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CONFORMATIONAL ANALYSIS OF DISUBSTITUTED SIDE - CHAIN OF VITAMIN D_3 ANALOGS: MOLECULAR MODELING AND SEMIEMPIRICAL CALCULATIONS

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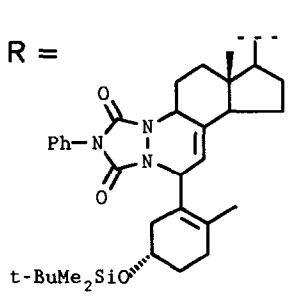
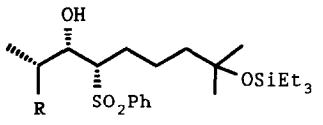
Abstract: The least-energy conformers were determined for side-chain disubstituted analogs of vitamin D_3 by molecular mechanics modeling and semiempirical calculations based on a generalized Karplus equation.

The recently discovered immunosuppressive activity of some vitamin D analogs with an "unnatural" geometry of the side chain[1] gave another impulse to undertake conformational analysis of this part of the vitamin D molecule. The analyses performed by now were limited to the cholesterol-type unsubstituted side chain[2]. Recent studies[3] revealed, however, that side-chain substituted analogues might represent a class of analogues with highly specific activity profile. It was, therefore, a need to develop the conformational analysis of this class of compounds. For this purpose we selected a set of diastereomeric ß-hydroxysulfones **1** - **4** as model compounds[4] for which both crystallographic data of vitamin D nucleus[5] and coupling constants for side-chain protons[6] were available.





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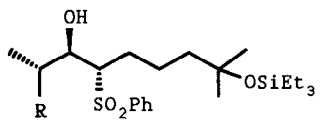

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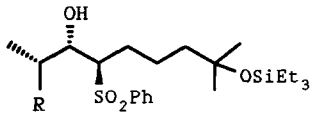

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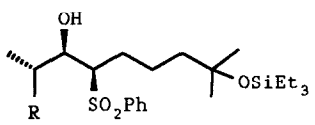

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In order to determine the conformation of the side-chain part of compounds **1** - **4** we developed the methodology comprising molecular modeling[7] and semiempirical calculations based on the generalized Karplus equation[8]. The starting coordinates for the vitamin D nucleus of compounds **1** - **4** were taken from X-ray crystal structure[5] of the Diels-Alder adduct of 4-phenyl-1,2,4-triazoline-3,5-dione with the side-chain unsubstituted previtamin D_3. To this basic structure the respective side-chains of compounds **1** - **4** were attached and the resulting molecules were subjected to the energy minimization procedure. A systematic search was conducted for the conformation that corresponds to the minimum value of the total energy of the molecule, calculated by MMX force field in a standard molecular mechanics program[9]. Of a number of rotatable bonds in compounds examined only three bonds and the respective dihedral angles were taken into account as a first approximation. These included C4-C5-C6- C7 angle between A-ring and a relatively rigid tetrahydropyridazine moiety, C16-C17-C20-C22 angle between D-ring and the side chain, and an angle in the side-chain (H-C22-C23-H) for which the experimental vicinal coupling constants were available[6]. Successive non-rigid rotations around the selected bonds were carried out and several minimum energy conformations were identified. The population of the conformer was calculated from the following equation:

$$N_i/N_{st} = \exp(-\Delta E/RT)$$

where: ΔE is the difference of energy between a given conformer and the most stable one at $T = 300$ K and N_i/N_{st} is the respective molar ratio. The percentage population of a given conformer was calculated as follows:

$$P_i = \frac{N_i/N_{st}}{\Sigma\, N_i/N_{st}} * 100$$

and it is given for the least-energy conformers of compound **4** in Table I.

The vicinal coupling constants $J_{22,23}$ for compounds **1** - **4** were calculated on the basis of the generalized Karplus equation[8]. Electronegativity effects of both α and ß substituents of C-22 and C- 23 carbons were included. Torsion angle H-C22-C23-H for each conformer was taken from the energy minimization procedure. The Karplus equation was obtained for each compound and it was shown for **4** in a graphic form in Figure 1. The values of calculated coupling constant for the least energy conformers of compound **4** are given in Table I.

