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Chemical Reactivities of Tetrapyrrole Pigments: A Comparison of Experimental Behaviour with the Results of s.c.f.-<latex>π</latex>-m.o. Calculations [and Discussion]

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Chemical reactivities of tetrapyrrole pigments: a comparison of experimental behaviour with the results of s.c.f.–π–m.o. calculations

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Porphyrins are highly σ-electron donating bases and very weak π-acids. Hence they increase the electron density on central metal ions, e.g. iron, which leads to the specific reactivity of haem cytochromes, haemoglobin and oxidizing enzymes. The macrocyclic chlorin ligand behaves similarly but to a lesser degree which explains the comparably low oxidation potential of chlorophyll.

Phlorins, oxophlorins, oxa- and aza-porphyrins, tetradehydrocorrins, corrins and biliverdins all produce metal complexes which have a similar geometry to that of metalloporphyrins, but their reactivity patterns are different. In contrast to the metalloporphyrins which undergo many fully reversible reactions, these compounds tend to irreversible addition and cleavage reactions. These tetrapyrrole ligands are stronger π-acids than porphyrins.

Results of some recent experimental work and π-electron s.c.f. calculations are presented in support of these generalizations.

1. Structure of tetrapyrrole pigments

The chromophores **1–17** constitute the main body of tetrapyrrole pigments which are encountered in nature or which have been used as model compounds in studies related to biochemical phenomena. This article will try to relate the various pyrrole pigments to each other on grounds of chemical and physical properties and compare the empirical reactivity patterns with predictions from theroretical models.

In the series of tetrapyrrole pigments of biological relevance the following seven fundamental modifications of the porphyrin π-core **1** are considered:

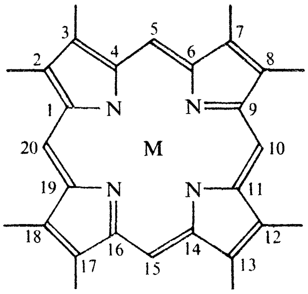
(1) Metal ions of varying charge and electronegativity are introduced into the cavity formed by four nitrogen atoms (all chromophores **1–17**).

(2) The peripherical double bonds are partly saturated with hydrogen atoms or alkyl groups (chlorophylls **2**, **3**, tridehydrocorphins **4** and corphins **5**).

(3) One methine bridge is hydrogenated or oxygenated (phlorins **6**, oxophlorins **7**).

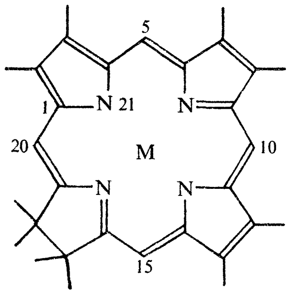
(4) A methine bridge is eliminated and two pyrrolic units are linked directly (corroles **8**). Often extra hydrogens or other substituents are found on the α-pyrrolic carbon atoms 1 and 19 (tetradehydrocorrins **9**). Additional saturation of peripherical double bonds leads to corrins **10**.

(5) One or more methine bridges are replaced by hetero atoms, in particular nitrogen (azaporphyrins **11**, **12**, phthalocyanines **12**), oxygen (oxaporphyrins **11***b*) and sulphur (thiaporphyrins **11***c*).



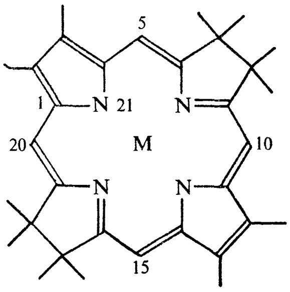
1

porphyrin



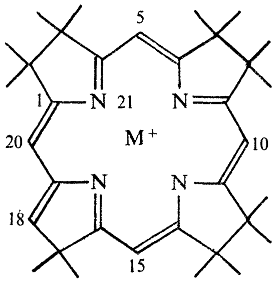
2

chlorin



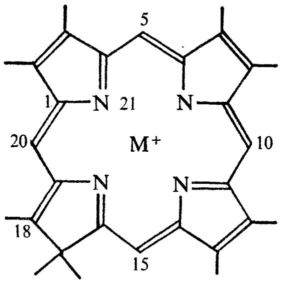
3

b-tetrahydroporphyrin
(bacteriochlorin)



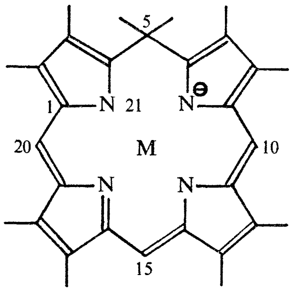
5

corphin



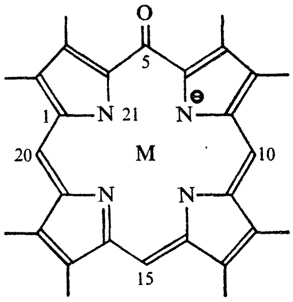
4

tridehydrocorphin



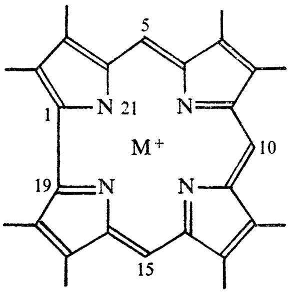
6

phlorin



7

oxophlorin anion



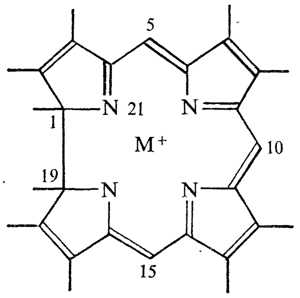
8

corrole

(6) A methine bridge is eliminated and the end rings of the open chain tetrapyrrole pigments bear α-pyrrolic functional groups (biliverdins **13**, **14**).

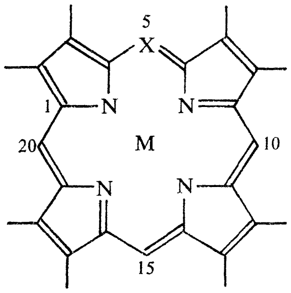
(7) The tetrapyrrolic system is divided into two dipyrromethene units **15–17**. Dipyrromethene complexes **17** themselves are the only complexes discussed here which are predominantly tetrahedral.

Although the reactivities of many of the above π-systems have not been investigated systematically so far, it is possible from the known facts, to draw a general outline of structure–reactivity relations. This could be a useful guide for further experimental and theoretical work.



