Computer-Assisted Pseudorotation Analysis of Five-Membered Rings by Means of Proton Spin–Spin Coupling Constants: Program PSEUROT

Frank A. A. M. de Leeuw and Cornelis Altona*

Gorlaeus Laboratories of the University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands
Received 11 November 1982; accepted 10 February 1983

A computer method for the calculation of the pseudorotational parameters in five-membered rings from vicinal proton spin–spin coupling constants is described. Some typical problems met in practice are discussed. Applications of the program in the conformational analysis of some substituted cyclopentanes are presented.

INTRODUCTION

Vicinal proton spin–spin coupling constants play an important role in conformational analysis. With the help of Karplus-like equations, the vicinal coupling constants can be translated into proton–proton torsion angles. When analyzing a five-membered ring, it should be recognized that these torsion angles are correlated via the laws of pseudorotation. The proton–proton torsion angles can be expressed as a function of the pseudorotation parameters P and Φ_m. In analyzing a five-membered ring one is usually more interested in the pseudorotation parameters than in the individual proton–proton torsion angles. We hereby describe a computer program which calculates the best fit of P and Φ_m to the measured vicinal $^3J_{HH}$ in the case of two-state conformational equilibria and discuss its scope and limitations in the light of the present knowledge.

PROCEDURE

A new empirical generalization of the classical Karplus equation was introduced recently.[1] The first three terms in eq. (1) describe the dependency of the vincinal coupling constant in a given H—C—C—H fragment on the proton–proton torsion angle ϕ. The remaining terms account for the dependency of $^3J_{HH}$ on the electronegativity and relative orientation of the substituent S_i.

$$^3J_{HH} = P_1 \cos^2\phi + P_2 \cos\phi + P_3 + \sum_i \Delta\chi_i[P_4 + P_5 \cos^2(\xi_i\phi + P_6|\Delta\chi_i|)] \quad (1)$$

ξ_i stands for +1 or −1, according to the orientation of S_i with respect to its geminal proton. The magnitude of the correction due to each substituent S_i is correlated with the difference $\Delta\chi_i$ in Huggins's electronegativity[2] between the substituent S_i and hydrogen. In addition, the primary (α) $\Delta\chi_i$ values are influenced by β substituents. As the influence of β substituents is opposite to that of the α substituents, the electronegativity effect of an α substituent can be considered to be moderated by a β substituent. The electronegativity of an α substituent may be expressed as

$$\Delta\chi^{\text{group}} = \Delta\chi^{\alpha\text{ substituent}} - P_7 \sum_j \Delta\chi_j{}^{\beta\text{ substituent}} \quad (2)$$

where the summation is over all the substituents j bonded to the α substituent S_i. Optimum values of $P_1 - P_7$ and the definition of the sign parameter ξ_i are given by Haasnoot, de Leeuw, and Altona.[1] It was found that separate treatment of fragments bearing three or four nonhydrogen substituents yields a significantly better agreement between observed and calculated coupling constants. In the

* Corresponding author.

CCC 0192-8651/83/030428-10$02.00

case of two nonhydrogen substituents the data set was too small to obtain accurate values of P_1–P_7; for this reason the use of parameters refined upon the complete data set was recommended for CH_2—CH_2 fragments.[1] The program selects automatically different sets of parameters depending on the number of substituents. As an option a user-supplied parameter set can be read in.

The conformational analysis of the five-membered ring is greatly facilitated by using the concept of pseudorotation.[3–6] It has been shown[4] that the endocyclic torsion angles can be described by

$$\phi_j = \Phi_m \cos(P + 4\pi j/5) \quad j = 0, \ldots, 4 \qquad (3)$$

where P is the phase angle of pseudorotation and Φ_m is the puckering amplitude. The proton–proton torsion angles are related to the corresponding endocyclic torsion angles. In general, ϕ_{HH} can be expressed by

$$\phi_{HH} = a + b\Phi_m \cos(P + \text{phase}) \qquad (4)$$

where, in the trigonal symmetry approximation, b will be 1 and a will be 0° for cis protons and ±120° for trans protons. However, in five-membered rings bond angles differ from their tetrahedral values and deviations from trigonal projection symmetry occur. In case accurate geometries for the five-membered ring under investigation are available, it is possible to correct for these deviations.[7,8]

Pitzer and Donath[9] were the first to propose that an energy barrier(s) restricting "free" pseudorotation of a five-membered ring will automatically occur when one or more substituents (endocyclic or exocyclic) are present. These ideas where subsequently applied by Altona, Buys, and Havinga[10] in the study of halogenated cyclopentanes and by Ouannes and Jacques[11] in the case of methylated cyclopentanones. In many instances two substituent-determined barriers are met during one full pseudorotation cycle, and their presence implies the existence of two stable conformational species, interconverting via the pseudorotational pathway.[5] Of course, this is only true if the barriers are of sufficient height compared with the torsional levels occupied at the temperature of the experiment. In the present article the discussion will be focused on five-membered sugar and cyclopentane rings in which this condition appears to be met, but the method presented is easily extended to other five-membered ring systems that display restricted pseudorotational freedom. The program is designed in a general way such that any five-membered ring may be analyzed as long as the assumption of a two-state equilibrium is valid, and couplings along at least two neighboring carbon–carbon bonds are known.

