molecule presented in Fig. 6 is a smooth curve with two broad minima corresponding to the classical twist conformations.

The parameters of the $^1$H NMR spectrum of dibromocyclopentane recorded in a $C_6D_6$ solution[22] and refined using the PAREMUS program[6] (Table 4) were chosen as initial approximation. Most of the spin-spin coupling constants calculated by the VALISA program were found to be rather close to those obtained using the PAREMUS program; however, the values of four spin-spin coupling constants changed by ~0.2 Hz and one of them ($J_{H(3),H(6)} = J_{H(4),H(5)}$) changed its sign. Detailed analysis of the spectra showed that the new total lineshape analysis program corrected some discrepancies between the experimental and theoretical spectra, which are clearly seen only in the region of combinatorial lines of low intensity at δ 4.258—4.263 (Fig. 7). Then, the PAREMUS program and the corrected set of parameters were used to

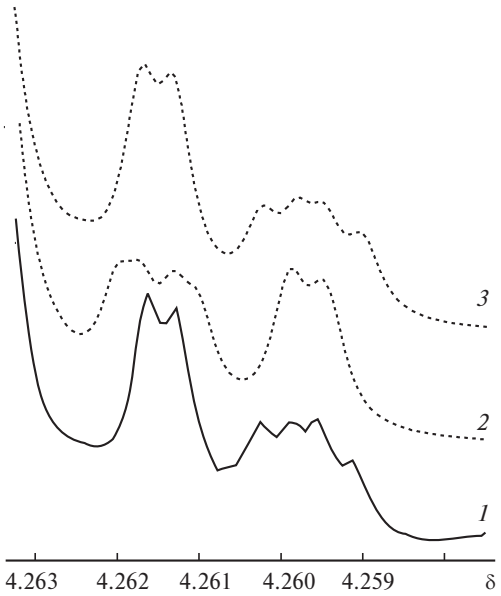



**Fig. 7.** The same region of the $^1$H NMR spectrum of *trans*-1,2-dibromocyclopentane: experimental (*1*), calculated using the PAREMUS program (*2*), and calculated using the VALISA program (*3*).

**Table 4.** Chemical shifts (δ) and spin-spin coupling constants ($J_{i,j}$) of *trans*-1,2-dibromocyclopentane in $C_6D_6$ obtained from calculations using the PAREMUS (*P*) and VALISA (*V*) programs

| Atom | δ | Program | $J_{i,j}$/Hz | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | H(1) | H(2) | H(3) | H(4) | H(5) | H(6) | H(7) |
| H(1) | 4.2747 | *P* | — | 1.647(4) | −0.570(4) | 5.620(4) | 1.196(4) | 1.876(4) | −0.382(9) |
| | | *V* | — | 1.631(1) | −0.5696(7) | 5.6154(8) | 1.1726(7) | 1.9118(7) | −0.486(1) |
| H(2) | 4.2747 | *P* | 1.647(4) | — | 5.620(4) | −0.570(4) | 1.876(4) | 1.196(4) | 0.480(9) |
| | | *V* | 1.631(1) | — | 5.6154(8) | −0.5696(7) | 1.9118(7) | 1.1726(7) | 0.337(1) |
| H(3) | 2.2811 | *P* | −0.570(4) | 5.620(4) | — | −0.576(4) | −15.205(8) | 0.203(4) | 10.170(8) |
| | | *V* | −0.5696(7) | 5.6154(8) | — | −0.573(1) | −14.990(1) | −0.011(1) | 10.173(1) |
| H(4) | 2.2811 | *P* | 5.620(4) | −0.570(4) | −0.576(4) | — | 0.203(4) | −15.205(8) | 7.402(8) |
| | | *V* | 5.6154(8) | −0.5696(7) | −0.573(1) | — | −0.011(1) | −14.990(1) | 7.400(1) |
| H(5) | 1.8137 | *P* | 1.196(4) | 1.876(4) | −15.205(8) | 0.203(4) | — | −0.134(4) | 3.909(8) |
| | | *V* | 1.1726(7) | 1.9118(7) | −14.990(1) | −0.011(1) | — | −0.551(1) | 3.930(1) |
| H(6) | 1.8137 | *P* | 1.876(4) | 1.196(4) | 0.203(4) | −15.205(8) | −0.134(4) | — | 8.960(8) |
| | | *V* | 1.9118(7) | 1.1726(7) | −0.011(1) | −14.990(1) | −0.551(1) | — | 8.951(1) |
| H(7) | 1.6118 | *P* | −0.382(9) | 0.480(9) | 10.170(8) | 7.402(8) | 3.909(8) | 8.960(8) | — |
| | | *V* | −0.486(1) | 0.337(1) | 10.173(1) | 7.400(1) | 3.930(1) | 8.951(1) | — |
| H(8) | 1.6118 | *P* | 0.480(9) | −0.382(9) | 7.402(8) | 10.170(8) | 8.960(8) | 3.909(8) | −13.430(8) |
| | | *V* | 0.337(1) | −0.486(1) | 7.400(1) | 10.173(1) | 8.951(1) | 3.930(1) | −13.221(7) |

revise the results obtained. The new results virtually coincided with those obtained using the VALISA program. Discrepancies of the order of some hundredth of Hz between a number of coupling constants, which lie outside the boundaries of the confidence interval in both models, can be due to both the errors of deconvolution (a necessary preliminary step for the PAREMUS procedure) and the lineshape distortions left out of consideration in the current version of the VALISA program. Indeed, our attempt at analyzing a spectrum of this complex system with strongly distorted base line showed that the VALISA program can find an incorrect solution. Namely, a number of spectral components of low intensity are placed in positions corresponding to the "rotation" satellites instead of being included in the main multiplet; however, the contours of more intense spectral lines match one another almost exactly. The $^1$H NMR spectra of *trans*-1,2-dibromocyclopentane recorded in other solvents were analyzed using the parameters obtained for the $^1$H NMR spectrum of *trans*-1,2-dibromocyclopentane in $C_6D_6$ solution as initial approximation.