9

tetradehydrocorrin

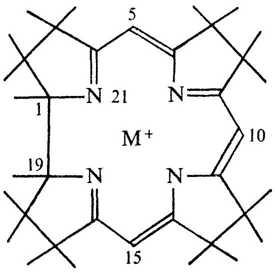


11a X=N

11b X=O⁺

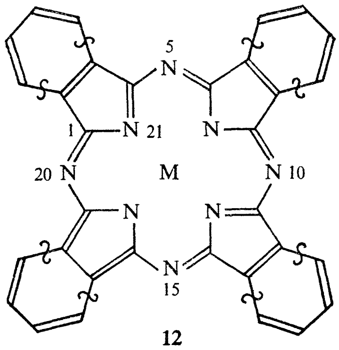
11c X=S⁺

aza-(oxa-, thia-)porphyrin



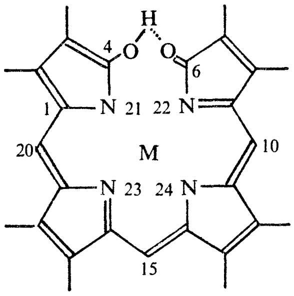
10

corrin



12

tetraaza-porphyrin
(here: a phthalocyanine)



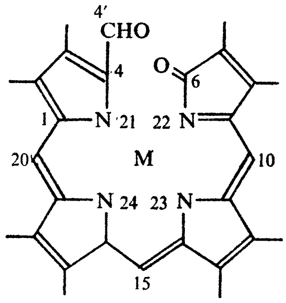
13

biliverdin

The descriptions of reactivity patterns which will be offered are, however, severely limited by the incomplete knowledge of the authors on some of the tetrapyrrole pigment classes. It is hoped that other groups may compare their experiences with the suggested generalizations in order to test the usefulness of the latter or to replace them by better rules.

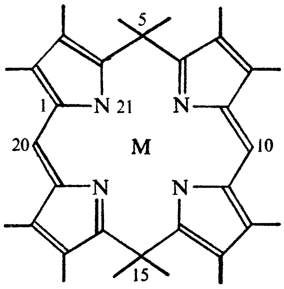
2. Theoretical models

A number of theoretical investigations have been reported on porphyrins. Most of the studies were concerned only with the π-framework of the porphyrins. s.c.f. calculations using the Pariser–Parr–Pople-π electron method (PPP method) were carried out by Weiss and others (Weiss, Kobayashi & Gouterman 1965; McHugh & Gouterman 1972) and Sundbom (1968)



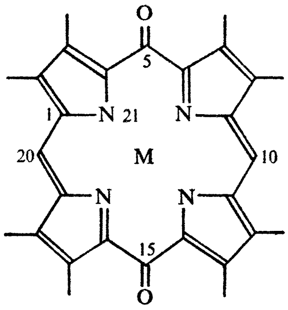
14

formyl biliverdin



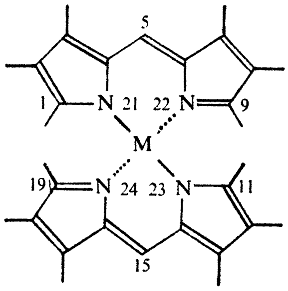
15

α, γ-porphodimethene



16

α, γ-dioxo-porphodimethene



17

dipyrromethene

who included the nitrogen lone pairs. Similar calculations are known for the chlorophylls (Weiss 1972; Roos & Sundbom 1970). All these π electron calculations indicate (1) that in metalloporphyrins (D_{4h} symmetry) the highest two occupied orbitals are nearly degenerate. (2) These two orbitals are separated from the next highest occupied orbital by a large energy gap ($\geqslant$ 3 eV). (3) The two lowest unoccupied orbitals are degenerate. The above results were essentially unchanged in the extensive all-valence electron calculations in the e.h.t. framework reported by Zerner & Gouterman (1966), and also in the c.n.d.o./2 studies which appeared recently (Maggiora 1973). For the partially hydrogenated porphyrin systems, mostly Pariser–Parr–Pople–π calculations have been used to interpret the spectral data and reactivities. In the present work we also have used the PPP type of π calculations in order to compare reactivities and some physical properties of a number of tetrapyrrole systems. These calculations are of limited applicability since they do not take the metal ion explicitly into account. But they give qualitative insight into the π electron structure of these ligands especially at a comparative level. The reactivities have been computed using Fukui's frontier electron model (Fukui, Yonezawa & Nagata 1957). It is gratifying to observe that the reactivity parameters are quite insensitive to the choice of s.c.f. parameter sets employed (e.g. traditional and standard parameters) (Weiss *et al.* 1965). Hence we believe that the calculated reactivities are quite meaningful for correlations with experimental data.

2.1. *Details of calculations*

The 'standard' set of parameters listed under table 1 have been used throughout the calculations. For the sake of uniformity the same bond lengths were used for both porphyrins and reduced porphyrins. The reactivities towards electrophilic and nucleophilic reagents were calculated using the formula:

$$F_l = (2-\nu)\, C^2_{mi} + \nu C^2_{m+1,\, i},$$

where $\nu = 0$, 2 and 1 for electrophilic, nucleophilic and radical reactivities respectively. C is the Hückel factor, C_{mi} and $C_{m+1,\,i}$ are respectively the ith atomic orbital coefficients for the h.o.m.o. (highest occupied molecular orbital) and l.u.m.o. (lowest unoccupied). The electrophilic and nucleophilic reactivities are presented in tables 1 and 2 respectively.

The total electronic charge density for each atomic centre is given in table 3. In cases where degeneracy or near degeneracy were observed in the h.o.m.o. or l.u.m.o., the reactivity indices are to be taken as the average of the parameters obtained from both the degenerate orbitals. Near degeneracy is when two orbitals differ in their energies by a value $\leqslant$ 0.5 eV. The longest wavelength transition for all the tetrapyrrole systems were also computed by c.i. method (see table 6) considering twenty configurations for each system.

3. RELATIVE REACTIVITIES OF CARBON ATOMS IN SOME SELECTED TETRAPYRROLE PIGMENTS

Some of the chromophores **1–17** will be discussed individually in respect to the relative reactivity of specific carbon sites. Comparisons between different systems will be drawn in the later sections.

3.1. *Porphyrins* **1**

The methine bridge carbon atoms of porphyrins and their metal complexes are generally more reactive in all types of chemical reactions than α- and β-pyrrolic sites. A few experimental

