NMR Spectra of Porphyrins. 29.[1] Conformation of the Propionic Ester Side Chain in Chlorophyll Derivatives

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The 360- and 500-MHz proton NMR spectra of the five nonequivalent protons in the C-7 propionic ester side chain of various chlorophyll derivatives have been completely analyzed in order to investigate the effect of structural variations in the chlorophyll nucleus on the side-chain conformation in solution. Analysis of the coupling constants and chemical shifts obtained shows that introduction of a central nickel atom into the chlorophyll nucleus causes profound variations in the side-chain conformation, presumably reflecting conformational changes in ring D. Less marked, but similar, effects occur upon opening of the exocyclic ring. In contrast, the introduction of δ substituents results in different, more localized, deformations, while introduction of a central magnesium atom causes little change in side-chain conformation.

Introduction

The precise conformation of the various side chains in the chlorophylls in vivo may well be of crucial importance to their fundamental roles as light harvesting and capturing pigments in plants and bacteria.[4] For this reason there have been a number of X-ray studies of chlorophyll and hydroporphyrin derivatives.[5-7] These studies have clearly demonstrated the considerable flexibility of the macrocyclic pyrroline ring (traditionally ring "D") and the consequential conformational mobility of the attached side chains in these molecules.

In ethyl chlorophyllide *a* (1),[5] ring D has almost C_2 symmetry, with C-7 out of the plane of the other ring atoms and the C-7 propionate group pseudo-axial, whereas the trans-reduced pyrroline rings of metal free octaethylisobacteriochlorin have half-chair (C_s) symmetry with pseudo-axial ethyl groups.[6] In ttt nickel(II) octaethylisobacteriochlorin and iron(III) *trans*-octaethylchlorin the pyrroline rings are shallow half-chairs with diequatorial ethyl substituents.[6,7]

It is of some interest to know whether these differences are intrinsic to the molecules or merely a result of crystal packing forces. No comparable studies of the solution conformations of these molecules have been described, largely due to difficulties in analysis of these complex spin systems, though data are available from the proton–proton couplings. In previous parts of this series[8,9] we have shown how the use of very high field NMR spectroscopy combined with decoupling and spectral simulation techniques permits complete analysis of the ring D and coupled C-7 propionate ester spectra in methyl pheophorbide *a*, methyl pyropheophorbide *a*, farnesyl 2-(1-hydroxyethyl)pyropheophorbide *a*,[8] and also of chlorophyll *a* and pheophytin *a*.[9] In this investigation we extend this analysis to a number of chlorophyll derivatives in order to study the effects of other structural variations. These include the introduction of a central metal atom [nickel(II) or magnesium(II)], the introduction of a δ substituent (cyano, nitro, methyl), reduction of the 9-carbonyl group on ring E (when present), and removal of ring E; some of these modifications have major influences on the conformation of ring D and its substituents.

Experimental Section and Spectral Analysis

The preparation and characterization of the compounds studied (Figure 1) are given elsewhere.[10-12] The proton NMR spectra were measured on either a Nicolet NT-500 (500 MHz) or Nicolet NT-360 (360 MHz) spectrometer. Typical conditions were as follows: probe temperature 23 °C, 16K or 32K data points, sweep width 3–4 KHz giving a digitization accuracy of 0.2–0.5 Hz/point, pulse width 8 μs, aquisition time 1–2 s. Spectra used for simulations were all zero filled to 32K data points and resolution enhanced with the Nicolet software (LB = 0.5 Hz, DM = 2.0). The simulations were performed by using the Nicolet ITRCAL routine and the line broadening parameter was adjusted to best approximate that of the real spectrum (1.2–1.8 Hz).

In these molecules, the proprionate side-chain protons give rise to a complex five-spin system as the four methylene protons of the side chain and the C-7 proton are all nonequivalent due to the chiral centers at C-7, C-8, and in some cases at C-10. The analyses of the complex multiplets were performed in a fashion analogous to those reported for methyl pheophorbide and derivatives.[8]

As in the methyl pheophorbide *a* case, the closely coupled multiplets are *vicinal* rather than geminal pairs. The observed and calculated spectra of a representative sample of the spectra analyzed are given in Figure 2, and the results of these analyses are collected in Table I, together with the previously recorded data,[8,9] for methyl pheophorbide *a* (**2**), methyl pyropheophorbide *a* (**3**), the farnesyl 2-(1-hydroxyethyl) derivative **4**, chlorophyll *a* (**5**), and pheophytin *a* (**6**) for comparison.

