Calcd for $C_{34}H_{35}O_7P$: C, 69.61; H, 6.01. Found: C, 69.87; H, 6.03.

Methyl (2*R*,2′*S*,3′a*R*,6′*S*,7′a*R*,4″*S*,5″*S*)-4″-[(*E*)-cinnamoyloxy]decahydro-5″-methyldispiro[oxirane-2,3′-(2′*H*)-benzofuran-2′,2″-[2*H*]pyran]-6′-carboxylate [(+)-Phyllanthocin, 1a]. To a solution of 32.6 mg (0.104 mmol) of the alcohol **17** and 63.8 mg (0.522 mmol) of 4-(dimethylamino)-pyridine in 1.0 mL of CH_2Cl_2 was added 50 μL of freshly distilled *trans*-cinnamoyl chloride. The resulting suspension was heated at reflux (bath temperature: 54 °C) for 19 h. The reaction was quenched with the addition of 10 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 2 × 60 mL of ether. These extracts were then washed with 15 mL each of H_2O, saturated $CuSO_4$, and H_2O, dried over $MgSO_4$, and concentrated to a brown oil. Flash chromatography on 30 g of 230–400-mesh silica gel (elution with 1:1 ether–hexanes) afforded 37.8 mg (82%) of (+)-phyllanthocin (**1a**) as pale yellow crystals. Recrystallization from ether–hexanes afforded colorless prisms: mp 129–129.5 °C; R_f 0.39 (2:1 ether–hexanes); $[\alpha]^{25}_D$ +27.2° (*c* 2.04, $CHCl_3$); IR ($CHCl_3$) 3012, 2955, 2940, 2885, 1728, 1704, 1640, 1579, 1498, 1450, 1437, 1387, 1372, 1344, 1328, 1308, 1278, 1254, 1232, 1201, 1173, 1126, 1111, 1085, 1073, 1051, 1021, 1009, 993, 979, 950, 908, 868, 710, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 1 H, *J* = 15.9 Hz), 7.52–7.50 (m, 2 H), 7.39–7.33 (m, 3 H), 6.46 (d, 1 H, *J* = 15.9 Hz), 5.06 (br q, 1 H, *J* = 2.8 Hz), 4.36 (q, 1 H, *J* = 3.4 Hz), 3.99 (t, 1 H, *J* = 11.5 Hz), 3.42 (dd, 1 H, *J* = 4.0, 11.2 Hz), 3.25 (s, 3 H), 2.92 (AB q, 2 H, J_{AB} = 5.4 Hz, $\Delta\nu_{AB}$ = 19.8 Hz), 2.39 (tt, 1 H, *J* = 3.5, 12.0 Hz), 2.20 (br d, 1 H, *J* = 14.8 Hz), 2.02 (dd, 1 H, *J* = 2.9, 15.2 Hz), 1.95–1.83 (m, 3 H), 1.73–1.55 (m, 2 H), 1.61 (dd, 1 H, *J* = 3.2, 15.2 Hz), 1.40–1.16 (m, 2 H), 0.85 (d, 3 H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 176.02, 166.58, 144.38, 134.65, 129.92, 128.71, 127.96, 118.93, 101.96, 72.61, 71.05, 69.79, 62.95, 51.12, 50.13, 38.58, 36.81, 34.32, 33.06, 29.90, 26.47, 22.16, 12.71; MS (14 eV) parent peak 442, base peak 182.[35] Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 67.72; H, 6.90.

Acknowledgment. We gratefully acknowledge the National Institutes of Health, the National Science Foundation, and the Alfred P. Sloan Foundation for generous financial support. High-field NMR spectra were obtained through the NSF Regional NMR Center at the University of South Carolina (CHE 82-07445).