TABLE 1. ELECTROPHILIC REACTIVITY PARAMETERS FOR SOME TETRAPYRROLE PIGMENTS†, ‡, §, ||

atomic position	por (**1**)	chl (**2**)	BChl (**3**)	trideh. corphin (**4**)	corphin (**5**)	corphin free base (V)	phlorin (**6**)
1	0.014 (0.186)	0.144 (0.001)	0.197	—	0.054	0.218	0.070
2	0.051 (0.062)	0.100 (0.039)	0.078	0.007	—	—	0.112
3	—	0.038 (0.032)	—	0.007	—	—	0.019
4	—	0.200 (0.030)	—	—	0.004	0.140	0.132
5	0.293 (0.000)	0.004 (0.238)	0.011	0.222	0.295	0.112	—
6	—	0.206 (0.006)	0.213	—	0.043	0.192	—
7	—	0.080 (0.045)	—	0.004	—	—	—
8	—	—	—	0.012	—	—	—
9	—	—	—	—	0.000	0.122	—
10	—	—	—	0.300	0.252	0.008	0.152
11	—	—	—	—	0.025	0.096	0.120
12	—	—	—	0.001	—	—	0.020
13	—	—	—	0.025	—	—	0.130
14	—	—	—	—	0.000	0.030	0.004
15	—	0.030 (0.309)	—	0.362	0.155	0.000	0.352
16	—	0.180 (0.054)	—	—	0.018	0.044	—
17	—	—	—	—	—	—	—
18	—	—	—	0.012	0.036	0.430	—
19	—	—	—	—	0.003	0.060	—
20	—	—	—	0.163	0.274	0.360	—
21	0.074 (0.000)	0.002 (0.062)	0.000	0.121	0.266	0.150	0.004
22	—	0.000 (0.049)	0.000	0.174	0.270	0.026	—
23	—	—	—	0.232	0.197	0.002	0.052
24	—	0.000 (0.230)	—	0.283	0.107	0.000	—

atomic position	oxophl. (**7**)	corrole free base (**8**)	tetradeh. corrin (**9**)	corrin free base (**10**)	azapor. (**11*a***)	oxapor. (**11*b***)	tetra azapor (**12**)	bili-verdin (**13**)	pyrro-methenes (**15, 17**)
1	0.021	0.140	—	—	0.170 (0.000)	0.114	0.187	0.145	0.347
2	0.129	0.076	0.009	—	0.069 (0.090)	0.096	0.063	0.004	0.137
3	0.000	0.026	0.002	—	0.046 (0.034)	0.008	—	0.250	0.117
4	0.115	0.168	0.010	0.014	0.188 (0.043)	0.185	—	0.004	0.398
5	—	0.074	0.300	0.316	0.000 (0.249)	0.037	0.000	—	0.000
6	—	0.128	0.002	0.020	—	0.168	—	—	—
7	—	0.106	0.024	—	—	0.107	—	—	—
8	—	0.040	0.016	—	—	0.054	—	—	—
9	—	0.192	0.012	0.016	—	0.226	—	—	—
10	0.295	0.000	0.370	0.372	0.002 (0.298)	0.000	—	0.114	—
11	0.046	—	—	—	0.185 (0.004)	—	—	0.114	—
12	0.076	—	—	—	0.075 (0.063)	—	—	0.106	—
13	0.067	—	—	—	0.062 (0.043)	—	—	0.040	—
14	—	—	—	—	0.200 (0.017)	—	—	0.192	—
15	0.305	—	—	—	0.000 (0.270)	—	—	0.000	—
16	0.058	—	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—	—	—
19	—	—	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—	—	—
21	0.028	0.038	0.170	0.168	0.001 (0.079)	0.004	0.000	—	0.000
22	—	0.004	0.244	0.274	—	—	—	—	—
23	0.152	—	—	—	0.000 (0.060)	0.114	—	0.010	—
24	—	—	—	—	—	—	—	—	—

† The s.c.f. parameters used are (Weiss, Kobayashi & Gouterman 1965): $U_C = -11.22$ eV, $U_N = (-38.74 + 12.10\ \mathrm{p})$ eV, $(\mathrm{ii/ii})_C = 9.49$ eV, $(\mathrm{ii/ii})_N = 12.12$ eV, $\beta_{C-C} = -2.39$ eV, $\beta_{C-N} = -2.32$ eV. Typical values of p used for U_N are: 1.5 for porphyrin, 1.75 for phlorin, 1.25 for corphin, 1.0 for pyridine and 2 for pyrrole. Two centre replusion integrals were computed using Nishimoto–Mataga relation (Mataga & Nishimoto 1957).

‡ See text for the definition of reactivity parameters.

§ In cases of near degeneracy of h.o.m.o. levels, the values obtained from the next highest m.o. are given in parantheses.

|| All calculations were carried out with the computer program QCPE 71.2 (Bloor & Gilson 1974).

TABLE 2. NUCLEOPHILIC REACTIVITY PARAMETERS FOR SOME TETRAPYRROLE PIGMENTS†

atomic position	por (**1**)	chl (**2**)	BChl (**3**)	trideh. corphin (**4**)	corphin (**5**)	corphin free base (V)	phlorin (**6**)	oxophl (**7**)	corrole free base (**8**)
1	0.062	0.128	0.113	—	0.035	0.032	0.002	0.020	0.080
2	0.074	0.086	0.105	0.056	—	—	0.128	0.091	0.032
3	—	0.140	—	0.004	—	—	0.006	0.004	0.046
4	—	0.080	—	—	0.160	0.142	0.106	0.080	0.082
5	0.156	0.224	0.125	0.123	0.027	0.168	—	—	0.136
6	—	0.047	0.072	—	0.207	0.200	—	—	0.128
7	—	0.036	—	0.060	—	—	—	—	0.000
8	—	—	—	0.038	—	—	—	—	0.130
9	—	—	—	—	0.283	0.352	—	—	0.000
10	—	—	—	0.000	0.002	0.032	0.314	0.238	0.434
11	—	—	—	—	0.270	0.328	0.002	0.023	—
12	—	—	—	0.026	—	—	0.170	0.133	—
13	—	—	—	0.050	—	—	0.011	0.050	—
14	—	—	—	—	0.150	0.034	0.196	—	—
15	—	0.069	—	0.095	0.080	0.020	0.000	0.054	—
16	—	0.072	—	—	0.135	0.026	—	0.137	—
17	—	—	—	—	—	—	—	—	—
18	—	—	—	0.546	0.305	0.224	—	—	—
19	—	—	—	—	0.018	0.014	—	—	—
20	—	—	—	0.329	0.103	0.166	—	—	—
21	0.028	0.004	0.000	0.151	0.105	0.144	0.020	0.029	0.052
22	—	0.096	0.171	0.022	0.014	0.088	—	—	0.090
23	—	—	—	0.020	0.035	0.010	0.034	0.017	—
24	—	0.112	—	0.063	0.083	0.012	—	—	—

atomic position	tetradeh. corrin (**9**)	corrin (**10**)	azapor (**11*a***)	oxapor (**11*b***)	tetraazapor (**12**)	biliverdin (**13**)	pyrromethenes (**15, 17**)
1	—	—	0.016	0.111	0.091	0.114	0.243
2	0.049	—	0.132	0.068	0.084	0.050	0.030
3	0.000	—	0.026	0.064	—	0.096	0.284
4	0.078	0.112	0.145	0.114	—	0.050	0.012
5	0.196	0.110	0.203	0.064	0.114	—	0.707
6	0.089	0.188	—	0.144	—	—	—
7	0.125	—	—	0.000	—	—	—
8	0.059	—	—	0.140	—	—	—
9	0.174	0.436	—	0.000	—	—	—
10	0.000	0.000	0.002	0.418	—	0.056	—
11	—	—	0.150	—	—	0.124	—
12	—	—	0.011	—	—	0.000	—
13	—	—	0.145	—	—	0.125	—
14	—	—	0.002	—	—	0.002	—
15	—	—	0.368	—	—	0.404	—
16	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—
19	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—
21	0.187	0.120	0.028	0.000	0.035	0.002	—
22	0.041	0.043	—	—	—	—	—
23	—	—	0.051	0.076	—	0.080	—
24	—	—	—	—	—	—	—

† See the footnote under table 1 for the s.c.f. parameters.

