+0.28 (m, 2, cyclopropyl CH_2), 0.47 (m, 1, cyclopropyl CH_3CH), 0.65 (d, 3, J = 5.9 Hz, CH_3), 0.80, 1.15, 1.35, 1.85 (m's, 10, cyclohexyl CH_2's), 3.30 (s, 3, OCH_3). Trans stereochemistry was assigned to this compound because of the 4.7-Hz coupling constant, which is too small to be due to cis coupling;[19] IR (CCl_4) 1740 cm^{-1} (C=O). Anal. ($C_{12}H_{20}O_2$) C, H.

E. 1-(Carbomethoxy)-1-(2-(carbomethoxy)cyclopropyl)-cyclohexane (6). Use of 0.27 g (0.55 mmol) of π-[1-(carbomethoxy)allyl]palladium chloride produced 0.098 g (37%) of compound 6 after purification by preparative-layer chromatography (silica gel, 2:1 hexane/ether, R_f 0.4): ^1H NMR (360 MHz, benzene-d_6/Me_4Si) δ 0.77 (apparent 8-line m, 1, cyclopropyl CH), 0.92, 1.30, 1.45, 2.08 (m's, 10, cyclohexyl CH_2's), 1.13 (m, 1, 1 H of cyclopropyl CH_2), 1.73 (m, 2, cyclopropyl CHCOOMe and other H of CH_2), 3.24 (s, 3, OCH_3), 3.36 (s, 3, OCH_3); ^{13}C NMR (benzene-d_6/Me_4Si) δ 11.44 (t, cyclopropyl CH_2), 16.52 (d, cyclopropyl CH), 23.70 (m, cyclohexyl C_3 and C_5), 25.81 (m, cyclohexyl C_4), 31.29 (d, cyclopropyl CHCOOMe), 33.16 (t, cyclohexyl C_2 and C_6), 46.53 (s, cyclohexyl quaternary C_1), 51.09 (q, CH_3O), 51.26 (q, CH_3O), 173.59 (s, C=O), 174.34 (s, C=O); IR (CCl_4) 1728 cm^{-1} (C=O). Anal. ($C_{13}H_{20}O_4$) C, H.

F. 1-(Carbomethoxy)-1-(3-phenyl-2-propenyl)cyclohexane (7). From 0.29 g (0.55 mmol) of π-(1-phenylallyl)palladium chloride, 0.14 g (48%) of compound 7 was obtained after purification by preparative-layer chromatography (silica gel, 2:1 hexane/ether, R_f 0.4): ^1H NMR (CCl_4/Me_4Si) δ 1.3, 2.1 (br m's, 10, cyclohexyl CH_2's), 2.33 (t, J = 6 Hz, 2, CH_2C=), 3.60 (s, 3, OCH_3), 6.1 (m, 2, CH=CH), 7.2 (m, 5, Ar H); IR (CCl_4) 1735 cm^{-1} (C=O). This material is identical in all respects with that made by the alkylation of cinnamyl bromide with the enolate of methyl cyclohexanecarboxylate.

G. Methyl 2-Ethyl-2-cyclopropylhexanoate (8). By use of 0.20 g (0.55 mmol) of π-allylpalladium chloride and 0.35 g (2.2 mmol) of methyl 2-ethylhexanoate, compound 8 (0.11 g, 50%) was obtained after purification by preparative-layer chromatography (silica gel, 4:1 hexane/ether, R_f 0.8): ^1H NMR (360 MHz, $CDCl_3$/Me_4Si) δ 0.32 (m, 4, cyclopropyl CH_2CH_2), 0.86 (t, 3, J = 7.2 Hz, CH_3), 0.91 (t, 3, J = 7.2 Hz, CH_3), 1.18 (m, 1, cyclopropyl CH), 1.3, 1.5 (m's, 6, CH_2's), 1.57 (q, 2, J = 7.3 Hz, CCH_2CH_3), 3.63 (s, 3, OCH_3); IR (CCl_4) 1725 cm^{-1} (C=O). Anal. ($C_{12}H_{22}O_2$) C, H.

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Registry No. 1, 53651-72-2; 3, 75266-48-7; 4, 75266-48-7; 5, 75266-49-8; 6, 75266-50-1; 7, 75266-51-2; 8, 75266-52-3; π-(2-deuterioallyl)palladium chloride, 75284-17-2; diethyl methylmalonate, 609-08-5; π-allylpalladium chloride, 12012-95-2; methyl cyclohexanecarboxylate, 4630-82-4; π-crotylpalladium chloride, 12081-22-0; π-[1-(carbomethoxy)allyl]palladium chloride, 12117-04-3; π-(1-phenylallyl)palladium chloride, 12131-44-1; methyl 2-ethylhexanoate, 816-19-3.

(19) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, pp 360-361.