Results and Discussion

Coupling Constants. The vicinal couplings around ring D and the propionate ester side chain can be used to deduce the rotamer populations and dihedral angles in this section of the molecule if the couplings in the distinct rotamers can be estimated and the appropriate relationship between dihedral angle and coupling for the C-7,C-8 fragment is known. For the side-chain populations we use

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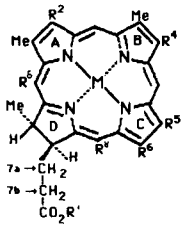


Compound	R^2	R^4	R^5	R^6	R^8	R^5	R'	M
1	V	Et	Me	-COCH(CO_2Me)-		H	Et	Mg
2	V	Et	Me	-COCH(CO_2Me)-		H	Me	2H
3	V	Et	Me	-$COCH_2$-		H	Me	2H
4	HE	Et	Et	-$COCH_2$-		H	Fn	2H
5	V	Et	Me	-COCH(CO_2Me)-		H	Phy	Mg
6	V	Et	Me	-COCH(CO_2Me)-		H	Phy	2H
7	Et	Et	Me	-CH_2CH_2-		H	Me	2H
8	V	Et	Me	CO_2Me	H	H	Me	2H
9	V	Et	Me	-$COCH_2$-		H	Me	Ni
10	Et	Et	Me	-CH_2CH_2-		H	Me	Ni
11	Et	Et	Me	CO_2Me	H	H	Me	Ni
12	V	Et	Me	-$COCH_2$-		H	Me	Mg
13	Et	Et	Me	-$COCH_2$-		Me	Me	Ni
14	Et	Et	Me	-$COCH_2$-		CN	Me	2H
15	Et	Et	Me	-$COCH_2$-		NO_2	Me	2H
16	Et	Et	Me	P(Me)	H	H	Me	2H
17	Et	Et	Me	-CH_2CH_2-		Me	Me	2H
18	HE	Et	Et	-$COCH_2$-		H	Me	2H

[a] Abbreviations: V=vinyl; HE=(1-hydroxyethyl); P(Me)=$CH_2CH_2CO_2$Me; Phy=phytyl; Fn=farnesyl.

Figure 1. Structures of compounds investigated.