Registry No. **1a**, 62948-37-2; **2**, 97860-62-3; **4** (R″ = TBS), 97826-89-6; (±)-**6c**, 97826-90-9; (±)-**6t**, 97826-97-6; (±)-**7**, 97826-91-0; (±)-**7** (acetate), 124603-86-7; (±)-*trans*-**7** (acetate), 124603-87-8; **8**, 97826-92-1; **8** (alcohol), 97826-98-7; **8** (*t*-BuO⁻ ring-opened diol), 124603-88-9; **9**, 97826-88-5; **9** (alcohol, isomer 1), 124603-89-0; **9** (alcohol, isomer 2), 124649-52-1; **10a**, 97905-63-0; **10a** (5,10-diol), 124603-90-3; **10a** (5,10,12-triol), 124603-91-4; **10b**, 97826-93-2; **10b** (5,10-diol), 124649-54-3; **11**, 124649-53-2; **12**, 124649-55-4; **13**, 124603-92-5; **14**, 97827-00-4; **15**, 124603-94-7; **15** (X = α-OH, β-H), 124649-56-5; **15** (X = α-H, β-OH), 124603-93-6; **15** (X = (*E*)-CHOMe), 124603-95-8; **15** (X = (*Z*)-CHOMe), 124649-57-6; **16a**, 124649-58-7; **16b**, 124603-96-9; **17**, 82167-85-9; **17** (TBS ether), 97827-01-5; **18a**, 97826-95-4; **18b**, 97905-64-1; **19**, 124603-97-0; **23**, 111692-59-2; **24**, 124603-99-2; **25**, 111675-18-4; **26**, 111767-82-9; **27**, 111692-60-5; **28a**, 111675-15-1; **28d**, 111767-81-8; **29**, 124649-59-8; **30**, 124603-98-1; *p*-$MeOC_6H_4CH_2OH$, 105-13-5; (*Z*)-$ClCH_2CH{=}CHCH_2Cl$, 1476-11-5; (*E*)-$CH_2{=}CHCH{=}CHOMPM$, 124603-84-5; (*Z*)-$CH_2{=}CHCH{=}CHOMPM$, 124603-85-6; $CH_2{=}CHCOCH_2OAc$, 38982-28-4; $Ph_3PMe^+Br^-$, 1779-49-3; (*R*)-$HOCH_2CH(Me)CO_2Me$, 72657-23-9; (*R*)-$TBSOCH_2CH(Me)CO_2Me$, 105859-44-7; (*S*)-$TBSOCH_2CH(Me)CH_2OH$, 105859-45-8; Ph_2PCH_2OMe, 43139-94-2; *p*-$Ph_2PC_6H_4CO_2H$, 2129-31-9; (*E*)-PhCH=CHCOCl, 17082-09-6; *m*-$Ph_2PC_6H_4CO_2H$, 2129-30-8.

Conformation Dynamics of 1,2-Dimethylenecyclohexane: A Model for Ring-A Mobility in Vitamins D

Hans-Jörg Hofmann*

Sektion Biowissenschaften of the Karl Marx University Leipzig, Talstrasse 33, DDR-7010 Leipzig, German Democratic Republic

Renzo Cimiraglia*

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56100 Pisa, Italy

Received July 17, 1989

The conformation dynamics of 1,2-dimethylenecyclohexane was examined by means of ab initio MO theory employing the STO-3G and 3-21G basis sets. The calculations show that the most economic mode of chair–chair interconversion begins with inversion of twist angles in the diene part of the chairlike minimum conformation and proceeds via pseudorotation and reinversion to the alternate chair. The results are discussed in relation to the ring A structure and mobility of vitamins D.

Introduction

The combination of a cyclohexane ring with an exocyclic diene system in the 1,2-dimethylenecyclohexane molecule **1** leads to questions about the conformational structure of this compound. On the one hand, the cyclohexane ring prefers the chair conformation, and on the other hand, the *s-cis*-diene tends to a planar orientation with most conjugation. Thus, competition between these two contrary structure aspects could be expected. Whereas the introduction of one exocyclic double bond into the cyclohexane ring leaves the chair conformation principally unchanged, e.g. exomethylenecyclohexane,[1,2] cyclohexanone,[2–5] the formation on an endocyclic double bond transforms the chair into a half-chair as minimum conformation, e.g. cyclohexene.[1–4,6]

Experimental structure data available from indirect methods (PE, UV, NMR spectroscopy) support the maintenance of the chair conformation in **1**.[7] Thus, tor-

(1) (a) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773. (b) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734.

(2) Eliel, E. L.; Allinger, N. L.; Angyal, S. A.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1965; p 111.

(3) Bucourt, R. *Top. Stereochem.* **1974**, *8*, 159.

(4) Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1.

(5) (a) Bucourt, R.; Hainaut, D. *Bull. Soc. Chim. Fr.* **1967**, 4562. (b) Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173. (c) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1969**, *91*, 337. (d) Allinger, N. L.; Allinger, J.; DaRooge, M. A. *J. Am. Chem. Soc.* **1964**, *86*, 4061.

(6) (a) Bucourt, R.; Hainaut, D. *Bull. Soc. Chim. Fr.* **1965**, 1366. (b) Favini, G.; Buemi, G.; Raimondi, M. *J. Mol. Struct.* **1968**, *2*, 137.

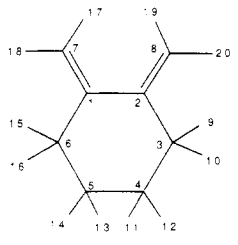
0022-3263/90/1955-2151$02.50/0

Table I. STO-3G and 3-21G Optimized Geometries for the Chair Conformation of 1[a,b]