If one assumes that a five-membered ring is engaged in a two-state conformational equilibrium (I ⇄ II), experimental nuclear magnetic resonance (NMR) coupling constants represent time-averaged couplings related to the couplings of the individual conformers and their relative populations in equilibrium as

$$J_{\text{obs}} = (1 - x_{\text{II}})J_{\text{I}} + x_{\text{II}}J_{\text{II}} \qquad (5)$$

where x_{II} is the mol fraction of the conformer II and J_{I} and J_{II} are the coupling constants belonging to the pure conformers I and II, respectively. Combination of eqs. (1), (4), and (5) gives J_{HH} as a function of the conformational parameters involved:

$$J_{HH} = f(P_I, \Phi_{m\,\text{I}}, P_{\text{II}}, \Phi_{m\,\text{II}}, x_{\text{II}}) \qquad (6)$$

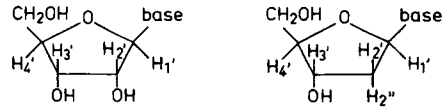
When coupling constants are measured under n different conditions (e.g., changes in temperature, solvent, pH) and one assumes that the ring geometry of conformer I and II is invariant under these changes—i.e. only the molar ratio of conformer I and II is temperature (solvent, pH) dependent—eq. (6) can be extended to a set of n equations:

$$J_{HHi} = f(P_{\text{I}}, \Phi_{m\,\text{I}}, P_{\text{II}}, \Phi_{m\,\text{II}}, x_{\text{II}i}) \quad i = 1, \ldots, n \qquad (7)$$

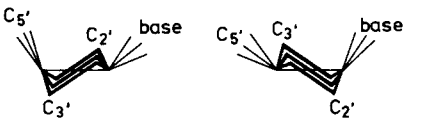
where n is the total number of sets involved. Equation (7) can also be solved for a series of closely related molecules, assumed to have similar type I and type II geometries but differing in mol fraction x_{II} from compound to compound. The program PSEUROT calculates the best fit of P_{I}, $\Phi_{m\,\text{I}}$, P_{II}, $\Phi_{m\,\text{II}}$, $x_{\text{II}i}, \ldots, x_{\text{II}n}$ using a standard Newton–Raphson minimization procedure which includes second derivatives. The program is designed in such a way that one (or more) conformational parameters can be constrained to assume a fixed value. The program will be submitted to the *Quantum Chemistry Program Exchange* (*QCPE*) for distribution.

DISCUSSION

In the course of our calculations some typical problems in running the program were encountered. In those cases where the number of ob-



Scheme 1



Scheme 2

servables is less than or equal to the number of parameters, it is advised or even necessary to constrain one or more conformational parameters to assume a fixed value. For example, in deoxyribofuranose rings (see scheme 1), five couplings can be determined and, assuming a two-state equilibrium, the number of conformational parameters is also five. Adjustment of all parameters simultaneously will lead to a fit with a residual rms deviation close to zero: An excellent fit from a mathematical point of view, this fit might be physically unrealistic. The optimized parameters will be greatly influenced by experimental errors in the coupling constants. However, in those cases where the system is overdetermined, random errors will tend to cancel.

Even when a large number of coupling constants is available from a variable-temperature study, this fact does not always guarantee the unambiguous description of the conformational parameters. When the equilibrium constant is nearly invariant over the fully available temperature range (e.g., mol fractions vary less than 5%), virtually only one set of couplings is used in the minimization step. In order to remove the deficiency, one or more parameters must then be constrained.

In these cases good results may be obtained in either two ways: (i) by constraining the pseudorotation parameters P and Φ_m of the less abundant—and therefore less well defined—conformer to assume fixed values, or (ii) by constraining both puckering amplitudes $\Phi_{m\ \mathrm{I}}$ and $\Phi_{m\ \mathrm{II}}$ to assume fixed values. The calculated mol fractions are found to be nearly independent of the particular constraint imposed.

Sometimes a strong correlation between the calculated pseudorotation parameters is noted; i.e., the minimum in solution space appears rather flat. The best approach in these cases appears to constrain one (or both) puckering amplitudes to adopt a range of acceptable values; in this way the upper and lower limits of the pseudorotation parameters that fit the experimental results can be delineated.

Now the question arises whether or not it is always possible to find a single unique solution. According to our experience the solution found is, in general, unique. An important exception is noted, however. In the pseudorotation analysis of β-D-ribofuranose (see scheme 1) the application of the constraint $\Phi_{m\ \mathrm{I}} = \Phi_{m\ \mathrm{II}}$ sometimes results in two virtually equivalent solutions. The one actually found depends on the estimated start values of the pseudorotation parameters. In the conformational analysis of furanose rings the two components involved in the two-state equilibrium are denoted by N- and S-type[6] (see scheme 2). The phase angle of pseudorotation for N- and S-types will be written as P_N and P_S, respectively. The puckering amplitudes Φ_m are defined analogously.