Table 3. Total π-electron densities for some tetrapyrrole pigments†

atomic position	por (**1**)	chl (**2**)	BChl (**3**)	trideh. corphin (**4**)	corphin (**5**)	corphin free base (V)	phlorin (**6**)	oxophlor (**7**)	corrole free base (**8**)
1	0.933	0.879	0.958	—	0.979	0.952	1.040	1.067	0.900
2	1.011	1.050	1.032	1.021	—	—	1.013	1.049	1.050
3	—	0.984	—	1.035	—	—	1.076	0.982	1.028
4	—	0.976	—	—	0.884	0.878	0.962	1.106	0.959
5	0.967	0.916	1.024	0.930	1.113	1.040	—	—	0.864
6	—	0.962	0.943	—	0.900	0.917	—	—	0.919
7	—	1.023	—	1.022	—	—	—	—	1.050
8	—	—	—	1.030	—	—	—	—	0.982
9	—	—	—	—	0.874	0.857	—	—	1.010
10	—	—	—	0.970	1.130	1.052	0.922	1.026	0.796
11	—	—	—	—	0.871	0.924	1.020	1.048	—
12	—	—	—	1.017	—	—	0.967	1.013	—
13	—	—	—	1.030	—	—	1.058	1.016	—
14	—	—	—	—	0.904	0.953	0.889	—	—
15	—	1.077	—	1.070	1.113	1.043	1.113	1.016	—
16	—	0.875	—	—	0.876	0.874	—	1.022	—
17	—	—	—	—	—	—	—	—	—
18	—	—	—	0.882	1.034	1.031	—	—	—
19	—	—	—	—	0.976	0.955	—	—	—
20	—	—	—	0.896	1.057	1.032	—	—	—
21	1.639	1.643	1.589	1.320	1.302	1.198	1.723	1.660	1.249
22	—	1.620	1.493	1.350	1.339	1.202	—	—	1.589
23	—	—	—	1.392	1.339	1.892	1.771	—	—
24	—	1.60	—	1.345	1.305	1.195	—	—	—

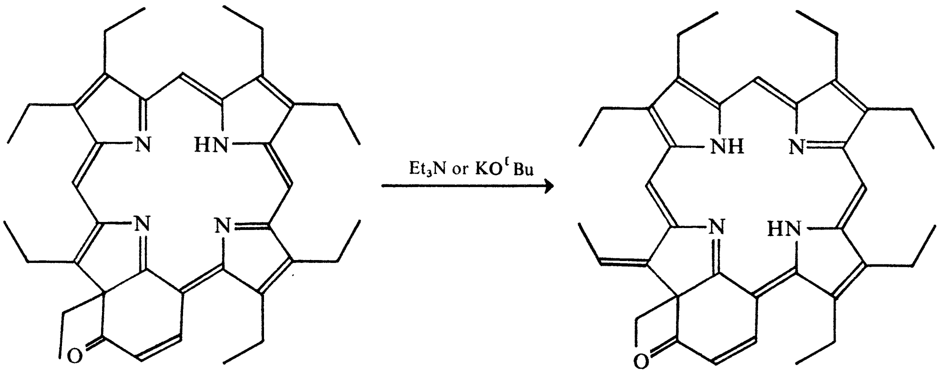
atomic position	tetradeh. corrin (**9**)	corrin (**10**)	azapor. (**11*a***)	oxapor. (**11*b***)	tetraazapor. (**12**)	biliverdin (**13**)	pyrromethenes (**15, 17**)
1	—	—	0.840	0.553	0.843	0.999	0.894
2	0.917	—	1.013	1.011	0.994	0.978	1.087
3	1.010	—	0.995	0.962	—	1.017	0.977
4	0.831	0.765	0.930	0.943	—	0.841	1.043
5	1.022	1.135	1.208	0.924	1.177	—	0.797
6	0.892	0.832	—	0.916	—	—	—
7	0.994	—	—	1.048	—	—	—
8	1.004	—	—	0.987	—	—	—
9	0.876	0.786	—	1.000	—	—	—
10	1.085	1.143	0.963	0.834	—	0.994	—
11	—	—	0.923	—	—	0.944	—
12	—	—	1.025	—	—	1.059	—
13	—	—	1.005	—	—	0.993	—
14	—	—	0.952	—	—	1.027	—
15	—	—	0.928	—	—	0.841	—
16	—	—	—	—	—	—	—
17	—	—	—	—	—	—	—
18	—	—	—	—	—	—	—
19	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—
21	1.432	1.457	1.650	1.636	1.648	1.754	1.599
22	1.507	1.452	—	—	—	—	—
23	—	—	1.630	1.607	—	1.560	—
24	—	—	—	—	—	—	—

† See the footnote under table 1 for the s.c.f. parameters.

examples will illustrate this: bromination of magnesium porphin yields meso tetrabromo porphin without appreciable attack of pyrrolic carbons (Schlözer & Fuhrhop 1975); oxidation of deuteroporphyrin IX dimethylester with lead dioxide leads to the meso tetraoxoporphinogen with no apparent attack of the pyrrole units (Inhoffen, Fuhrhop & v. d. Haar 1966); hydrogenation of porphyrins under a variety of conditions gives porphyrinogens with all four bridge carbons reduced and only subsequent attack of pyrrole sites (Fischer & Orth 1940; Chapman *et al.* 1971). Woodward had predicted such regioselectivity from simple valence bond arguments for nucleophilic reactions (Woodward 1962). The same preference in the other reaction types, however, cannot be rationalized on this ground. The results from m.o. calculations combined with the frontier orbital model on the other hand reproduce this experimental finding nicely: in both the h.o.m.o. and the l.u.m.o. it happens that the coefficients are higher in the meso carbons (0.15 and 0.16; from table 1) than in the pyrrolic sites (0.10; 0.06 and 0.06; 0.07) (see also Knop & Fuhrhop 1970).