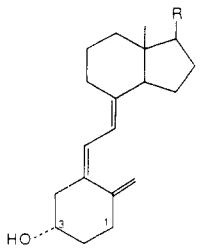
bond lengths[c,d]		bond angles[c,d]		torsion angles[c,d]	
C(1)C(2)	1.511/1.491	C(1)C(2)C(3)	115.1/114.0	C(1)C(2)C(3)C(4)	47.0/51.9
C(2)C(3)	1.532/1.519	C(2)C(3)C(4)	111.8/110.6	C(2)C(3)C(4)C(5)	-54.3/-55.7
C(3)C(4)	1.545/1.545	C(3)C(4)C(5)	110.9/110.4	C(3)C(4)C(5)C(6)	58.6/58.4
C(4)C(5)	1.542/1.540	C(2)C(1)C(7)	122.5/122.6	C(3)C(2)C(1)C(6)	-43.9/-50.8
C(1)C(7)	1.314/1.319	C(2)C(3)H(9)	109.9/110.2	C(7)C(1)C(2)C(8)	-43.7/-53.1
C(3)H(9)	1.087/1.084	C(2)C(3)H(10)	108.8/108.7	C(1)C(2)C(3)H(9)	169.7/174.4
C(3)H(10)	1.091/1.087	C(3)C(4)H(11)	109.5/109.7	C(1)C(2)C(3)H(10)	-73.0/-67.3
C(4)H(11)	1.088/1.085	C(3)C(4)H(12)	109.6/109.2	C(2)C(3)C(4)H(11)	-175.7/-177.3
C(4)H(12)	1.088/1.085	C(1)C(7)H(17)	122.1/121.6	C(2)C(3)C(4)H(12)	66.6/64.7
C(7)H(17)	1.081/1.073	C(1)C(7)H(18)	121.9/121.6	C(2)C(1)C(7)H(17)	-0.3/-0.6
C(7)H(18)	1.081/1.074			C(2)C(1)C(7)H(18)	180.0/-179.9

[a] Structure formula 1. [b] E_T(STO-3G) = -306.202133 au; E_T(3-21G) = -308.184121 au. [c] Bond lengths in angstroms, angles in degrees. C_2 chair symmetry gives the missing geometry parameters. [d] STO-3G/3-21G values.

sion angles of approximately 55° and about 60° were estimated for the diene system of 1 by means of NMR and PE spectroscopy,[7e,f] respectively. The chair conformation of 1 was also subject of complete geometry optimization with Allinger's force field[8a] and the semiempirical MINDO/3[8b,c] and MNDO[8c] MO methods.



1



2

The interest in the conformational aspects of 1 may be increased when considering that this molecule is an essential structure element of vitamins D 2 mimicking the ring A and part of the cleaved ring B there. All X-ray examinations on vitamin D derivatives are in favor of an approximate chair arrangement of ring A.[9] Numerous NMR studies[10] confirm Havinga's suggestion[11] of a dynamic equilibrium between the α and β chair conformations of this ring. Ring A conformational mobility of vitamin D derivatives is of interest in connection with the biological activity of these compounds since it was postulated that in hormonally active 1α,25-dihydroxyvitamin D_3 only the conformation having OH at C(1) in an equatorial orientation has the proper geometry for binding to the receptor.[10b-d,12] Theoretical calculations[13] show that the *s-cis*-diene system in the *trans-Z-cis*-hexatriene molecule, which is part of 2, is twisted by about 50°, in close correspondence, therefore, to a torsion angle expected and experimentally suggested for the diene system of 1 when the cyclohexane chair is approximately retained. The calculations[13a] predict facile rotation of the approximately planar transoid diene system in the *tZc*-hexatriene. Thus, ring A inversion should not essentially be influenced by the rest of the molecule, and 1 may be considered as a good model for the study of the ring A mobility in vitamins D. In this way, reference data could be obtained for the synthesis of vitamin D derivatives with an optimum biological conformation.

In order to characterize the special structural features of 1, we have performed a theoretical conformational analysis comprising the determination of the structure and the description of the dynamic processes of ring inversion and pseudorotation. The chair geometries obtained by means of the above-mentioned semiempirical MO methods indicate a considerable flattening of the ring. This artefact is well documented for cyclohexane rings.[14] Thus, these methods do not appear to be appropriate for the examination of the conformational aspects in 1. Therefore, we employed ab initio MO theory in our studies. Contrary to the well-introduced and successful molecular mechanics,[2,4,15] which also provides a very reasonable chair geometry for 1,[8a] ab initio data for dynamic conformational

(7) (a) Blomquist, A. T.; Longone, D. T. *J. Am. Chem. Soc.* **1957**, *79*, 3916. (b) Bailey, W. J.; Golden, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 4780. (c) Bailey, W. J.; Lawson, W. B. *J. Am. Chem. Soc.* **1957**, *79*, 1444. (d) Henri, V.; Pickett, L. W. *J. Chem. Phys.* **1939**, *7*, 439. (e) Asmus, P.; Klessinger, M. *Tetrahedron* **1974**, *30*, 2477. (f) Pfeffer, H. U.; Klessinger, M. *Org. Magn. Reson.* **1977**, *9*, 121. (g) Huebers, R.; Klessinger, M. *Magn. Reson. Chem.* **1986**, *24*, 1016. (h) Hemmersbach, P.; Klessinger, M.; Bruckmann, P. *J. Am. Chem. Soc.* **1978**, *100*, 6344. (i) Bates, R. B.; Gordon, B.; Highsmith, T. K.; White, J. J. *J. Org. Chem.* **1984**, *49*, 2981.