The existence of a double minimum in solution space is best illustrated with the aid of an experimental example. Coupling constants for the ribose part of adenylyl-(3'-5')-2'-deoxyadenosine (rAdA) are available from measurements at four temperatures[12]; a fifth set is found by extrapolation of the coupling constants to the situation that corresponds to the fully stacked conformer.[12] Using these data, we detect only one single minimum for (constrained) puckering amplitudes of 38° or smaller, but when the puckering amplitude is constrained to assume larger values two solutions are found. Figure 1 shows contour lines for the rms deviation as function of P_N and P_S. In the calculation illustrated in Figure 1(a) the N- and S-type conformers are kept fixed at equal puckering amplitudes: $\Phi_N = \Phi_S = 35°$. In Figure 1(b) a puckering amplitude of 39.5° is chosen. This figure clearly demonstrates the occurrence of a single minimum in the low puckering case. The high puckering case [Fig. 1(b)] shows two minima separated by a small ridge with a height of 0.20 Hz. Depending on the estimated starting values of the conformational parameters, it is even possible that the minimization converges to the saddlepoint which is characterized by $P_N = 24.1°$ and $P_S = 159.1°$. However, a saddlepoint is easily detected by the program because the Hessian matrix in such a point is not positive definite. Obviously the exact size and location of the double minimum depends on the particular set of experimental coupling constants used as input, but one always must be aware of this possible pitfall when analyzing

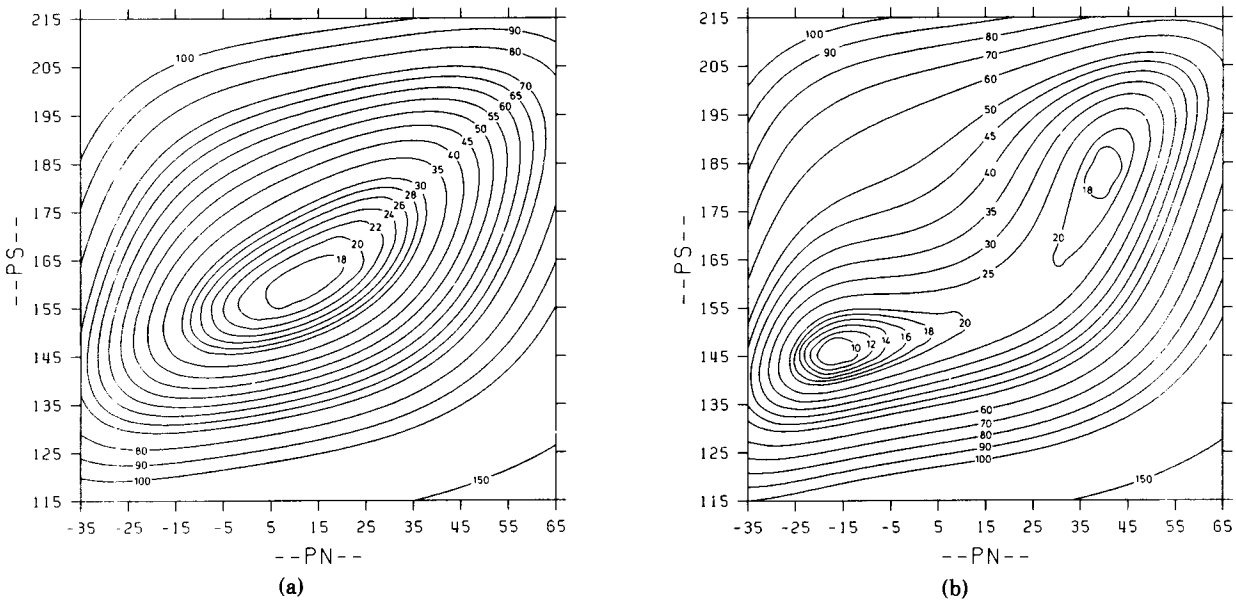


Figure 1. Contour plots of rms deviation as function of P_N and P_S for β-D-ribofuranose systems for two puckering amplitudes. A regular 21 × 21 grid was calculated with both P_N and P_S varied in steps of 5°. For each P_N–P_S pair the mol fractions x_S were optimized. Contour lines were plotted by means of the subroutine package MMAP [D. H. Faber, E. W. M. Rutten-Keulemans, and C. Altona, *Comput. Chem.*, **3**, 51 (1979)]. The numbers in the contour lines correspond to 100× the rms deviation. (a) $\Phi_N = \Phi_S = 35°$. (b) $\Phi_N = \Phi_S = 39.5°$.

Table I. Calculated coupling constants (Hz) and pseudorotational parameters of *N*- and *S*-type conformers for the ribosepart of rAdA.

	calculation 1		calculation 2	
	J_N	J_S	J_N	J_S
1' - 2'	1.11	8.13	2.10	7.26
2' - 3'	4.64	5.41	5.74	4.46
3' - 4'	7.61	1.94	9.23	0.76
P	-16.1°	146.0°	40.3°	183.8°
Φ_m	39.5°	39.5°	39.5°	39.5°

[a] Constrained value (see text).