3.2. *Chlorins* **2**

This macrocycle contains two methine bridges 5 and 10 which connect two pyrrole units as in the porphyrins and two methine bridge carbons 15 and 20 which are adjacent to a pyrrolin unit. It has been found that electrophilic attack and oxidation occur at positions 15 and 20 first. Relevant examples are the deuteration in deuterated acids (Woodward 1962), halogenation (Bonnett, Gale & Stephenson 1968), nitration (Bonnett & Stephenson 1965), photo-oxygenation (Fuhrhop, Wasser, Subramanian & Schrader 1974) and oxidation with thallium(III) salts (Smith & Cavaleiro 1973) which occur exclusively at these sites under mild conditions. Electrochemical reduction of chlorin-e_6-trimethylester on the other hand, yields the chlorin 10-phlorin (Inhoffen, Jäger & Mählhop 1971), which indicates a higher nucleophilic reactivity of carbon atom 10 as compared to 20. Both observations can again be rationalized with frontier orbital arguments: in the h.o.m.o. carbon atoms 15 and 20 have a charge density of 0.17 as compared to 0.12 for 5 and 10, whereas in the l.u.m.o. the corresponding values are 0.07 and 0.22.



18 **19**

3.3. *Tridehydrocorphins* **4**

Cross-conjugated porphyrin derivatives of type **4** have only recently been described (Inhoffen & Müller 1969; Witte & Fuhrhop 1975). An example of this class of compounds is given with formula **18** which rearranges to **19** under basic conditions (Witte & Fuhrhop 1975).

Its fundamental chemical property examined so far is the extreme ease of its one electron reduction to π-radicals. ($E^{\mathrm{red}}_{\frac{1}{2}} = -0.2$ V s.c.e.) Neither chlorins nor bacteriochlorins are of comparable reactivity in this respect. It is found difficult by the authors to rationalize this fact by comparison with related systems or by chemical intuition. The results from molecular orbital calculations, on the other hand, agree satisfactorily with experimental results: the cross-conjugated carbon atom 18 has the highest nucleophilic reactivity value (0.55) of any carbon atom of all tetrapyrrole pigments discussed here. Thus it seems probable that the primary attack of reductants, e.g. triethylamine is on this position. It has also been found, that alkyl substituents on this position are very easily deprotonated, e.g. an ethyl to an ethylidene group.

3.4. *Corphins* **5**

Protonation and hydrogenation of this ligand takes place on the cross-conjugated double bond between carbons 18 and 19 (Müller *et al.* 1973; Müller 1973). Oxidative attack with osmium tetroxide occurs at the double bond between carbon 1 and 20. The left-hand part of the molecule therefore seems to be the most reactive part in all kinds of reaction, be it attack by electron-rich or -deficient reagents. This behaviour is clearly different from the previously discussed regioselectivity observed in chlorins.

The model calculations do reproduce the experimental observations if the metal (or hydrogen) bond to the nitrogen is fixed to position 23. This may be justified for this specific π-system, which does not contain any symmetry axis, but an X-ray structural analysis is certainly necessary to clarify this point. The corresponding molecular orbital parameters are given in tables 1 and 2 under the heading V, free base. Electrophilic and nucleophilic reactivities are highest in both positions 18 and 20. In the corphin metal complex with no particular preference of metal to nitrogen bonds (**5** in tables 1 and 2) the agreement between calculations and experiment is rather poor.

3.5. *Phlorin* **6** *and oxophlorin* **7**

From the available literature data it is difficult to define the site of primary hydrogenation when phlorins **6** are reduced to the tetrahydroporphyrin stage. Mauzerall found that 10,15-dihydrophlorin is the first detectable product, which makes both opposite and adjacent methine bridges likewise candidates (Mauzerall 1962). Oxidation of this dihydrophlorin leads to 5,15-porphodimethenes **15** which in the case of dimethyl derivatives are quite stable (Buchler & Puppe 1970). The theoretical data of table 2 would strongly suggest a primary attack on the bridge atom 10 adjacent to the methylene bridge. Nucleophilic reactivity is 0.31 in position 10 and zero in position 15. Oxidation of oxophlorins **7** occurs with high preference on the bridge atom 15 opposite to the oxo bridge leading to 5,15-dioxoporphodimethenes **16** (Besecke & Fuhrhop 1974). The 5,10 dioxo isomer is usually formed in yields which are less by a factor of about 3–5 (Besecke 1974). The same regioselectivity is found in Vilsmeier formylation of oxophlorins (Besecke 1974). The calculated reactivities of table 5 reproduce this order qualitatively correct.

3.6. *Corrole* **8**, *tetradehydrocorrin* **9**

Hydrogenations of tetradehydrocorrins, e.g. with sodium borohydride occur primarily on position 5 (Klinzmann 1970). Oxygen converts tetradehydrocorrins in basic solutions first into the 5-oxo derivatives, which can be further oxidized to the 5,10,15-trioxo compounds (Hamilton & Johnson 1971). Halogenations also occur selectively at positions 5 and 15 (Hamilton & Johnson 1971). The calculated reactivities agree with this for 'nucleophilic' reduction, but not for the 'electrophilic' oxidations and halogenations. For corroles the values of table 2 would predict the opposite order of reducibility of methine bridges, but no relevant experiments are known to the authors.

3.7. *Corrins* **10**

Electrophilic deuteration, cyanation with chlorosulfonic isocyanate and alkylation of synthetic cobalt(II) corrins with chloromethyl-phenyl sulphide occur selectively at positions 5 and 15 (Bormann, Fischli, Keese & Eschenmoser 1967; Winacker 1968). Only when positions 5 and 10 are already occupied by alkyl substituents, e.g. methyl groups in vitamin B_{12} derivatives, further substitution in 10 is observed. This sequence is not reflected in the calculated reactivity parameters of table 1 which suggest the inverse order. Keese calculated the differences between the π-energies of the intact corrin chromophor and the 5 respective 15 complexes with an electrophile. The result indicated that the 5 σ-complex was more stable by about 4 kJ (1 kcal), which would agree with experimental findings (Bormann *et al.* 1967).

3.8. *Azaporphyrin* **11***a*, *oxaporphyrin* **11***b and tetraazaporphyrin* **12**

Hydrogenation of aza and oxaporphyrins occurs on position 15 as has been judged from the bilirubin like electronic spectrum of the products (Krüger & Fuhrhop, in preparation). This is in good agreement with the calculated nucleophilic reactivity.

In tetraazaporphyrins high reactivity of position 1 against electrophilics would be predicted from table 1. This is confirmed by one experiment on phthalocyanines where addition of benzoyl peroxides to this position has been reported (Pedersen 1957).

3.9. *Bilatrienes* **13, 14**

These biliverdins and their metal complexes form unstable radicals on oxidation which add rapidly molecular oxygen to form oxoviolins (see, for example, Fuhrhop & Mauzerall 1971), which bear an oxygen atom on position 10 or 20. Hydrogenation occurs primarily on position 15 to form bilirubins (see, for example, Nichol & Morell 1969). Agreement with data from tables 1 and 2 is perfect (only biliverdins have been computed, not the formylbiliverdins).