(8) (a) Pfeffer, H. U.; Klessinger, M. *Chem. Ber.* **1979**, *112*, 890. (b) Scharf, H. D.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* **1979**, *112*, 862. (c) Bartzsch, C., personal communication.

(9) (a) Hodgkin, D. C.; Rimmer, B. M.; Dunitz, J. D.; Trueblood, K. N. *J. Chem. Soc.* **1963**, 4945. (b) Knobler, C.; Romers, C.; Braun, P. B.; Hornstra, J. *Acta Crystallogr., Sect. B* **1972**, *28*, 2097. (c) Trinh-Toan; De Luca, H. F.; Dahl, L. F. *J. Org. Chem.* **1976**, *41*, 3476. (d) Trinh-Toan; Ryan, R. C.; Simon, G. L.; Calabrese, J. C.; Dahl, L. F.; De Luca, H. F. *J. Chem. Soc., Perkin Trans. 2* **1977**, 393. (e) Hull, S. E.; Leban, I.; Main, P.; White, P. S.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1976**, *32*, 2374.

(10) (a) La Mar, G. N.; Budd, D. L. *J. Am. Chem. Soc.* **1974**, *96*, 7317. (b) Wing, R. M.; Okamura, W. H.; Pirio, M. R.; Sine, S. M.; Norman, A. W. *Science* **1974**, *186*, 939. (c) Wing, R. M.; Okamura, W. H.; Rego, A.; Pirio, M. R.; Norman, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 4980. (d) Okamura, W. H.; Hammond, M. L.; Rego, A.; Norman, A. W.; Wing, R. M. *J. Org. Chem.* **1977**, *42*, 2284. (e) Berman, E.; Luz, Z.; Mazur, Y.; Sheves, M. *J. Org. Chem.* **1977**, *42*, 3325. (f) Berman, E.; Friedman, N.; Mazur, Y.; Sheves, M. *J. Am. Chem. Soc.* **1978**, *100*, 5626.

(11) Havinga, E. *Experientia* **1973**, *29*, 1181.

(12) (a) Okamura, W. H.; Norman, A. W.; Wing, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4194. (b) Okamura, W. H.; Mitra, M. N.; Procsal, D. A.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1975**, *65*, 24.

(13) (a) Hofmann, H.-J.; Köhler, H.-J.; Weller, T. *Tetrahedron* **1976**, *32*, 1303. (b) Tai, J. C.; Allinger, N. L. *J. Am. Chem. Soc.* **1976**, *98*, 7928. (c) Mosquera, R. A.; Rios, M. A.; Tovar, C. A. *THEOCHEM* **1988**, *168*, 125.

(14) (a) Iratcabal, P.; Liotard, D.; Grenier-Loustalot, M. F.; Lichanot, A. *THEOCHEM* **1985**, *124*, 51. (b) Todeschini, R.; Pitea, D.; Favini, G. *J. Mol. Struct.* **1981**, *71*, 279. (c) Komornicki, A.; McIver, J. W. *J. Am. Chem. Soc.* **1972**, *95*, 4512. (d) Iratcabal, P.; Liotard, D. *J. Comput. Chem.* **1986**, 7, 482.

(15) (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics, ACS Monograph No. 177*; American Chemical Society: Washington, DC, 1982. (b) Osawa, E.; Musso, H. *Top. Stereochem.* **1982**, *13*, 117. (c) Ermer, O. *Struct. Bonding* **1976**, *27*, 161.

(16) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York 1986.

(17) Peterson, M. R.; Poirier, R. A. *MONSTERGAUSS*; University of Toronto: Toronto, Canada, 1981 (updated version 1987).

(18) Dupuis, M.; Watts, J. D.; Villar, H. O.; Hurst, G. J. B. *HONDO7*; IBM Corporation: Kingston, 1987.

(19) Cerjan, C. J.; Miller, W. H. *J. Chem. Phys.* **1981**, *75*, 2800.

Table II. Comparison of the ab Initio Chair Torsion Angles of 1 with X-ray Data for Some Vitamin D Derivatives[a]

torsion angle[b]	ab initio data		X-ray data				
			ref 9c		ref 9b	ref 9a	ref 9d
	STO-3G	3-21G					
C(1)C(2)C(3)C(4)	47.0	51.9	51.6[c]	−51.2[d]	−55.0[d]	54[c]	51.1[c]
C(2)C(3)C(4)C(5)	−54.3	−55.7	−53.8	51.9	55.1	−57	−54.0
C(3)C(4)C(5)C(6)	58.6	58.4	57.0	−51.2	−53.3	57	53.8
C(4)C(5)C(6)C(1)	−54.3	−55.7	−58.2	48.0	50.8	−52	−51.8
C(5)C(6)C(1)C(2)	47.0	51.9	53.1	−48.3	−49.1	49	50.0
C(6)C(1)C(2)C(3)	−43.9	−50.8	−49.3	50.0	51.6	−49	−49.8
C(7)C(1)C(2)C(8)	−43.7	−53.1	−53.6	55.2	56.3	−61	−56.7

[a] See structure formula 1 and 2. [b] In degrees. [c] α-chair. [d] β-chair.

processes are still relatively scarce in the field alicyclic chemistry.