β-D-ribofuranosides. Detailed information concerning the two solutions calculated for a puckering of 39.5° is presented in Tables I and II. The overall rms deviations are 0.07 Hz and 0.17 Hz for calculations 1 and 2, respectively. Note that the mol fractions computed in these solutions are equal within 3%. Calculation 1 shows a good correspondence with the single solution that is found with an assumed puckering amplitude of 38° ($P_N = -6.8°$, $P_S = 150.1°$). In view of the fact that Φ_m values usually occur in the range 36°–38° (in cases where the solution was proven to be unique) calculation 1 is preferred.

Table II. Experimental and weighed (calculations 1 and 2) coupling constants (Hz) for the ribose part of rAdA. Data from ref. 12.

	1' - 2'			2' - 3'			3' - 4'				
set	J_{exp}	J^a_{calc}	J^b_{calc}	J_{exp}	J^a_{calc}	J^b_{calc}	J_{exp}	J^a_{calc}	J^b_{calc}	x^a_s	x^b_s
1	4.8	4.76	4.85	5.0	5.04	5.06	4.7	4.66	4.72	0.52	0.53
2	5.0	5.03	5.03	5.0	5.07	5.01	4.4	4.44	4.42	0.56	0.57
3	5.4	5.48	5.30	5.2	5.12	4.94	4.0	4.08	3.98	0.62	0.62
4	5.6	5.65	5.39	5.3	5.14	4.92	3.9	3.94	3.83	0.65	0.64
5	4.2	4.13	4.45	4.9	4.97	5.15	5.25	5.17	5.37	0.43	0.46

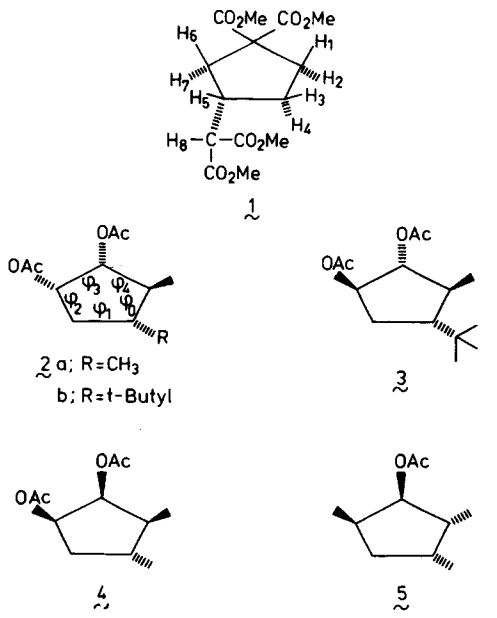
[a] Calculation 1, overall rms deviation is 0.07 Hz.
[b] Calculation 2, overall rms deviation is 0.17 Hz.

The existence of a double minimum in the case of β-D-ribofuranose appears rather exceptional. In investigations of other systems, like β-D-xylofuranose or β-D-arabinofuranose, we were not able to detect a second minimum. In the analysis of β-D-deoxyribofuranose or proline, where the five-membered ring is described in terms of five or ten coupling constants, respectively, the appearance of a double minimum seems highly unlikely.

In the analysis of proline residues, an experimental difference of *ca* 1 Hz is noted between the two cis couplings around the C^{β}—C^{γ} bond.[13] The cis couplings around the C^{γ}—C^{δ} bond show a corresponding difference. As torsion angles and substitution pattern for the two cis couplings differ only slightly, the calculated couplings using the generalized Karplus equation (1) are equal within 0.5 Hz.[8] The experimental difference between the cis couplings can be ascribed to the "Barfield transmission effect" [14]; i.e., in the proline ring there exists an extra coupling pathway due to interactions of the C—H bonds of the C^{β}—C^{γ} fragment (C^{γ}—C^{δ} fragment) with the orbitals of the opposite nitrogen or carbon atom. This transmission effect is quite efficient. It is operative in envelope-like conformers of any five-membered ring and tends to reduce relatively and specifically the cis coupling between pairs of protons located trans to the carbon or hetero atom that resides at or near the "flap" of the envelope. Other examples of cis couplings which will be decreased by the transmission effect are the 1′-2″ and 2′-3′ couplings in β-D-deoxyribofuranose and the 2′-3′ coupling in β-D-ribofuranose. A more complete account of this effect will be given in a companion paper.[15]

Suffice it to say that, whenever during the conformational analysis large deviations are found between calculated and experimental cis couplings, one must take the transmission effect into consideration.* Calculations on the deoxyribofuranose systems indicate that the inclusion of a correction term for the transmission effect decreases the final rms deviation between experimental and calculated couplings but has only a small influence on the optimized geometries: The phase angle of the *S*-type conformer tends to be 2°–5° higher, whereas the puckering amplitude is slightly decreased with respect to the uncorrected PSEUROT computations.