3.10. *Pyrromethenes* **17**

The electron densities in the frontier orbitals of pyrromethenes (tables 1 and 2) suggest that electrophilic substitutions should occur at α-pyrrolic sites 1 and 10 but not on the methine bridge. The meso carbon should however be very vulnerable to nucleophilic attack. Both predictions are generally confirmed by chemical experiments, which have been recently reviewed by Gossauer (1974) in his book on pyrroles.

3.11. *Summary*

Experimental data on the reactivities of tetrapyrrole pigments are limited in many cases. Also the PPP method and frontier orbital model have their own serious limitations. On the other hand, the authors have attempted to obtain the reactivity patterns by using a uniform parameter scheme throughout the computations. No parameter variations were made to give a better fit to the experimental data. In spite of the above simplifications, it has been observed in the present work that in about nine out of ten cases the frontier orbital model gives the right reactivity pattern. None of the differentiated reactivity patterns could have been concluded from simple chemical analogies or straightforward valence bond arguments. Therefore we think that Fukui's frontier orbital model is a useful tool to rationalize relative reactivities of carbon atoms within one tetrapyrrolic chromophore.

4. Metal–ligand interactions

Metal ions bound in the porphyrin cavity can dramatically change the properties of the ligand's π-system. Magnesium, for example, activates the porphyrin optimally toward reactions with oxidants (e.g. photo-oxygenation: Fuhrhop *et al.* 1974) or electrophiles (e.g. deuteration: Kenner Smith & Sutton 1973), whereas tin(IV) porphyrins are the most easily hydrogenated (e.g. phlorin formation with amines: Fuhrhop & Lumbantobing 1970). On the other hand, tin(IV) porphyrins are largely inert against bromine, because the positively charged central ion renders the π-system extremely stable against electrophiles (Fuhrhop *et al.* 1970). The trends in the reactivity patterns are best described quantitatively by the electrochemical potentials of one-electron oxidations and reductions of the porphyrin ligand in the metalloporphyrins. Here it is found that magnesium (low electronegativity, low oxidation number) makes the porphyrin easy to be oxidized $E^{\text{ox}}_{\frac{1}{2}} = 0.54$ V), but difficult to be reduced ($E^{\text{red}}_{\frac{1}{2}} = -1.68$ V), whereas tin(IV) has the opposite effect ($E^{\text{ox}}_{\frac{1}{2}} = > 1.4$ V, $E^{\text{red}}_{\frac{1}{2}} = -0.90$ V, Fuhrhop, Kadish & Davis 1973). All the other metals have effects intermediate between these two extremes. The difference $E^{\text{ox}}_{\frac{1}{2}} - E^{\text{red}}_{\frac{1}{2}}$ for the ligand reactions in 25 octaethylporphyrin-metal complexes is always around 2.2 V with only two exceptions (Mn, Mo). This has been interpreted with the most simple assumption that the porphyrin–metal bonds are largely localized in the porphyrin plane. The porphyrin π-system perpendicular to this plane is then only influenced by 'electrostatic' or 'inductive' forces of the more or less positively charged central ions (Fuhrhop *et al.* 1973). The same model has been extended for the chlorins (Fuhrhop 1970). The metal ions, on the other hand, take up electrons from the porphyrin ligand and their oxidation potentials are lowered by 0.5–0.8 V as compared to the corresponding hydrated metal ions (e.g. FeII/FeIII in water:

Table 4. Eigenvalues of the h.o.m.o. and l.u.m.o. for some tetrapyrrole pigments†

(The eigenvalues (in eV) of the two highest occupied (h.o.m.o.) and two lowest unoccupied (l.u.m.o.) molecular orbitals of some tetrapyrrole pigments.)

	por (**1**)	chl (**2**)	BChl (**3**)	trideh. corphin (**4**)	corphin (**5**)	phlorin (**6**)	oxophl. (**7**)	corrole (**8**)
h.o.m.o. I	−9.00	−9.06	−8.27	−8.36	−8.70	−8.49	−8.72	−9.06
h.o.m.o. II	−9.32	−9.30	−9.31	−9.61	−9.70	−9.80	−10.05	−10.39
l.u.m.o. I	−4.58	−4.75	−4.81	−5.29	−4.22	−4.86	−5.05	−5.53
l.u.m.o. II	−4.58	−4.03	−3.21	−4.08	−3.18	−3.73	−4.30	−3.89

	tetradeh. corrin (**9**)	corrin (**10**)	azapor (**11*a***)	oxapor (**11*b***)	tetra azapor. (**12**)	bilatriene (**14**)	pyrro-methenes (**15, 17**)
h.o.m.o. I	−8.89	−9.30	−9.29	−9.21	−9.15	−8.90	−9.69
h.o.m.o. II	−10.47	−10.31	−9.32	−10.24	−10.26	−9.84	−11.31
l.u.m.o. I	−4.90	−4.09	−4.74	−5.25	−4.84	−5.10	−4.48
l.u.m.o. II	−3.65	−2.80	−4.54	−4.14	−4.84	−4.00	−1.20

† For the s.c.f. parameters see table 1. The symmetries of the molecules are chosen to be those of the metal complexes.

0.53 V; in cytochrome *c*: 0.0 V). Further, the electron-rich metal ions cannot release part of their electrons into antibonding π-orbitals of the porphyrins by π-backbonding, because the energy of these orbitals is high (see table 4). Thus the high basicity of the nitrogen atoms and low π-acid strength are thought to determine the redox potentials of metals in metallo-porphyrins and -chlorins. For corrins, the same argument holds (see table 4) and the redox potentials are very similar to those of porphyrins ($E_{\frac{1}{2}}$ CoI/II: cobalt tetraphenylporphyrin: −0.85 V, vitamin B_{12}: −0.85 V).

In aza-, oxa- and tetraazaporphyrins as well as in phthalocyanines the nitrogen bridge atoms pull the electron density from central nitrogens. This raises the oxidation potential of the FeII/FeIII pair, e.g. in phthalocyanine by about 0.6 V as compared to porphyrins (Beck, Heiss, Hiller & Polster 1973). In bilatrienes the antibonding orbital is of considerable less energy than in porphyrins (see table 4), which would favour backbonding. It has been observed that manganese(II) biliverdinates are stable against oxygen and that the MnII/MnIII potential is at least 600 mV higher than in porphyrins (Fuhrhop *et al.* 1975). A possible rationalization would be that inductive effects of metal–nitrogen bonds on the π-system and effects of π-backbonding roughly cancel each other. Therefore we would also expect, that the reactivity of the π-system of such ligands is much less effected than in porphyrins by variations of the metals. We would also propose that electron donating power of the central nitrogens, perhaps best described by the p*K* of their protonation, together with π-acid strength, as roughly described by the energy of the l.u.m.o. of the framework, determine the redox potentials of central metal ions. More experimental data are certainly needed to substantiate or reject these generalizations. It may, however, be noted that geometrical differences of ligand fields are certainly of minor importance because all ligands **1–16** produce square planar fields around the metals with only very small deviations from planarity and bond distances found in metalloporphyrins.