Results and Discussion

First, the optimum structure of 1 was determined. Geometry optimization based on the STO-3G and 3-21G basis sets provided an approximate chair conformation as the global minimum for this molecule in agreement with experimental findings. Obviously, the competition between maximum conjugation in a planar diene system and a chair arrangement is decided in favor of the latter one. In Table I, complete structure information is given for the optimum conformation. The 3-21G geometry in the nonconjugated molecular part is in rather close correspondence to a cyclohexane ring with twist angles of about 56°.[2-4,14a,20] Contrary to this, a contraction of the dihedral angles within and around the diene system can be observed. The external and internal torsion angles of 53.1° and 50.8° in the diene system are near the experimental estimates. Using Allinger's force field, the diene twist angle is 53.3°. Here, the other ring torsion angles are between 52 and 54°.[8a] The flattening of the ring around the exocyclic diene system is accompanied by an enlargement of the corresponding bond angles and a shortening of the bond lengths at the sp^2-hybridized carbons referred to cyclohexane. The STO-3G results show a somewhat different behavior with a rather correct ring puckering in the nonconjugated molecular part but smaller torsion angles in the diene system. This may be caused by a certain overestimation of conjugation observed in STO-3G calculations on conjugated molecules.[21] Thus, the planar s-cis conformation of butadiene is determined as minimum,[21c] whereas most other ab initio calculations are in favor of a *gauche* conformation as second conformer in butadiene.[21d] This aspect has to be remembered when comparing the structure data of the STO-3G and 3-21G calculations in the discussion of pseudorotation and ring inversion.

In order to demonstrate the close relation to the natural vitamins, a comparison of the ab initio ring torsion angles with corresponding X-ray data for some vitamin D derivatives is performed in Table II. Of course, the C_2 ring symmetry is lost in the vitamins because of the continuation of the molecular system. Especially the 3-21G geometry reflects well the experimentally determined data.

The existence of the chairlike conformation of 1 as the global minimum structure opens the possibility to discuss ring inversion and pseudorotation of this molecule in close correspondence to cyclohexane. For the description of both phenomena, we follow the torsional angle concept in

Scheme I. C_2 Inversion and Pseudorotation in 1

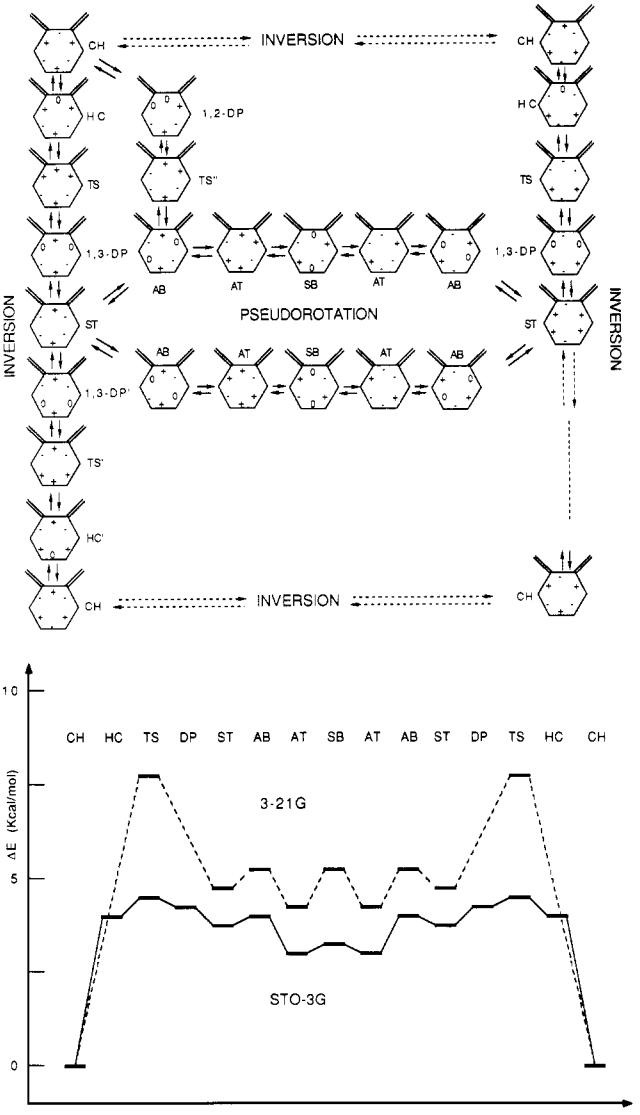


Figure 1. STO-3G and 3-21G energy profiles of C_2 inversion and pseudorotation of 1 (CH = chair; HC = half-chair; TS = transition state; 1,2- and 1,3-DP = 1,2- and 1,3-diplanar; ST, AT = symmetric and asymmetric twist; SB, AB = symmetric and asymmetric boat).