* This can be done optionally in program PSEUROT.



Scheme 3

APPLICATIONS

This section is devoted to the pseudorotation analysis of some arbitrarily chosen five-membered rings. It will be shown that sometimes knowledge of the coupling constants alone is insufficient to carry out a reliable analysis and that in these cases the aid of molecular mechanics is indispensable.

Dimethyl-3-Dicarbomethoxy Methylcyclopentane-1,1-Dicarboxylate (1)

Castellano[16] has reported the NMR spectrum of compound (1) (scheme 3). The conformation proposed by Castellano can be described as follows: The cyclopentane ring adopts an envelope-type conformation with a C_2-type of symmetry in which the positions of H_1, H_4, and H_7 are pseudoaxial, whereas those of H_2, H_3, and H_6 and of the side chain substituent are pseudoequatorial; the side chain was assumed to adopt a staggered position with proton H_8 trans to proton H_5.

In our pseudorotation analysis the torsion angle around the carbon–carbon bond opposing the carbon atom (C_1) bearing the two carbomethoxy substituents is chosen as reference angle ϕ_0. The conformation proposed by Castellano then corresponds to $P \sim -30°$.

Cyclopentane conformation. The proton–proton torsion angles are interrelated to the endocyclic torsion angles by eq. (4). The values of *a* and *b* were approximated by the trigonal projection symmetry. The best fit found for the pseudorotation parameters is given in Table III. It is seen that

Table III. Pseudorotation parameters and mol fraction for 1 calculated from NMR coupling constants on the basis of a two-conformer assumption (see text).

No	P_I	Φ_I	P_{II}	Φ_{II}	X_{II}[a]	rms(Hz)
1	-13.4	41.1	88.2	62.7	0.24	0.51
2	-15.1	45.2	84.3	45[b]	0.29	0.52

[a] Mol fraction of conformer II.
[b] Constrained value (see text).

(at least) two conformers exist in fast equilibrium, a major form I which corresponds to the one proposed[16] and a hitherto unsuspected minor form II. The suspiciously high puckering resulting for conformer II is taken be an artifact resulting from a strong correlation between the two puckering amplitudes. Indeed, constraining this parameter on $\Phi_{m\ II} = 45°$ causes only an insignificant increase in the rms deviation (Table III, second calculation). The analysis cannot be regarded as completely satisfactory, however, The rms deviation (0.51 Hz) appears rather high compared to the rms deviations obtained from furanose[12,17-22] and proline derivatives.[8] In the first instance, the reason for this could be sought in a breakdown of the pseudo-threefold symmetry. In earlier articles[8,12,17-22] the values of a and b [eq. (4)] were derived from a statistical treatment of neutron-diffraction and x-ray data[7] in the case of the furanose ring and from a precise neutron-diffraction study in the case of the proline ring.[8] Unfortunately, no x-ray or neutron-diffraction study of (1) appears available and an experimental relation between proton–proton torsion angles and pseudorotation parameters cannot be obtained. However, the same standard procedure (Table IV, footnote a) can be employed, now starting from the heavy-atom skeleton calculated with the aid of molecular mechanics, which is well capable to reproduce this skeleton (C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, unpublished results). Throughout the force-field calculations the Ermer field (CFF3)[23] was used. This force field does not contain oxygen functions, and therefore a model compound was chosen in which all the carboxylate groups were replaced by methyl groups. To our surprise the calculations revealed that this model compound is predicted to adopt six conformations, all within a range of 1.1 kcal/mol. For each of the three side-chain rotamers the cyclopentane ring exhibits two conformations: an envelope with C_1 exo with respect to the side chain ($P = 77–91°$) and a conformation varying from a twist form C_3-*endo*-C_4-*exo* ($P = 5°$) to a C_3-*endo* envelope ($P = -30°$). In all these conformations the side chain invariably occupies a pseudoequatorial position.

Table IV. Pseudorotation parameters and side-chain proton–proton torsion angles[a] of compound 1 calculated by means of molecular mechanics (compare Table III).

Conformer	P_I	Φ_I	ϕ_{58}	E[b]
I_t	-8.0	41.8	179.8	0.150
II_t	77.1	40.4	-177.2	0.0
I_{g^-}	-30.4	41.0	-59.6	0.884
II_{g^-}	90.8	40.6	-62.3	0.608
I_{g^+}	5.5	42.4	63.9	1.079
II_{g^+}	85.4	40.6	62.9	0.778

[a] From the heavy-atom skeleton the hydrogen coordinates were computed according to the following rules: (i) CH_2 groups were constrained to adopt C_{2v} symmetry with tetrahedral H—C—H angle; (ii) Methine hydrogens on tertiary sp^3-carbon atoms were fixed in positions having equal bond angles to the other nonhydrogen substituents.
[b] Relative energy (kcal/mol).