5. Effects of substituents on the tetrapyrrolic periphery

The influence of substituents on the reactivity of the tetrapyrrolic π-systems is known only in porphyrins in some detail. It is found here that electron-withdrawing substituents like formyl cyano or nitro groups raise the oxidation potential of the π-system and redox active central metal ions by up to 0.2 V. Mild electrophilic substitution, e.g. Vilsmeier formylation, is usually impossible in such inactivated porphyrins (see, for example, Inhoffen *et al.* 1966). More important is the special role played by meso-hydroxy and amino substituents. Both these groups tend to donate electrons to the porphyrin ring, thereby forming oxo (or imino-) phlorins like **7**, which are easily oxidizable and in the form of their π-radicals undergo irreversible addition reactions (Fuhrhop, Besecke & Subramanian 1973). A qualitative idea of this behaviour is obtained if one correlates porphyrin and its derivatives with benzene and its corresponding derivatives like phenol and anilin. Typical points of similarity are the easy oxidation of hydroxy and amino derivatives to radicals and quinones, e.g. in the porphyrins series to **16**.

6. p*K* values of protonation of central nitrogen atoms

Only a few p*K* values of tetrapyrrole pigments are known with some certainty. The author's collection of p*K* values of the formation of a monoprotonated cation is given in table 5. It is seen that the p*K* is lowered if one follows the series phlorin–porphyrin–chlorin–bacteriochlorin.

This is also the order of π-electron density of the nitrogens which are to be protonated. The electron densities in the h.o.m.o. are all very low in these four cases. In corphin and corrin a sharp rise in p*K* is observed, although the total number of π-electrons on the nitrogens drops to five and charge density is further lowered. In these two cases, however, rather high reactivity against electrophilics is indicated by the large atomic orbital coefficients in the h.o.m.o. These few cases suggest that these coefficients also determine protonation reactions in the hetero atoms. Only when they are small, charge densitities appear to be the dominating factors. This general conclusion from the few available data is, of course, rather uncertain.

TABLE 5. p*K* VALUES OF PROTONATED TETRAPYRROLIC MONOCATIONS, ELECTRON DENSITIES AND ELECTROPHILIC REACTIVITY PARAMETERS OF NITROGEN ATOMS

	approx. p*K*†	π-electronic charge density‡		electrophilic parameter
phlorin **6**	9[1]	1.72	**7**	0.07
porphyrin **1**	4[2]	1.64	**6**	0.07
chlorin **2**	2[2]	1.62	**6**	0.02
bacteriochlorin **3**	⩽ 0[3]	1.49	**6**	0.00
corphin **5**	7.3[4]	1.20	**5**	0.15
corrin **10**	8.6[5]	1.46	**5**	0.27

† [1] Woodward (1962). [2] Phillips (1960); Falk (1964). [3] Estimated from 'Säurezahl', see Phillips (1960). [4] Müller *et al.* (1973). [5] Bormann, Fischli, Keese & Eschenmoser (1967).

‡ In the free base the protons are placed on the nitrogens starting with the one with the highest charge density. Of the nitrogen atoms which are free, the one with higher charge density is considered here for protonation to form the monocation.

7. THE EFFECTS OF GRADUAL SATURATION OF β-PYRROLIC DOUBLE BONDS

Both the one-electron oxidation and reduction of the π-electron systems become easier in the series porphyrins, chlorins and bacteriochlorins (Fuhrhop & Mauzerall 1969; Fuhrhop 1970). This would suggest that the eigenvalues of the h.o.m.o. increases in the same order and the energy of the l.u.m.o. decreases. This is only partly born out qualitatively by the calculated data of table 4. It is also known that methine bridges 15 and 20 in chlorins are more reactive against electrophiles than the meso carbons in porphyrins. This is not reflected in the corresponding parameters of table 1. These are two examples of the quite general finding that differences between reactivities of different tetrapyrrole classes are not paralleled by equivalent differences in reactivity parameters, which have been so successful in evaluating reactivity patterns of single systems. On the whole hydrogenation of one or two peripheric double bonds makes methine bridges more nucleophilic and simplifies redox reactions of the π-systems, but the general aromatic properties of the porphyrin nucleus exemplified by the formation of stable π-radicals and reversible phlorin–porphyrin equilibria, remain unaltered. A dramatic change in the reactivity is observed in tridehydrocorphins (**4**), which have the same oxidation state as a porphyrin. These compounds contain a highly non-uniform charge distribution in the l.u.m.o. (table 2) and are reduced to π-radicals at potentials about 1.5 V higher than porphyrins (e.g. **8** at −20 mV; Witte & Fuhrhop 1975). This radical formation is partly reversible. The corphin free bases (V) show a similar situation in the h.o.m.o., which explains the easy protonation of the cross conjugated double bond (Müller *et al.* 1973*a*).

8. THE EFFECTS OF AN INTERRUPTION OF THE MACROCYCLIC CONJUGATION AT A METHINE BRIDGE

The π-system of all the tetrapyrrolic pigments with no macrocyclic conjugation pathway exhibit quite similar chemical properties, irrespective of whether a methine bridge is hydrogenated (phlorins **6**), oxidized (oxophlorin **7**) or eliminated (corroles **8**, corrins **10** and bilatrienes **14**). They are easily oxidized ($E_{\frac{1}{2}}^{\text{ox}}$ approx. 0.3 V) and reduced ($E_{\frac{1}{2}}^{\text{red}}$ = approx. -0.5 V) but the radicals produced are generally not stable in solutions. Irreversible additions of electrophiles and nucleophiles usually follow radical formation and structures of products are often unknown. A possible explanation of this behaviour may be that the systems which lack one methine bridge are more easily distorted from planarity than the porphyrins. This renders α-pyrrolic sites, which have often high atomic orbital coefficients in the frontier orbitals (see tables 1 and 2), open to attack by reagents, which cannot reach these positions in the porphyrins and chlorins. The reaction would then be completed by the addition of a second partner to an adjacent methine bridge. Under rigorous conditions, porphyrins can also be reduced or oxidized at α-pyrrolic sites, and such reactions are also irreversible and lead to opening of the macrocycle.

TABLE 6. EXPERIMENTAL AND CALCULATED (SINGLET–SINGLET) ELECTRONIC TRANSITIONS IN THE LONGEST WAVELENGTH REGION FOR SOME TETRAPYRROLE PIGMENTS

(Systems in which the β pyrrolic positions are hydrogenated.)