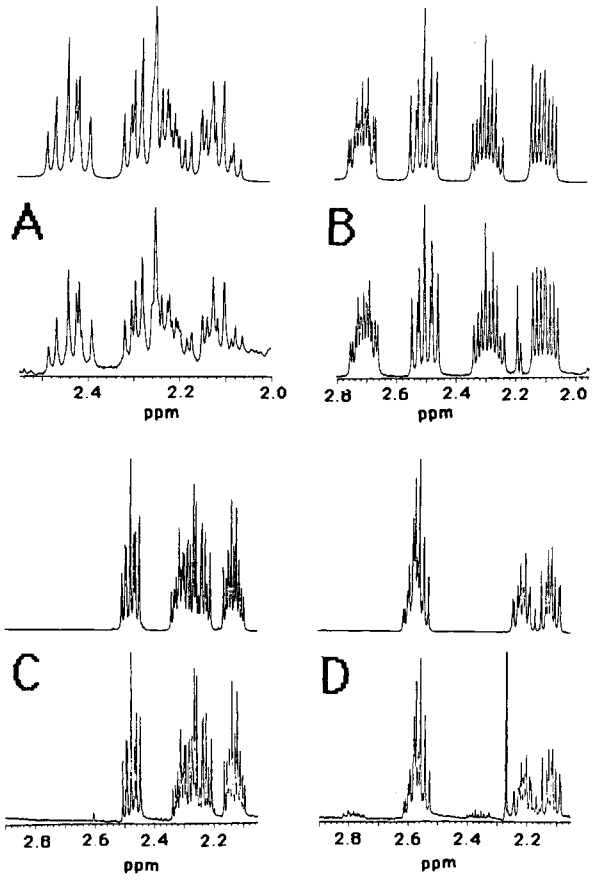


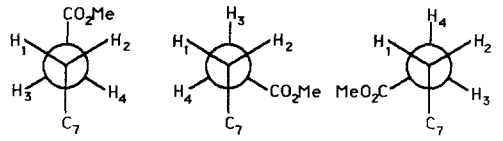
Figure 2. Proton NMR spectra (360 MHz, in $CDCl_3$ solution) and simulated spectra of propionic side-chain methylenes in A, nickel(II) methyl pyropheophorbide *a* (**9**); B, methyl 9-deoxomesopyropheophorbide *a* (**7**); C, nickel(II) methyl 9-deoxomesopyropheophorbide *a* (**10**); D, methyl δ-mesomethyl-9-deoxomesopyropheophorbide *a* (**17**).

the same approach as previously,[8] in which the anti H–H coupling is given by recourse to a cyclohexane fragment

Table I. Chemical Shifts (ppm) and Coupling Constants (Hz) for the 7-Propionic Side Chains in Chlorophylls and Derivatives[a]

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
ν(1) 7a	2.636	2.703	2.675	2.530	2.629	2.805	2.730	2.229	2.303	2.225	2.522	2.163	2.530	2.528	2.765	2.576
ν(2) 7a′	2.319	2.313	2.279	2.410	2.339	2.385	2.473	2.118	2.129	2.136	2.255	2.006	2.130	2.189	2.485	2.209
ν(3) 7b	2.515	2.562	2.539	2.380	2.486	2.598	2.592	2.438	2.475	2.451	2.379	2.376	2.616	2.615	2.608	2.557
ν(4) 7b′	2.233	2.286	2.250	2.080	2.194	2.199	2.367	2.277	2.238	2.407	1.976	2.318	2.299	2.166	2.366	2.114
ν(5) 7-H	4.204	4.798	4.270	4.150	4.203	4.510	4.483	3.967	5.045	4.070	4.166	3.814	4.161	4.233	4.537	4.311
J(1,2)	−14.0	−14.2	−14.0	−14.7	−14.2	−13.8	−13.6	−14.2	−13.8	−13.9	−14.2	−14.2	−13.6	−14.2	−14.0	−14.1
J(1,3)	6.7	7.1	7.0	7.4	6.5	7.1	5.7	6.7	7.0	6.5	6.7	6.5	7.5	7.5	5.9	7.1
J(1,4)	9.9	9.5	9.7	8.3	9.7	9.4	10.1	8.5	8.9	10.1	9.9	9.0	8.4	8.5	9.9	9.5
J(1,5)	3.2	2.8	3.1		3.1	2.8	4.4	4.4	4.6	6.9	2.8	7.2	2.9	3.6	4.4	3.1
J(2,3)	9.3	9.4	9.6	8.5	9.5	9.2	9.4	8.9	8.7	9.6	9.7	8.7	8.5	8.0	9.4	9.0
J(2,4)	5.2	5.0	5.0	6.3	5.0	4.9	5.1	5.7	5.2	5.7	5.0	6.0	5.2	5.3	5.1	5.0
J(2,5)	9.0	9.0	8.5		8.5	9.0	9.1	8.1	8.3	6.8	9.0	7.8	9.3	8.0	9.1	8.7
J(3,4)	−15.7	−15.8	−16.0	−15.7	−15.5	−15.8	−15.4	−16.0	−15.8	−15.9	−15.8	−16.2	−15.9	−15.5	−15.4	−15.9
J(3,5)	−0.2	0.0	0.2	0.0	−0.2	−0.1	−0.2	0.0	0.0	−0.2	0.0	−0.2	−0.1	0.0	−0.2	−0.2
J(4,5)	−0.2	−0.2	−0.2	0.0	−0.1	0.0	−0.1	0.0	0.0	0.2	−0.2	0.2	−0.2	−0.5	−0.2	0.0
J(7,8)	1.6	2.1	1.9	*e*	2.0	*e*	2.5	*e*	<1	2.4	*e*	*e*	<1	0.7	2.6	<1
rms error[f]	0.22	0.20	0.15		0.37	0.22	0.28	0.29	0.39	0.25	0.24	0.28	0.23	0.30	0.24	0.22
concn (mM)	8.0	7.1	5.0	2.8[b]	16.0[b]		1.0	6.6	18.0		4.3[d]	5.5[c]		38.0		20.0