The pseudorotation parameters for the calculated structures are given in Table IV. Certainly, the carboxylate groups will influence both geometry and energy; nevertheless, the force-field calculations indicate that the presupposition of a two-state equilibrium should be rejected in favor of a multistate one. For this reason no further two-state pseudorotation analysis on compound (1) was performed. It is satisfying to note that the pseudorotation parameters derived from NMR coupling constants occur within the range spanned by the parameters calculated with the aid of molecular mechanics (compare Tables III and IV). Both methods indicate that the solution conformation of (1) cannot be described by a single conformer, as proposed earlier,[16] but rather by an equilibrium between a number of states, which show approximate two-state behavior.

In principle, an exact mathematical procedure can be employed to solve a three-state or higher-state equilibrium. In practice, this will often be fruitless because of an unfavorable ratio of the observables (i.e. the proton–proton couplings) to the parameters pertaining to the equilibrium, and this approach was abandoned.

Side-chain conformation. The solution conformation of the side chain relative to the cyclopentane ring in principle can comprise three types of rotamers which are denoted g^+, g^-, and t (delineating the relative orientation of the protons H_5 and H_8). In solution a rapid interconversion between the three rotamers yields a weighted time-averaged coupling that is related to the couplings of the individual rotamers and their relative population by

$$J_{58} = X_t J_t + X_{g^-} J_{g^-} + X_{g^+} J_{g^+} \qquad (8)$$

where X denotes the mol fraction of each of the rotamers present.

Assuming ϕ_{HH} values of −178°, 62°, and −62°—according to the force-field calculations—for the t, g^+, and g^- conformers, respectively, the individual couplings J_t, J_{g^+}, and J_{g^-} are calculated [eq. (1)] to be 12.9, 2.5, and 2.5 Hz, respectively. Generally, with only one coupling constant available, the three mol fractions cannot be calculated separately. Fortunately, the couplings J_{g^+} and J_{g^-} are equal in this case; therefore J_{58} can be expressed in X_t and the total amount of gauche conformers X_g:

$$J_{58} = 12.9\, X_t + 2.5\, X_g$$
$$X_g = X_{g^+} + X_{g^-} = 1 - X_t$$

Using the experimental value of 9.6 Hz, a trans : gauche ratio of 68 : 32 is deduced. This ratio appears in fair agreement with that predicted by the molecular-mechanics approach, viz. 60 : 40.

1,2-Diacetoxy-4-Alkyl-3-Methylcyclopentanes

The proton NMR spectral parameters of isomeric 1,2-diacetoxy-4-tert-butyl-3-methyl cyclopentanes (**2b, 3**) and 1,2-diacetoxy-1,3-dimethyl cyclopentanes (**2a, 4, 5**) were reported by Hanselaer and De Clerq[24] (scheme 3). In the pseudorotation analysis the torsion angle opposite to the C_1 atom was chosen as the reference angle ϕ_0. The parameters in eq. (4) were chosen in correspondence with the trigonal projection symmetry approximation.

During the pseudorotation analysis it was noted that a strong correlation exists between the puckering amplitudes $\Phi_{m\,\mathrm{I}}$ and $\Phi_{m\,\mathrm{II}}$ and they cannot be obtained independently. Therefore one (or two) puckering amplitude(s) was (were) constained to assume a constant value in a number of calculations. In a series of calculations the puckering amplitude of the less abundant conformer—being the most ill-defined parameter—was constrained to assume a constant value (48°, 50°, or 52°). For compound **2a** and **3** both conformers are (almost) equally populated; in these cases both puckering amplitudes were constrained. The results are given in Table V. On the whole, the constraints on Φ_m have a marginal influence both on geometry and mol fraction. In most cases the iterations with $\Phi_m = 50°$ gave the smallest rms deviations, but the differences in rms values are minor, and one must conclude that the range $\Phi_m = 50 \pm 2°$ is acceptable. For three compounds (**2a, 2b, 5**) NMR data are available for two solvents, benzene and carbon tetrachloride. Our analysis shows that the solution conformations are identical in these solvents.

Comparison of the results of **2a** and **2b** reveals that replacement of a methylgroup by a tert-butylgroup not only has a large influence on the population of type I and type II conformers but also gives rise to a large shift of approximately 75° in the phase angle of the type I conformer. A corresponding phase shift is found in force-field calculations. For these calculations Allinger's MM1 field[25] was used; the acetoxy groups were replaced by hydroxyl groups. The results of the force-field calculations are presented in Table VI.