The average coupling constant for each compound was calculated as follows:

$$J_{calcd} = \Sigma\, (P_i * J_i)/100$$

where P_i is defined above and J_i represents the vicinal coupling constant H-C22-C23-H of a given conformer. The calculated $J_{22,23}$ for **4** was 8.8 ± 0.4 Hz, while the experimental data was 10 ± 1 Hz. The stick model of 3D structure of the least-energy conformer 1 of compound **4** is shown in Fig. 2. Preliminary calculations indicate also a good correlation for other compounds (**1** - **3**) from the set examined. This

correlation might be considered as a partial validation of the conformation generated by this methodology for side-chain substituted analogs.

The use of the present conformational analysis for the selection of side-chain substituted vitamin D_3 analogs to be synthesized is under way in these laboratories.

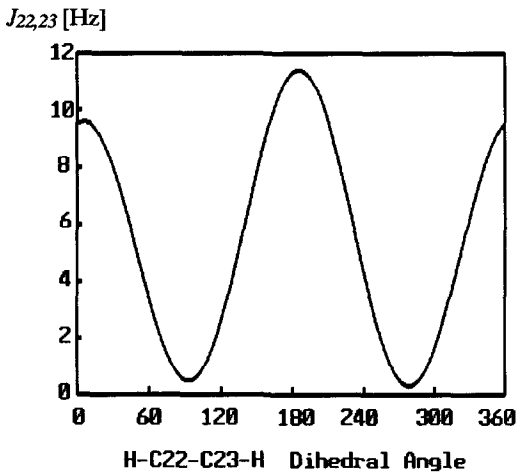

Fig. 1. Graphic presentation of the generalized Karplus equation for compound **4**

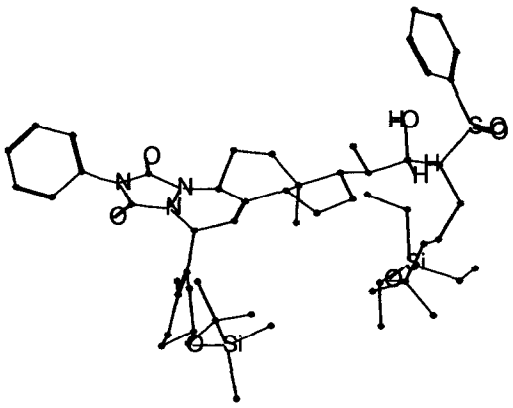

Fig. 2. Stick model of the least- energy conformer of compound **4**

Table I. Least-energy conformers of ß-hydroxysulfone **4**

Conformer	1	2	3	4
Dihedral angle [°]:				
C4-C5-C6-C7	66.0	49.9	61.8	61.7
C16-C17-C20-C22	56.8	303.4	174.9	304.2
H-C22-C23-H	213.6	245.3	204.0	66.4
E [kJ/mol]	308.8	317.1	328.9	330.5
Δ E [kJ/mol]	0	8.3	20.1	21.7
Pi [%]	96.6	3.4	0.03	0.02
Ji [Hz]	9.0	3.4	10.3	2.4

Acknowledgment

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References and Notes

1. Binderup, L.; Latini, S.; Binderup, C.; Calverley, M.; Hansen, K. *Biochem. Pharmacol.* **1991**, *42*, 1569.

2. a) Wilson, S. R.; Guarnieri, F. *Proceedings of the Eight Workshop on Vitamin D*, Bouillon, R.; Norman, A. W.; Thomasset, M., Eds, Walter de Gruyter, Berlin, 1991, pp. 186-187.
b) Hofer, O.; Kahlig, H.; Reischl, W. ibid, pp. 190-191.
c) Okamura, W. H.; Palenzuela, A.; Plumet, J.; Midland, M. M. *J. Cell. Biochem.* **1992**,*49*, 10.

3. a) Chodyński, M.; Kutner, A. *Steroids* **1991**, *56*, 311. b) Kutner, A. *Pol. J. Chem.* **1993**, *67*, 1. Activity data of analogs described in these papers will be disclosed elsewhere.