(*a*) Effect of hydrogenation in the β pyrrolic position

chromophore	BChl **3**	chl **2**	por **1**	corphin **5**
λ_{max} (exper.)†	(~ 700)[1]	614[2]	574[3]	547[4]
λ_{max} (theor.)‡	700	640	630	540

(*b*) Effect of substitution or elimination of a methine bridge

chromophore	phl **6**	biliverdin **13**	oxophl. **7**	oxapor. **11** *b*	azapor **11** *a*	corrole **8**	corrin **10**
λ_{max} (exper.)†	~ 810[5]	790[6]	675[7]	660[8]	570[9]	549[10]	514[11]
λ_{max} (theor.)	850	760	750	740	610	570	530

† Where available spectra of zinc complexes of chromophores with alkyl groups or hydrogen as substituents have been selected. The exceptions are the phlorin derivative, which is a tetraphenylporphyrin; the corrole example (**8**) is a copper complex.

‡ The transition energies were computed employing twenty configurations for CI in each case.

[1] Extrapolated from free base octaethyl bacteriochlorin (Eisner 1957) and from spectral shifts observed in octaethylchlorin and its zinc complex (Fuhrhop 1970). [2] Fuhrhop (1970). [3] Fuhrhop & Mauzerall (1969). [4] Müller (1973). [5] Closs & Closs (1963). [6] Fuhrhop *et al.* 1975. [7] Jackson, Kenner & Smith (1968). [8] Besecke (1974). [9] Fuhrhop & Krüger (in preparation). [10] Johnson & Kay (1965). [11] Bormann *et al.* (1967).

9. ELECTRONIC SPECTRA

All the chromophores **1–14** and **16** produce one or two absorption bands in the near u.v. (usually around 400 nm) and another group of bands in the visible and near infrared (between 500 and 900 nm). Usually one strong band ($\varepsilon \approx 10^4$–10^5) is found in each region. In porphyrins (**1**) the near u.v. band is of exceptional high intensity. (Soret band $\varepsilon \geqslant 10^5$). The bands have usually a half-line width of more than 100 nm, but are much narrower in porphyrins and chlorins. (Collections of spectra: porphyrins, Falk (1964); Fuhrhop (1974*a*); corrinoids, Pratt (1972); bilatrienes, Rüdiger (1971) and Fuhrhop *et al.* (1975).) The most variable and therefore most descriptive characteristic of tetrapyrrole chromophore electronic spectra is the position of the longest wavelength absorption (α band). This value is listed for the zinc complexes of tetrapyrrole compounds which contain only hydrogen and alkyl groups as peripherical substituents, in table 6. It is seen that the order of these transition energies in the two series of related pigments is almost identical with the order of calculated transitions, although the numerical values are often far apart. We believe that this feature adds to the usefulness of the molecular orbital approach, because it allows to establish some expectancy values for yet unknown tetrapyrrolic systems, e.g. some possible intermediates in biosynthetic pathways.

10. N.M.R. AND E.S.R. SPECTRA

Porphyrin derivatives **1–4** (see, for example, Abraham, Jackson, Kenner & Warburton 1963; Katz *et al.* 1963) and **11***a–c* (Fuhrhop *et al.* 1975) show strong paramagnetic shifts of methine proton signals in the p.m.r. spectra by ring current effects (chemical shifts: $\tau = 9–10$ parts/10^6). In the other pigments this effect is absent (τ (methine protons) = 6 parts/10^6).

E.s.r. spectra of tetrapyrrolic complexes with paramagnetic central ions, e.g. copper(II) or cobalt(II), reveal that all known complexes of ligands **1–16** are essentially planar and that the metal to nitrogen bond is covalent to an extent of 30 % or more (Subramanian, Fuhrhop, Salek & Gossauer 1974; Roberts & Koski 1960; Kivelson & Neiman 1961; Manoharan & Rogers 1969; Bohandy, Kim & Jen 1974).

11. POSSIBLE BIOLOGICAL IMPLICATIONS

Uroporphyrins are easily accessible by prebiotic synthesis from simple precursors such as glycine and succinic acid (Granick & Mauzerall 1961; Burnham 1969). In the course of evolution various porphyrins, chlorins, bacteriochlorins, corrins and bile pigments were formed from the original uroporphyrins. Metallation, hydrogenation and oxygenation, electrophilic alkylation, expulsion of an oxidized methine bridge in the form of carbon monoxide and intramolecular rearrangements are the most important types of reactions found in the course of these biosynthetic processes. All of the reactions are inherent in the *in vitro* chemistry of porphyrins (Fuhrhop 1974*b*). Biologically useful variations of the porphyrin ligand have been selected by evolution as specific reagents and catalysts for a variety of reactions. We would now like to speculate briefly on bio-organic properties of tetrapyrrole pigments as a basis of their selection in biological systems. The intense long-wavelength α-band of chlorins helps the efficient use of sunlight and complexation with magnesium facilitates energy conversion by chlorophyll radical formation. This is one of the central reactions in photosynthesis. The electron rich nitrogen atoms of porphyrin dianions together with low π-acidity of the chromophor lead, after complexation with iron, to central iron ions which are ideally suited to donate electrons into the antibonding orbitals of molecular oxygen, thereby activating it in reactions with organic substrates. This made possible the reversal of photosynthesis. In the presence of organic peroxides, however, iron porphyrins are easily autoxidized to biliverdins, which are further degraded. The macrocycle therefore had to be protected by a protein cover, which only let free the central iron for oxygen attack. The reactivity and redox potentials of cobalt with corrin and porphyrin ligands are very similar. Therefore one may ask why the complicated vitamin B_{12} structures, e.g. for methyl transfer reactions, has been developed. A possible rationalization would be that reaction of cobalt porphyrins with, for example, *S*-adenosylmethionine yielded highly methylated porphyrins, which then rearranged to corrins when methylation of an α-pyrrolic position lead to a splitting of the porphyrin macrocycle. The cobalt(II) corrins did then react as 'supernucleophilic' similar to the cobalt porphyrins, since for both these ligands the ligand fields and π-acidity are comparable. The corrins mainly because of steric hindrance, could not be destroyed by further methylation. This could also explain why a protein is not needed in this specialized coenzyme to protect the chromophore against the reagent it activates.

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Discussion

J. W. BUCHLER (*Institut für Anorganische Chemie der Technischen Hochschule Aachen*, 51 *Aachen*, *Professor-Pirlet-Str.* 1). Dr Fuhrhop mentioned that π-backbonding to metals is not important in transition metal porphyrins quoting earlier results of Professor Gouterman. Both Professor Gouterman and myself have now ample evidence that π-back donation to the porphyrin ligand occurs with many transition metal ions, especially with those having d^6 to d^7 configurations. This follows from optical absorption and emission spectra as well as from i.r. and n.m.r. spectra.

J.-H. FUHRHOP. I am not aware of any i.r. or n.m.r. data which unequivocally point to significant π-back-bonding. With a few exceptions like Mn (III) porphyrins, π-back-bonding does not appear to be significant at least in the porphyrin complexes with the metals of the first transition series. More experimental approaches which are quite sensitive to this aspect must be undertaken to settle this problem.