In the type I conformer of **2a** the methyl group occupies a pseudoequatorial position; in the type I conformer of **2b** the tert-butyl group is nearly

Table V. Geometry and conformational distribution of the compounds 2–5 deduced from NMR coupling constants.[24]

Compound	Solvent	P_I	Φ_I	P_{II}	Φ_{II}	X_{II}	rms (Hz)
2a	CCl_4	13.9	48*	297.9	48*	0.51	0.48
		12.8	50*	297.0	50*	0.51	0.42
		11.1	52*	295.8	52*	0.50	0.40
2a	benzene	13.6	48*	301.3	48*	0.53	0.59
		12.9	50*	300.5	50*	0.53	0.55
		11.6	52*	299.6	52*	0.53	0.55
2b	CCl_4	87.0	52.6	330.6	48*	0.28	0.35
		86.5	51.8	328.8	50*	0.28	0.35
		86.0	51.2	327.3	52*	0.27	0.35
2b	benzene	86.4	51.3	329.4	48*	0.31	0.32
		85.9	50.5	328.0	50*	0.30	0.32
		85.4	49.8	326.6	52*	0.29	0.32
3	CCl_4	80.9	48*	316.3	48*	0.46	0.24
		83.7	50*	318.2	50*	0.46	0.20
		86.2	52*	320.0	52*	0.46	0.22
4	benzene	53.2	48*	311.5	48.5	0.85	0.20
		54.8	50*	311.7	48.2	0.86	0.20
		55.9	52*	311.9	47.9	0.86	0.20
5	CCl_4	101.6	44.2	188.3	48*	0.25	0.24
		102.2	43.6	189.9	50*	0.24	0.24
		103.0	43.1	191.7	52*	0.22	0.25
5	benzene	98.7	45.3	180.1	48*	0.25	0.30
		99.4	44.8	181.9	50*	0.23	0.30
		99.9	44.3	183.0	52*	0.22	0.30

[a] Constrained value (see text).

Table VI. Pseudorotation parameters of 2 and 5,[a] calculated with molecular mechanics.[b]

Compound	P_I	Φ_I	P_{II}	Φ_{II}	E^b
2a	5.5	41.2	305.1	41.5	0.08
2b	98.9	43.2	280.0	40.9	0.10
5	90.3	42.8	200.7	42.3	0.35

[a] OAc groups replaced by OH.
[b] Allinger's MM1 field (ref. 25).
[c] Relative energy of type II conformer with respect to type I conformer (kcal/mol).

eclipsed with the C_3 proton. In **2b** the type I conformer is calculated, from NMR couplings constants and from molecular mechanics, to be more populated than the type II conformer in which the tert-butyl groups occupies a pseudoequatorial position. If the methyl- and tert-butyl substituents are in a near staggered conformation, the nonbonded distance between some of the tert-butyl protons and the methyl protons becomes small (<2.5 Å), and this will give rise to large steric interactions. The hydrogen–hydrogen nonbonded distances are enlarged by a shift of the phase angle from 12° to 85°. In the type II conformer of **2b** the nonbonded distances are still relatively small, which fact explains why this conformer is less populated than the type I conformer. However, in **3**, which has nearly the same pseudorotation parameters as **2b**, the type II conformer is more populated in comparison with **2b**. The driving force behind this shift in mol fraction is presumably to be sought in the gauche effect, i.e. an anomalous preference for gauche over anti geom-

etry in *X*—*C*—*C*—*Y* fragments in which *X* and *Y* represent highly electronegative substituents (*X*, *Y* = N, O, Cl, F).[26] In **3** the O—C_1—C_2—O torsion angle is −170° and −84° in type I and II, respectively: The type II conformer is stabilized with respect to the type I conformer due to a favorable gauche O—C—C—O situation. In **2b** the O—C_1—C_2—O torsion angles are −50° and 36° for type I and II, respectively, and the gauche stabilization in both conformers will be approximately equal.

Isomer **4** has virtually the same type II conformer as **2a**. Once again the phase angle of the type I conformer is shifted to a larger value. In a ${}^3_4T$ conformation ($P = 0°$) there are two large 1–3 interactions between the proton on C_4 and the two acetoxy substituents; in order to release this strain, the cyclopentane ring will pseudorotate to $P = 54°$ (${}_4E$) in which the C_4 substituent occupies a pseudoequatorial position.

In isomer **5** the ${}^3_4T$ conformation is disfavored on the same grounds, a shift to an ${}_4E$ conformation now introduces an 1–3 interaction between the C_3-methyl substituent and $H_{5'}$ (cis to 4-Me) and a further pseudorotation will occur. In the type II conformer the interactions between the two methyl groups are minimized. With the aid of molecular mechanics a corresponding shift in pseudorotation parameters is calculated (see Table VI).

Methylcyclopentane

The complete NMR spectral analysis for two specifically deuterated methylcyclopentanes at three temperatures has been published by Lipnick.[27] In the PSEUROT analysis of this compound no acceptable mathematical solution could be found: The residual rms deviation did not drop below 1.2 Hz. The reason for this apparent failure appears to be a breakdown of the two-state conformational equilibrium model. Force-field calculations carried out for the full pseudorotation itinerary with use of the Ermer field[23] predict the existence of two minima. These minima correspond to envelope forms with C_1 at the flap and the methyl group occupying pseudoequatorial and pseudoaxial positions, respectively. The difference is strain energies between the stable conformers is calculated to be 0.51 kcal/mol. These minima are separated by an energy barrier of only 0.81 kcal/mol. Such a low barrier implies that even at the lowest temperature at which measurements were carried out (−100°C) the ring is subject to large-amplitude pseudorotational motions. In this case a more sophisticated model is called for, which model should include the shape of the potential energy curve associated with pseudorotation of methylcyclopentane. Such an approach appears quite feasible (F. A. A. M. de Leeuw and C. Altona, unpublished) but will not be discussed in the present paper. Further applications of the program PSEUROT to the conformational analysis of sugar rings can be found in refs. 12, 17–22.