4. Compounds **1 - 4** were obtained as key intermediates in our novel concurrent method of the synthesis of both series of vitamins D_2 and D_3. Kutner, A.; Chodyński, M.; Halkes, S. J.; Brugman, *J. Bioorg. Chem.* **1992**, *20*, in press.

5. Van Meersche, M.; Tinaut, B.; Germain, G.; Declercq, J.P.; Vanmaele, J.L. *Bull. Soc. Chim. Belg.* **1982**, *91*, 205.

6. ^{1}H NMR ($CDCl_3$). **1**: δ 0.77 (3H, s, 18-CH_3), 0.94 (3H, d J = 6.5 Hz, 21-CH_3), 1.02, 1.11 (3H, s, 26,27-CH_3), 1.77 (3H, s, 19-CH_3), 2.55 (1H, m, 14-H), 2.79 (1H, d J = 2 Hz, 22-OH), 2.93 (1H, d $J_{22,23}$ = 1Hz, 23-H), 3.13 (1H, m, 11-H), 3.73 (1H, m, 3-H), 4.31 (1H, m, 22-H), 4.44 (1H, d J = 12 Hz, 9-H), 5.16 (1H, m, 7-H), 5.30 (1H, m, 6-H).
2: δ 0.81 (3H, s, 18-CH_3), 1.06 (3H,d J = 6.5 Hz, 21-CH_3), 1.11, 1.12 (3H, s, 26,27-CH_3), 1.77 (3H, s, 19-CH_3), 2.58 (1H, m, 14-H), 3.15 (1H, m, 11-H), 3.33 (1H, m, $J_{22,23}$ = 6Hz, 23-H), 3.56 (1H, d J = 6 Hz, 22-OH), 3.76 (1H, m, 3-H), 3.85 (1H, m, 22-H), 4.45 (1H, d J = 12.4 Hz, 9-H), 5.18 (1H, m, 7-H), 5.30 (1H, m, 6-H).
3: δ 0.73 (3H, s, 18-CH_3), 0.94 (3H, d J = 6.5 Hz, 21-CH_3), 1.05, 1.09 (3H, s, 26,27-CH_3), 1.77 (3H, s, 19-CH_3), 2.14 (1H, d J = 2Hz, 22-OH), 2.63 (1H, m, 14-H), 2.94 (1H, m, $J_{22,23}$ = 3Hz, 23-H), 3.13 (1H, m, 11- H), 3.75 (1H, m, 3-H), 4.30 (1H, m, 22-H), 4.44 (1H, d J = 12 Hz, 9-H), 5.18 (1H, m, 7-H), 5.30 (1H, m, 6-H).
4: δ 0.77 (3H,s,18-CH_3), 0.94 (3H, d J = 6.5 Hz, 21-CH_3), 1.09, 1.12 (3H, s, 26,27-CH_3), 1.77 (3H, s, 19-CH_3), 2.68 (1H, m, 14-H), 3.15 (1H, m, 11-H), 3.18 (1H, m, $J_{22,23}$ = 10Hz, 23-H), 3.74 (1H, m, 3-H), 4.16 (1H, d J = 8.9Hz, 22-H), 4.47 (1H, d J = 10.6 Hz, 9-H), 5.18 (1H, m, 7-H), 5.30 (1H, m, 6-H).

7. The modeling procedure followed the methods outlined in *Computer Modeling of Carbohydrate Molecules;* French, A. D.; Brady, J. W. Eds; American Chemical Society: Washington, 1990. The description was made according to the guidelines for publications in molecular modeling related to medicinal chemistry.
a) Gund, P.; Barry, D. C.; Blaney, J. M.; Cohen, N. C. *J. Med. Chem.* **1988**, *31*, 2230.
b) Cohen, N. C.; Blaney, J. M.; Humblet, C.; Gund, P.; Barry, D. C. *J. Med. Chem.* **1990**, *33*, 883.
c) also cf. Martin, Y. C. *J. Med. Chem.* **1992**, *35*, 2145.

8. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

9. Serena Software, P.O.Box 307, Bloomington, IN 47402-3076. The option with a dielectric constant of the medium was used ($CDCl_3$, 4.7).