[a] At 360 or 500 MHz. Samples in $CDCl_3$, except as noted. Chemical shifts relative to $CHCl_3$ (7.260 ppm) or tetramethylsilane. [b] $CDCl_3$ (0.5 mL) + CD_3OD. [c] Spectrum unchanged by addition of 5 molar equiv of pyrrolidine. [d] $CDCl_3$ (0.5 mL) + pyridine-d_5 (30 μL). [e] Could not be determined. [f] rms = root mean square.



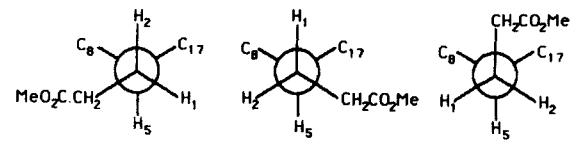
	anti	g_+	g_-
$J_{2,4}$	4.4	13.2	2.8
$J_{1,4}$	13.2	3.6	3.6
$J_{2,3}$	13.2	3.6	3.6
$J_{1,3}$	4.4	2.8	13.2
2	0.63	0.10	0.27
9	0.52	0.19	0.29
14	0.50	0.14	0.36

Figure 3. Rotamer populations and coupling constants about C-7a,C-7b. For structural formulas, see Figure 1.

with similar substituents and the gauche couplings from known equations.[13] The estimated coupling constants of the individual rotamers together with the derived populations of the C-7a,C-7b fragment are given in Figure 3 for the free bases and the nickel derivatives. This analysis does not by itself differentiate between the two gauche conformers (g_+ and g_-) as there is no absolute assignment of the geminal pairs of protons 1,2 and 3,4 (Figure 3). However, inspection of molecular models shows clearly that the g_+ conformer (and also conformer [2] about C-7,C-7a, see later) is sterically very disfavored. This supports the assignment given, in which g_+ is the most disfavored conformer in all cases. In the solid state only the g_- conformer is observed.[5]

In the new compounds studied here, the most marked changes in the coupling constants are observed upon insertion of nickel in the macrocycle. The general trend upon conversion of **3**, **7**, and **8** into the nickel complexes [**9**, **10**, and **11** (2-Et), respectively] is a slightly more equal distribution of rotamers about C-7a,C-7b (Figure 3 and Table I) as evidenced by a decrease in $J_{1,4}$ and $J_{2,3}$ and an increase in $J_{2,4}$ and $J_{1,3}$. The same change was observed in the comparison between metal-free pheophytin *a* (**6**) and chlorophyll *a* (**5**). The couplings for methyl pyrochlorophyllide *a* (**12**), however, show that the rotamer distribution about C-7a,C-7b is somewhat more unequal in this molecule than in the corresponding metal-free methyl pyropheophorbide *a* (**3**).

A similar analysis can be performed for the couplings of the C-7,C-7a fragment though in this case the nontetrahedral angles of C-7 and the consequent departure from the perfectly staggered dihedral angles in the fragment make such analyses less rigorous. Reasonable estimates for the gauche and trans (anti) couplings in this fragment are ca. 3.0 and 11.5 Hz,[14] and these are given with the three possible conformers in Figure 4. Consideration of these values with the observed values of $J_{1,5}$ and $J_{2,5}$ (Table I) shows that in many of the compounds studied in which $J_{1,5}$ = 3.0 (±0.2) Hz, one conformer of [1] and [2] must be of essentially zero population. Molecular models for the pheophytin molecule show clearly that conformer [2] is sterically very disfavored and this may be identified as the least populated conformer in these molecules. This also provides the assignment given of protons 1 and 2.