CONCLUSIONS

The application of the generalized Karplus equation, combined with the pseudorotation model of the five-membered ring, was shown earlier to yield a quantitative picture of the solution conformations of heterocyclic five-membered rings. It is now demonstrated that the same method can be applied to cyclopentane derivatives provided that the carbocyclic ring is involved in a two-state equilibrium. If the ring is involved in a three-state or higher-state equilibrium or pseudolibrates, the procedure must be employed with caution.

In the case of the diacetoxy compounds **2b** and **3**, it is again demonstrated that a tert-butyl group is not able to block the cyclopentane ring in one single conformation.[28] In replacing a methyl group by a tert-butyl group one must consider that, besides a shift of the equilibrium, changes in geometry may occur. The optimized values of the pseudorotation parameters must not be seen as the exact values but rather as centers of an acceptable (small) range.

We wish to thank A. J. Hartel for his support in writing the program and G. M. Visser for his valuable contributions during this research.

References

1. C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, **36**, 2783 (1980).
2. M. L. Huggins, *J. Am. Chem. Soc.*, **75**, 4123 (1953).
3. H. J. Geise, C. Altona, and C. Romers, *Tetrahedron Lett.*, 1383 (1967).
4. C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, **24**, 13 (1968).
5. C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **95**, 2333 (1973).
6. C. Altona and M. Sundaralingam, *J. Am. Chem. Soc.*, **94**, 8205 (1972).
7. H. P. M. de Leeuw, C. A. G. Haasnoot, and C. Altona, *Isr. J. Chem.*, **20**, 108 (1980).
8. C. A. G. Haasnoot, F. A. A. M. de Leeuw, H. P. M. de Leeuw, and C. Altona, *Biopolymers*, **20**, 1211 (1981).
9. K. S. Pitzer and W. F. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1957).

10. C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85,** 973, 983 (1966); H. R. Buys, C. Altona, and E. Havinga, *ibid*, **85,** 998 (1966).
11. C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3601 (1965).
12. C. S. M. Olsthoorn, J. Doornbos, H. P. M. de Leeuw, and C. Altona, *Eur. J. Biochem.*, **125,** 367 (1982).
13. H. Kessler, W. Bermel, A. Friedrich, G. Krack, and W. E. Hull, *J. Am. Chem. Soc.*, **104,** 6297 (1982); H. Kessler, A. Friedrich, and W. E. Hull, *J. Org. Chem.*, **46,** 3892 (1981).
14. J. L. Marshall, S. R. Walter, M. Barfield, A. P. Marchand, N. W. Marchand, and A. L. Segre, *Tetrahedron*, **32,** 537 (1976).
15. F. A. A. M. de Leeuw, A. A. van Beuzekom, and C. Altona, *J. Comp. Chem.*, **4,** 438 (1983).
16. S. Castellano, *J. Magn. Reson.*, **21,** 143 (1976).
17. C. S. M. Olsthoorn, L. J. Bostelaar, J. H. van Boom, and C. Altona, *Eur. J. Biochem.*, **112,** 95 (1980).
18. J. R. Mellema, C. A. G. Haasnoot, J. H. van Boom, and C. Altona, *Biochim. Biophys. Acta*, **655,** 256 (1981).
19. A. J. Hartel, G. Wille-Hazeleger, J. H. van Boom, and C. Altona, *Nucleic Acid Res.*, **9,** 1405 (1981).
20. C. A. G. Haasnoot, F. A. A. M. de Leeuw, H. P. M. de Leeuw, and C. Altona, *Org. Magn. Reson.*, **15,** 43 (1981).
21. J. Doornbos, J. A. J. den Hartog, J. H. van Boom, and C. Altona, *Eur. J. Biochem.*, **116,** 403 (1981).
22. F. A. A. M. de Leeuw and C. Altona, *J. Chem. Soc. Perkin Trans. 2*, 375 (1982).
23. O. Ermer and S. Lifson, *J. Am. Chem. Soc.*, **95,** 4121 (1973).
24. R. Hanselaer and P. De Clerq, *Org. Magn. Reson.*, **13,** 376 (1980).
25. N. L. Allinger, *Adv. Phys. Org. Chem.*, **13,** 1 (1976).
26. S. Wolfe, *Acc. Chem. Res.*, **5,** 102 (1972); B. Fuchs and A. Ellencweig, *J. Org. Chem.*, **44,** 2274 (1979); N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, **34,** 2953 (1978).
27. R. L. Lipnick, *J. Am. Chem. Soc.*, **96,** 2941 (1974).
28. See, for example, R. J. Abraham, H. A. Bergen, and D. J. Chadwick, *Tetrahedron Lett.*, **22,** 2807 (1981).