Table III. STO-3G and 3-21G Ring Torsion Angles for the Minimum and Transition-State Conformations Involved in the Pseudorotation of 1[a]

torsion angle[b]	ST[a,c]	AT[a,c]	SB[a,c]	AB[a,c]
C(1)C(2)C(3)C(4)	−12.3/−22.2	−38.5/−32.6	51.1/53.5	−36.7/−43.7
C(2)C(3)C(4)C(5)	−40.0/−37.3	61.2/63.8	−50.4/−52.6	−11.0/−10.3
C(3)C(4)C(5)C(6)	67.8/69.0	−23.2/−29.9	0.0/0.0	57.8/59.8
C(4)C(5)C(6)C(1)	−40.0/−37.3	−34.0/−30.6	50.4/52.6	−57.1/−55.7
C(5)C(6)C(1)C(2)	−12.3/−22.2	57.7/63.6	−51.1/−53.5	9.7/2.4
C(6)C(1)C(2)C(3)	40.2/54.8	−19.4/−29.8	0.0/0.0	37.8/48.7

[a] See Scheme I. [b] In degrees. [c] STO-3G/3-21G values.

(20) Geise, H. J.; Buys, H. R.; Mijlhoff, F. C. *J. Mol. Struct.* **1971**, *9*, 447.
(21) (a) Barone, V.; Lelj, F.; Russo, N. *Int. J. Quantum Chem.* **1986**, *29*, 541. (b) Orti, E.; Sanchez-Marin, J.; Merchan, M.; Tomas, F. *J. Phys. Chem.* **1987**, *91*, 545. (c) Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4786. (d) Breulet, J.; Lee, T. J.; Schaefer, H. F. *J. Am. Chem. Soc.* **1984**, *106*, 6250.

conformational analysis extensively described by Bucourt[3] and illustrated for our purposes in Scheme I.

Compared with cyclohexane, pseudorotation in 1 is somewhat more complex because of the presence of symmetric and asymmetric types of twist and boat conformations. The pseudorotation profiles obtained with the STO-3G and 3-21G basis sets are visualized in Figure 1.

The ring torsion angles of the minimum and transition-state conformations are given in Table III. The minimum structures (critical points of order zero) of the two types of twist forms and the transition-state character (critical points of order one) of the asymmetric and symmetric boat conformations were confirmed by the determination of the matrix of the force constants. The results for both basis sets agree with respect to the small pseudorotation barrier which amounts to 1.1 kcal/mol (3-21G) and 1.2 kcal/mol (STO-3G), respectively. This value is in rather perfect accordance with the estimated data for cyclohexane and comparable derivatives.[2-4]

The asymmetric twist form as most stable conformation in pseudorotation lies 4.3 kcal/mol (3-21G) and 3.0 kcal/mol (STO-3G) above the global chair minimum. The corresponding energy difference in cyclohexane is about 5.0 kcal/mol.[2-4,14a] The asymmetric twist form is preferred to the symmetric one by 0.7 kcal/mol in the 3-21G and by 0.8 kcal/mol in the STO-3G calculations. Whereas the two types of boat forms are of practically the same energy with only a negligible numerical advantage of the asymmetric one according to the 3-21G results, STO-3G favors the symmetric boat arrangement with 0.9 kcal/mol more. Thus, this conformation lies even below the symmetric twist minimum in the STO-3G pseudorotation profile. The corresponding 3-21G profile exhibits both twist conformations as more stable than the boat forms. The somewhat different energetic relations between some conformations according to STO-3G and 3-21G may be due to the above-mentioned overestimation of conjugation by the minimum basis set which would be in favor of the symmetric boat form.