The contributions of each of the eleven molecular conformations to the averaged conformational state of the *trans*-1,2-dibromocyclopentane molecule were calculated using a total of thirteen vicinal spin-spin coupling constants obtained for solutions in $CCl_4$, $C_6D_6$, and acetonitrile (Table 5). Statistical significance of the contributions of particular conformations was determined by the least squares method; the functional to be minimized had the form

$$\chi^2_{\text{inhabit}} = \sum_i (J_i^{\text{exp}} - \sum_k^N x_k J_i^k)^2, \qquad (4)$$

where $J_i^{\text{exp}}$ is the $i$th experimental spin-spin coupling constants, $x_k$ is the relative population of the $k$th conformation, $J_i^k$ is the $i$th spin-spin coupling constants for the $k$th conformation calculated using Eq. (3), and $N$ is the number of theoretical conformations.

The results obtained in the experiments with different solvents using the two-conformation and full models are listed in Tables 6 and 7, respectively. As can be seen, the solution of *trans*-1,2-dibromocyclopentane in $CD_3CN$ (a solvent of the highest polarity) is characterized by high population of the diequatorial conformation $^2T_1$, which is consistent with the published results.[14] However, no diaxial conformation $^1T_2$ (the second classical conformation) was observed in the full model. Instead, different neighboring conformations ($^1E$, $^4E$, $^4T_5$, and $^1T_5$) arranged on the "walls" of the global minimum are involved in the conformation equilibrium. This can be rationalized in terms of large-amplitude vibrations along the pseudorotation coordinate (phase angle). In fact, the *trans*-1,2-dibromocyclopentane molecule occupies the global minimum position for a short time; rather, it oscillates when moving along the sector of the pseudorotation path. Thus, a large number of accurately determined experimental vicinal spin-spin coupling constants allowed the use of a full conformation model. As can be seen, a conventional treatment of the conformational state of the disubstituted cyclopentane as an equilibrium between the diaxial and diequatorial twist conformations is sufficient for qualitative description of changes in the properties; however, actually the dibromocyclopentane molecule spends much longer time in other conformations. We also showed that other disubstituted cyclopentanes behave analogously.[22]

Thus, in this study we performed a detailed analysis of some convergence and solution stability problems as applied to the total lineshape analysis of high-resolution NMR spectra. This allowed us to develop a new strategy of analysis of the multiplet structure of complex NMR spectra and to evaluate its parameters using the VALISA program. The possibilities of the new computational tech-

**Table 5.** Vicinal spin-spin coupling constants of *trans*-1,2-dibromocyclopentane ($J_{i,j}$/Hz) in different solvents

| Solvent | $J_{1,2}$ | $J_{1,4}$, $J_{2,3}$ | $J_{1,6}$, $J_{2,5}$ | $J_{3,7}$, $J_{4,8}$ | $J_{3,8}$, $J_{4,7}$ | $J_{5,7}$, $J_{6,8}$ | $J_{5,8}$, $J_{6,7}$ |
|---|---|---|---|---|---|---|---|
| $C_6D_6$ | 1.631 | 5.615 | 1.912 | 10.173 | 7.400 | 3.93 | 8.951 |
| $CCl_4$ | 1.171 | 5.446 | 1.395 | 10.314 | 7.594 | 3.635 | 8.918 |
| $CD_3CN$ | 2.352 | 5.877 | 2.685 | 10.002 | 7.087 | 4.346 | 9.053 |

**Table 6.** Relative contributions (in per cent) of the $^1T_2$ and $^2T_1$ conformations of *trans*-1,2-dibromocyclopentane molecule in solvents with different dielectric constants (ε) obtained using the two-conformation model

| Solvent | ε | $^1T_2$ | $^2T_1$ | RMS error/Hz* |
|---|---|---|---|---|
| $CD_3CN$ | 37.5 | 83(8) | 18(8) | 1.1 |
| $C_6D_6$ | 2.3 | 93(8) | 7(8) | 1.1 |
| $CCl_4$ | 2.2 | 99(8) | 0(8) | 1.0 |

* Root mean square deviation of experimental and calculated spin-spin coupling constants.

**Table 7.** Relative contributions (in per cent) of statistically significant conformations $^1E$, $^1T_5$, $^4T_5$, $^4E$, and $^2T_1$ of *trans*-1,2-dibromocyclopentane in different solvents

| Solvent | Computational Procedure | $^1E$ | $^1T_5$ | $^4T_5$ | $^4E$ | $^2T_1$ | RMS error /Hz* |
|---|---|---|---|---|---|---|---|
| $CD_3CN$ | VALISA | 46(6) | 35(4) | 15(5) | 8(5) | 6(4) | 0.49 |
| $C_6D_6$ | VALISA | 52(7) | 43(4) | 12(5) | — | — | 0.58 |
| | PAREMUS* | 52(7) | 43(4) | 13(5) | — | — | 0.59 |
| $CCl_4$ | VALISA | 58(9) | 41(5) | 8(6) | — | — | 0.73 |

* See the note in Table 6.

nique were demonstrated taking a complete interpretation of the $^1$H NMR spectrum of *trans*-1,2-dibromocyclopentane as an example. The accuracy and reliability of the spin-spin coupling constants obtained using the VALISA program made it possible to carry out the conformational analysis taking into account all conformational states described by pseudorotation of the five-membered cycle. The VALISA program was also successfully employed for solving other complicated structural[24] and conformational[25] problems.

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