	[1]	[2]	[3]
$J_{1,5}$	3.0	11.5	3.0
$J_{2,5}$	11.5	3.0	3.0
Compound			
3	0.63	0.0	0.37
7	0.71	0.0	0.29
8	0.72	0.16	0.12
9	0.60	0.16	0.24
10	0.62	0.19	0.19
11	0.45	0.46	0.09
12	0.60	0.16	0.24
13	0.52	0.48	0.0
14	0.67	0.0	0.33
15	0.59	0.07	0.34

Figure 4. Rotamer populations and coupling constants about C-7,C-7a. For structural formulas, see Figure 1.

The structural variations considered here give rise to much larger variations in the C-7,C-7a couplings than in the C-7a,C-7b ones, reflecting the proximity to the perturbation induced. In particular, the introduction of nickel(II) into the chlorin ring produces a marked change in the couplings. The nickel complexes **9**, **10**, and **11** all show a marked increase in $J_{7,7a}$ ($J_{1,5}$) and a corresponding decrease in $J_{7,7a'}$ ($J_{2,5}$) relative to their metal free analogues **3**, **7**, and **8**. Indeed, in **11** the combined effects of the opening of the exocyclic ring and the introduction of nickel(II) results in equalization of $J_{1,5}$ and $J_{2,5}$ and therefore equal populations of conformers [1] and [2].

In Figure 4 the calculated proportions of the conformers are given for some of the molecules studied, on the basis of the conformer couplings. On this admittedly simple basis all the nickel complexes show an increased population of conformer [2], and this could be due to ruffling of the porphyrin core in the nickel compounds with a consequent distortion of ring D.[6] However, where the coupling $J_{7,8}$ could be measured (compound **11**) the value obtained is the same as in the free bases (2–2.5 Hz), suggesting no large distortion of this fragment. Interestingly, the introduction of a δ substituent (methyl, cyano, nitro), which might also have been expected to introduce additional steric interactions in ring D, does not appreciably affect the population of conformer [2], but removal of the exocyclic ring does increase the population of conformer [2]. This has an obvious rationalization in that the major unfavorable steric interaction in conformer [2] is between the 7b CH_2 group and the C10 CH. Opening the exocyclic ring removes this repulsive interaction completely.

The trend toward equality of $J_{7,7a}$ and $J_{7,7a'}$ is accompanied by a marked change in the appearance of the 7-H multiplet. In metal-free compounds such as methyl pyropheophorbide *a* this resonance appears as a broadened doublet, or in favorable cases, as a doublet of triplets. In nickel(II) methyl δ-methylmesopyropheophorbide *a* (**13**), the 7-H resonance now appears as a pseudo triplet.

Chemical Shifts. The chemical shifts for the four propionic side-chain protons of all the compounds studied are presented schematically in Figure 5. The broken line connects the 7a and 7a′ protons, while the solid line connects the 7b and 7b′ protons (in this nomenclature the prime is assigned to the highest field resonance of each methylene group). It can be seen that many of the compounds follow the general pattern previously observed for methyl pheophorbide *a* (**2**), i.e., 7a, 7b, 7a′, 7b′ in order to

(13) Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Wiley-Heyden: London, 1979; p 23.

(14) The equations of ref 13 give J_g values of 3.8 and 3.0 Hz for conformers [1] and [3], respectively, and the observed coupling in a similarly substituted cyclohexane fragment[15] are 11.5 Hz (axial, axial) and 3.5 Hz (axial, equatorial).