During the process of chair–chair interconversion, all ring torsion angles change their signs passing through the value zero. An upper limit of 19.0 kcal/mol of the inversion barrier of 1 was estimated by means of an empirical force field, when all torsion angles simultaneously pass through zero in a completely planar transition state.[8a] The barrier value for this improbable process may be compared with the corresponding value of about 23.0 kcal/mol for cyclohexane[3] retaining the symmetry center. The comparison shows a generally indicated tendency, viz. the decrease of the inversion barrier after introduction of sp^2-hybridized carbon atoms into the cyclohexane ring. This effect was also observed in other compounds. It is explained by the lower rotational barrier around single bonds with sp^2-hybridized carbons[3,4] Thus, the diene system of 1 should be the starting point for ring inversion. Compared with the two symmetric pathways in cyclohexane (C_2 and C_s mode), only one symmetric transformation retaining the C_2 axis is possible for 1. All other possibilities proceed via asymmetric inversion modes. In our calculations, only the C_2 mode is completely considered which is illustrated in Scheme I. The comparison of symmetric and asymmetric inversion profiles in cyclohexane shows close energetic correspondence, which is partially caused by the fact that conformations of the same type are involved in the transition-state region of inversion.[3] Hence, consideration of the C_2 mode may be sufficient to describe the energetic relations in the chair–chair interconversion of 1. Starting the C_2 inversion mode from the chair by inverting the torsion angle of the diene system, the half-chair form is reached followed by a conformation with three consecutive torsion angles of the same sign. Subsequently, the two neighboring torsion angles invert simultaneously, and the symmetric twist form appears. The continuation of the inversion process for the remaining torsion angles involves the same conformation types encountered before to give finally the inverted chair form. However, unlike cyclohexane, the corresponding conformations differ in energy now. In the first half of the inversion, the torsion angles within and around the diene system are inverted, in the second half, inversion concerns cyclohexane-like torsion angles. According to the aforementioned arguments, the cyclohexane inversion has a higher energy barrier. Thus, the energetic advantage when starting inversion at the diene system would get lost. Alternatively, inversion of the cyclohexane-like torsion angles may be realized by pseudorotation of the symmetric twist form into its alternate conformation. Of course, this pseudorotation is connected with a reinversion of the diene system torsion angles to the original ones. However, the alternate chair form can be reached now by a second inversion of these angles passing conformations of the same energy as before (Scheme I). Thus, ring inversion via pseudorotation should be the most economical mode for 1. The energy profile for the chair-twist interconversion is illustrated in Figure 1 together with the pseudorotation profile. All conformations involved in the pseudorotation process have a lower energy than the transition state of inversion, which corresponds to the conformation with the three consecutive torsion angles of the same sign. The ring torsion angles of important conformations involved in the chair-twist interconversion are given in Table IV. The calculated inversion barriers are 4.4 kcal/mol (STO-3G) and 7.7 kcal/mol (3-21G). Corresponding to the expectations, both values are below the cyclohexane barrier, for which values between 10 and 11 kcal/mol were determined.[2-4,14a,22] The smaller STO-3G barrier value may be caused by the a priori more flattened chair conformation in the diene part.

Table IV. STO-3G and 3-21G Ring Torsion Angles for Important Conformations of 1 Involved in the Ring Inversion[a]

torsion angle[b]	HC[a,c]	TS[a,d]	1,3-DP[a,c]	1,2-DP[a,c]
C(1)C(2)C(3)C(4)	16.7	9.5/13.0	0.0	0.0
C(2)C(3)C(4)C(5)	−49.5	−47.5/−50.0	−44.8	−30.7
C(3)C(4)C(5)C(6)	66.3	67.2/68.8	68.3	61.3
C(4)C(5)C(6)C(1)	−49.5	−47.5/−50.0	−44.8	−61.4
C(5)C(6)C(1)C(2)	16.7	9.5/13.0	0.0	30.7
C(6)C(1)C(2)C(3)	0.0	10.1/6.1	23.4	0.0

[a] See Scheme I. [b] In degrees. [c] STO-3G values. [d] STO-3G/3-21G values.

The monoplanar half-chair and the 1,3-diplanar conformation passed in the C_2 inversion are critical points of higher order. They are more stable only by 0.26 and 0.16 kcal/mol than the transition state. Therefore, their energies are good estimates for the inversion barrier. This gives us a certain justification for an estimation of the inversion barrier in one of the asymmetric inversion modes, which proceeds via an 1,2-diplanar conformation (half-boat form) with five ring carbon atoms in a plane (Scheme I, Table IV). This inversion mode leads to the asymmetric boat form of the pseudorotation cycle from where continuation may follow different modes. The STO-3G energy difference between the half-boat and the chair amounts

(22) (a) Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1967**, *89*, 760. (b) Binsch, G. *Top. Stereochem.* **1968**, *3*, 97.

to 4.9 kcal/mol, which is somewhat higher, but practically comparable with the inversion barrier for the symmetric C_2 mode.

The magnitude of the barrier determined for various inversion modes of **1** is not only in good agreement with those estimated for simple alicyclic compounds of comparable type, it also corresponds to rough estimations of the ring A inversion barrier of vitamins D. Based on NMR experiments,[10f] it was concluded that the upper limit of this barrier amounts to about 8.5 kcal/mol for the naturally occurring vitamins D. Thus, chair–chair interconversion is easily possible in these compounds, realizing the biologically active conformation at the receptor site.

Conclusions

Both ab initio basis sets provide a satisfactory description of the most important conformational aspects in the 1,2-dimethylenecyclohexane molecule, although the 3-21G results should be preferred with respect to the quantitative reproduction of geometry and energy data. A chairlike minimum structure is indicated, which may easily undergo ring inversion via an inversion/pseudorotation process as the most economical pathway. The dynamic behavior of the ring system of the title compound is generally comparable with that of the cyclohexane molecule. However, the introduction of the sp^2-hybridized carbons increases the ring mobility. The conformational data provide a good reference basis for a consideration of the ring-A properties of vitamin D derivatives but also for the discussion of the conformation of 2-methylenecyclohexanones[7i,23] and 1,2-cyclohexanediones.[7i,24] These structures are frequently realized in biologically active compounds.