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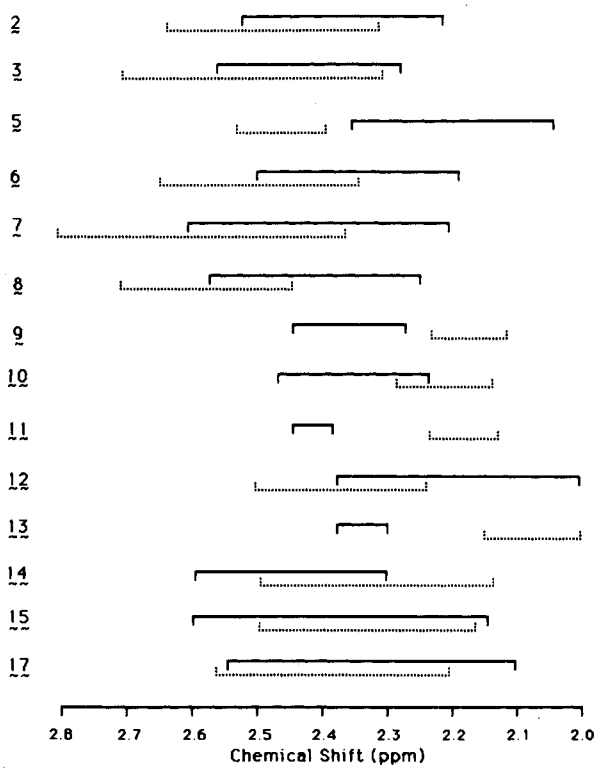
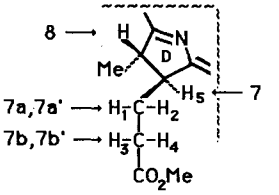


Figure 5. Chemical shifts of the 7a,7a′ (broken line) and 7b,7b′ (solid line) propionic methylene protons in chlorophyll derivatives. For structural formulas, see Figure 1.

higher field, while others such as methyl mesocyanomesopyropheophorbide *a* (**14**) and methyl mesonitromesopyropheophorbide *a* (**15**) show a different pattern, i.e., 7b to low field of 7a. Still a third set (**9**, **13**, **11**, all nickel complexes) shows a striking alteration—now the *geminal* rather than vicinal protons are paired (7b, 7b′, 7a, 7a′ in order to higher field). The analysis further revealed that in most cases the lack of similarity in the spectra (Figure 2) is due to chemical shift differences rather than coupling constant differences. However, the nickel complexes, which show the most striking changes in chemical shifts, also show the most significant conformational alterations.

The effect of structural variations on the chemical shifts may now be examined. For this purpose it is helpful to consider the anisochronies between each geminal pair and this is shown in Table II. Complexation with nickel causes upfield shifts of 7a (0.48–0.51 ppm) and 7a′ (0.26–0.34 ppm) as judged by comparison of the pairs nickel pyropheophorbide *a* (**9**) and pyropheophorbide *a* (**3**), nickel 9-deoxomesopyropheophorbide *a* (**10**) and 9-deoxomesopyropheophorbide *a* (**7**), and nickel mesorhodochlorin dimethyl ester (**11**) and rhodochlorin dimethyl ester (**8**). The anisochrony between 7a and 7a′ in each of these pairs also decreases upon conversion to the nickel complex—from $\Delta\delta$(7a–7a′) = 0.26–0.42 ppm for the metal-free compounds to $\Delta\delta$(7a,7a′) = 0.09–0.17 for the nickel complexes. The shielding effect caused by introduction of nickel into the macrocycle is also reflected in the chemical shift of the 7-H (see Table I). The *average* value of the chemical shift of 7b and 7b′ is not changed greatly in the nickel complexes vs. the free-bases, but again the anisochrony [$\Delta\delta$(7b,7b′)] is reduced upon complexation with nickel. It is possible that complexation with the small nickel atom (ionic radius 0.69 Å) causes considerable deformation of the central nitrogen atoms of the macrocycle from their positions in the free base, thus distorting the aromatic π-system. Unfortunately, the crystal structure of a nickel chlorophyll *a* derivative has yet to be performed, but it has been shown

Table II. Chemical Shift Anisochrony (ppm) between the 7a′,7a and 7b,7b′ Proton Pairs



compd	$\Delta\delta$(7a,7a′)	$\Delta\delta$(7b,7b′)	compd	$\Delta\delta$(7a,7a′)	$\Delta\delta$(7b,7b′)
2	0.317	0.282	**10**	0.174	0.237
3	0.290	0.276	**11**	0.089	0.044
4	0.396	0.289	**12**	0.267	0.403
5	0.12	0.30	**13**	0.157	0.058
6	0.290	0.292	**14**	0.400	0.317
7	0.420	0.399	**15**	0.339	0.450
8	0.257	0.225	**16**	0.280	0.242
9	0.111	0.161	**17**	0.367	0.443

that nickel octaethylporphyrin can adopt either a strongly twisted or a nearly flat conformation depending on the crystalline modification.[6]

The absence of isocyclic ring E in compounds **8** and **16** appears to result in only a small decrease in the anisochrony of the 7a,7a′ and 7b,7b′ pairs relative to the corresponding chlorophyll *a* derivatives possessing ring E.

Complexation of methyl pyropheophorbide *a* (**3**) with magnesium to give methyl pyrochlorophyllide *a* (**12**) results in upfield shifts of 7a and 7a′, although $\Delta\delta$(7a,7a′) is about the same in both molecules. Unlike the nickel complexes, however, large *upfield* shifts are also observed for 7b (0.19 ppm) and 7b′ (0.32 ppm) in this conversion. These data could suggest a greater population of the conformation in which the propionic side chain is over the chlorin macrocycle, possibly due to interactions between the central magnesium atom and the ester carbonyl. However, it must be cautioned that a satisfactory disaggregated spectrum of **12** could only be obtained upon addition of pyridine, and this may have affected the analysis. Relatively large (0.11 ppm) upfield shifts of both the 7b and 7b′ protons were also observed in the comparison between magnesium-free pheophytin *a* (**6**) and chlorophyll *a* (**5**). It is interesting that in the comparison of **6** with **5** the anisochrony between 7b and 7b′ is unchanged upon introduction of magnesium, while that between 7a and 7a′ decreases ($\Delta\delta$ = 0.17 ppm), while in the comparison of **3** with **12**, introduction of magnesium affects the 7a,7a′ anisochrony only slightly while increasing the 7b,7b′ anisochrony significantly ($\Delta\delta$ = 0.13 ppm). Again, it must be emphasized that it was necessary to add CD_3OD to chlorophyll *a* in order to obtain a satisfactory disaggregated spectrum.

The comparison of pyropheophorbide *a* (**3**) with 9-deoxomesopyropheophorbide *a* (**7**) and nickel pyropheophorbide *a* (**9**) with nickel 9-deoxomesopyropheophorbide *a* (**10**) shows that removal of the 9-carbonyl group results in *downfield* shifts of 7a, 7a′, and 7b and in an upfield shift for 7b′. These effects are smaller in the nickel complexes than in the free-bases. The anisochronies between 7a and 7a′ and between 7b and 7b′ are uniformly larger in the 9-deoxo compounds. These results may reflect the ca. 10% increase in the global ring current of the macrocycle which occurs upon elimination of the C-9 carbonyl.[16]

Introduction of a δ-cyano (**14**) or δ-nitro (**15**) group onto methyl mesopyropheophorbide *a* shifts the 7a and 7a′ protons to higher field and the 7b proton to lower field [the assumption here is that the analysis of methyl meso-

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pyrophenophorbide *a* with a 2-Et group will be the same as 2-vinyl methyl pyropheophorbide *a* (**3**)]. In the case of meso-nitro compound **15**, 7b′ is shifted upfield relative to **3**, while in δ-cyano derivative **14** the shift of 7b′ is hardly affected. The net result of these changes is that the 7a,7a′ and 7b,7b′ anisochronies are increased in both meso-substituted compounds relative to **3**. Thus, in **15**, 7a and 7b, and 7a′ and 7b′ have switched places relative to their ordering in **3**. The anisochrony of 7a,7b′ (0.45 ppm) is significantly larger in δ-nitro compound **15** than in δ-cyano derivative **14** (0.32 ppm).

A comparison of δ-methyl-substituted compounds **17** and **13** with the corresponding δ-unsubstituted compounds **7** and **9** shows upfield shifts for 7a (0.23, 0.17 ppm) and 7a′ (0.18, 0.11 ppm) in the former. The changes in 7b and 7b′ are much smaller. The changes in the anisochrony of 7a,7a′ and 7b,7b′ within each series do not seem to follow a predictable pattern. Unfortunately, the four protons of metal-free methyl bacteriopheophorbide *c* [Et,Et] (**18**) appeared as a pair of multiplets too closely coupled to simulate, thus a comparison with the corresponding δ-unsubstituted methyl pyropheophorbide a was not possible. The 7-H in all the δ-substituted compounds experienced an upfield shift of 0.07–0.20 ppm relative to their meso-unsubstituted analogues.