Experimental Section

All calculations were performed within the ab initio SCF molecular orbital theory employing the STO-3G and 3-21G basis sets.[16] The geometries of the various conformations were completely optimized using the MONSTERGAUSS[17] and HONDO7[18] program systems. In order to characterize the critical points, the eigenvalues of the matrix of force constants were determined. In some special cases, the transition-state search procedure of the HONDO7 program package[19] was used. The character of the structures obtained in this way was confirmed by a separate force constant calculation.

Acknowledgment. Considerable part of this work was performed during a stay of one of us (H.-J.H.) at the University of Pisa in the research group of Prof. J. Tomasi, who deserves thanks for hospitality, interest, and support. A substantial amount of computer time made available by the computational center of the CNR (CNUCE) is gratefully acknowledged.

Registry No. 1, 2819-48-9; 2, 1406-16-2.

(23) (a) Mühlstädt, M.; Köhler, H.-J.; Porzig, D.; Scholz, M. *J. Prakt. Chem.* **1970**, *312*, 292. (b) Izsák, D.; Le Fèvre, R. J. W. *J. Chem. Soc., Sect. B* **1966**, 251.

(24) (a) Leonard, N. J.; Mader, P. M. *J. Am. Chem. Soc.* **1950**, *72*, 5388. (b) Cumper, C. W. N.; Leton, G. B.; Vogel, A. I. *J. Chem. Soc.* **1965**, 2067.

Synthesis and Characterization of Di-disubstituted Phthalocyanines

Joseph G. Young* and William Onyebuagu

Department of Chemistry and Physics, Chicago State University, Chicago, Illinois 60628

Received December 15, 1988

An improved approach to the synthesis of di-disubstituted phthalocyanines from two different phthalyl precursors is described. The method combines substituted 1,3 diiminoisoindoles and 6/7-nitro-1,3,3-trichloroisoindolenine to synthesize phthalocyanine. The method can be applied to the synthesis of hydrogen and metallo phthalocyanine. The yields are variable, ranging from 17% to 72% depending on the substituents.

Phthalocyanine (Pc) has been the subject of a great deal of wide-ranging research for over 50 years.[1] This has led to over 7000 citations of Pc in *Chemical Abstracts*, most of which are patents.[2] The synthesis of a variety of substituted Pc's both metallo and nonmetallo have been reported.[3] The main purpose for these substitutions has been to enhance Pc's very limited solubility. These compounds have, with few exceptions, been synthesized by the tetramerization of a single type of substituted phthalyl compound. This results in the substitution of identical groups on all of the benzenoid rings, giving tetra, octa substitution or higher orders of four. The regioselectivity of this reaction is poor and gives mixtures of all possible orientation patterns for the substituents.

Exceptions to this synthetic approach are found in the work done by Lever and Leznoff[4] in the synthesis of mono-trisubstituted Pc's. This involved the polymer support of one type of substituted phthalyl unit and its reaction with a differently substituted phthalyl unit to form a Pc. However, this process is limited in the scope of potential Pc's synthesized.

Direct reaction of two different phthalyl compounds has been tried.[5] This led to a mixture of possible compounds of different substitutions and isomers. Lever and Leznoff[6] also synthesized their "clamshell" Pc by direct mixing of two different phthalyl units. This compound is interesting in that it contains two mono-trisubstituted Pc rings bound

(1) Linstead, R. P. *Brit. Assoc. Advance. Sci., Rep.* **1933**, 465.

(2) Moser, F. H.; Thomas, A. L. *The Phthalocyanines*; CRC Press Inc.: Boca Raton, FL, 1983.

(3) (a) Derkacheva, M. V.; Iodko, S. S.; Kaliya, O. L.; Luk'yanets, E. A. *Zh. Obsh. Khim.* **1981**, *51*, 2319 (and previous works by Luk'yanets). (b) Pawlowski, G.; Hanack, M. *Synth. Commun.* **1981**, *11*, 351. (c) Hanack, M.; Pawlowski, G.; Subramanian, L. R. *J. Organmet. Chem.* **1981**, *204*, 315. (d) Cuellar, E. A.; Marks, T. J. *Inorg. Chem.* **1981**, *20*, 3766.

(4) (a) Leznoff, C. C.; Hall, T. W. *Tetrah Lett.* **1982**, *23*, 3023. (b) Leznoff, C. C.; Greenberg, S.; McArthur, C. R.; Khouw, B. *Nouv. J. Chem.* **1982**, *6*, 653.

(5) Shirai, H.; Kobayashi, K.; Takemae, Y.; Suzuki, A.; Hirabaru, O.; Hojo, N. *Makromol. Chem.* **1979**, *180*, 2073.

(6) (a) Leznoff, C. C.; Greenberg, S.; Marcuccio, S. M.; Minor, P. C.; Seymour, P.; Lever, A. B. P.; Tomer, K. B. *Inorg. Chim. Acta* **1984**, *89*, L35. (b) Marcuccio, S. M.; Svirskaya, P. I.; Greenberg, S.; Lever, A. B. P.; Leznoff, C. C.; Tomer, K. B. *Can. J. Chem.* **1985**, *63*, 3057.

0022-3263/90/1955-2155$02.50/0