Conclusions

Both the chemcial shifts and coupling constants observed for the propionate ester side-chain protons are consistent with the premise that introduction of a nickel atom into the chlorin ring causes a pronounced conformational change in the side chain, and by inference, in ring D. The introduction of δ substituents, in contrast, appears to have only a local minor perturbation of the ring D substituents, but removal of the exocyclic ring also appears to perturb the side chains appreciably.

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Asymmetric Synthesis via Acetal Templates. 13.[1] Preparation of Aldol Compounds from Butane-1,3-diol Acetals

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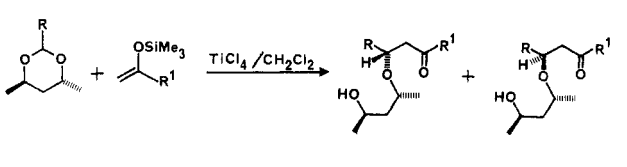
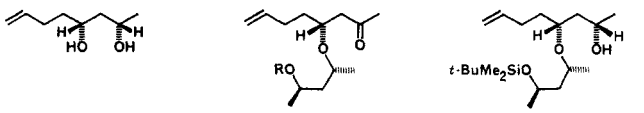
The acetals **8**, derived from (3*S*)-butane-1,3-diol, undergo $TiCl_4$-catalyzed coupling with acetone trimethylsilyl enol ether (**11**) to give the aldol ethers **12**/**13** in high yield and diastereoselectivity in favor of **12** (Table I). The chiral auxiliary is readily removed from **12** by oxidation to the aldehyde **14** followed by selective β-elimination under conditions (dibenzylammonium trifluoroacetate) to which the aldol product **16** is stable (Table II). This methodology has been applied to an efficient asymmetric synthesis of (2*R*,4*S*)-oct-7-ene-2,4-diol (*enantio*-**5**), a key intermediate in the synthesis of nonactic acid.

Recently we disclosed methodology for the asymmetric synthesis of aldol ethers **3**/**4** based upon the coupling of chiral acetals **1**, derived from pentane-2,4-diol, with α-silyl ketones or enol silyl ethers (Scheme I),[2] the product being generated in high yield and with excellent diastereoselectivity (>95:5) in favor of **3**. As previously noted, however, this method is not generally applicable to the production of aldol compounds themselves. Thus removal of the chiral auxiliary from aldol ethers **3**/**4** cannot be achieved via the oxidation/β-elimination sequence without concommitant destruction of the aldol, except when R^1 is bulky (e.g., *tert*-butyl).[2] This limitation can be circumvented by appropriate elaboration of the carbonyl group of **3**/**4** prior to removal of the chiral auxiliary, an approach that was successfully applied (see below) to the preparation of diol **5**, a key intermediate in the Bartlett synthesis of nonactic acid.[3]

Scheme I



1 2 3 4



5 6 7

There still remains a need to develop a general route to the free homochiral aldol products. Thus, in our synthesis of **5**, the coupling product **6** (R = H) was conveniently obtained according to the method of Scheme I (89% yield, 94% de). However, stereoselective reduction of the carbonyl group proved to be difficult, and the most favorable result, involving L-Selectride (Aldrich) reduction of **6** (R = $SiMe_2$-*t*-Bu), gave only a 4:1 preference for the desired syn alcohol **7**.[2] On the other hand, reduction of aldol compounds of type **16** with *n*-Bu_3B/$NaBH_4$ has been reported[4] to yield the corresponding syn diols highly stereoselectively. The present paper discloses the use of some acetals of butane-1,3-diol in a scheme (Tables I and II) which affords direct access to the free aldol compounds. Also disclosed is the application of this modified methodology to an improved synthesis of the enantiomeric form of diol **5**[5] via the aldol **16a**.

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