Reactions of Protoporphyrin with Tetracyanoethylene

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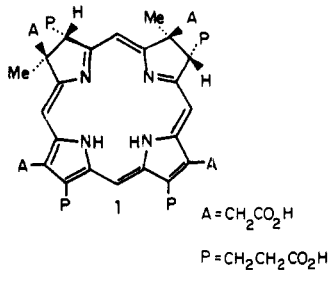
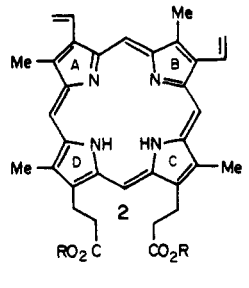
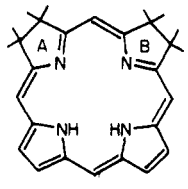
The vinyl groups of protoporphyrin react with tetracyanoethylene (TCNE) in a [2 + 2] reaction to give adducts containing one and two cyclobutane rings. In addition, the vinyl groups and the porphyrinic β-β cross-conjugated double bonds in rings A and B react with TCNE in a [4 + 2] cycloaddition reaction, giving chlorins when either ring A or B reacts or an isobacteriochlorin when both rings react. Reactions in which one vinyl group reacted in a [2 + 2] and the other in a [4 + 2] fashion were also observed.

The recent appreciation of the role of sirohydrochlorin (1) in the biosynthesis of vitamin B_{12}[1] and that of siroheme (the iron complex of 1) in the enzymatic reduction of nitrite and sulfite[2] has highlighted the importance of the isobacteriochlorin chromophore in nature.

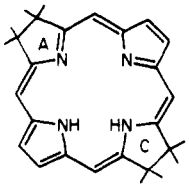




Isobacteriochlorins (3), in which the β-β' cross-conjugated double bonds in rings A and B of the porphyrin nucleus have been reduced, can be prepared from the reduction of porphyrins under a variety of reducing conditions.[3] Reduction of metalloporphyrins with sodium in amyl alcohol[4] increases the yield of the isobacteriochlorin over that of bacteriochlorin (4) where the cross conjugated



isobacteriochlorin 3



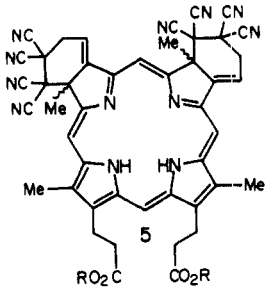
bacteriochlorin 4

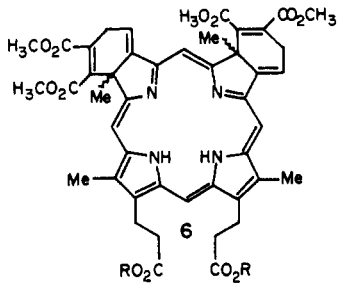
(1) A. R. Battersby, E. McDonald, R. Weier, and M. Thompson, *J. Chem. Soc., Chem. Commun.*, 960 (1979), and references therein.
(2) J. M. Vega and H. Kamin, *J. Biol. Chem.*, **252**, 896 (1977), and references therein.
(3) H. Scheer in "The Porphyrins", Vol. II, D. Dolphin, Ed., Academic Press, New York, 1978, Chapter 1.
(4) A. M. Stolzenberg, L. O. Spreer, and R. H. Holm, *J. Am. Chem. Soc.*, **102**, 364 (1980).

0022-3263/80/1945-5196$01.00/0

double bonds in rings A and C are reduced. The low yields and subsequent isolation and separation of the products make these systems difficult to prepare, and the instability of the tetrahydroporphyrins toward oxidation makes their study, especially as models of enzymic prosthetic groups, tenuous. This problem has recently been alleviated by preparing model isobacteriochlorins with alkyl rather than hydrogen substituents at the periphery.[5]

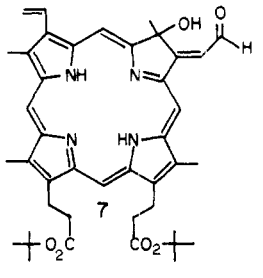
The suggestion[6] that protoporphyrin dimethyl ester **2** (R = CH_3) gave the isobacteriochlorin **5** (R = CH_3) when reacted with tetracyanoethylene (TCNE), and **6** (R = CH_3)

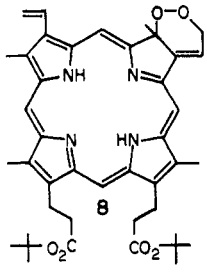




with dimethyl acetylenedicarboxylate, appeared to provide a simple route to the isobacteriochlorin chromophore. However, we have reexamined the reaction of protoporphyrin with TCNE and find a more complicated system than was initially reported.

[2 + 2] and [4 + 2] cycloaddition reactions have been extensively investigated from both theoretical and synthetic viewpoints.[7-11] Such reactions, however, have not had extensive application in the field of porphyrin chemistry. Excepting the report of Callot, Johnson, and Sweeny,[6] the only example of a Diels–Alder reaction in the porphyrin field is that of protoporphyrin with singlet oxygen to give photoprotoporphyrin **7** via the singlet oxygen adduct **8**, with the cycloaddition occurring in either ring A or B but not both.





Results

We have examined the products from the reaction of protoporphyrin esters with TCNE and describe in detail here the use of protoporphyrin di-*tert*-butyl ester (**2**, R = $(CH_3)_3C$) which in our hands was more amenable to manipulation than the corresponding dimethyl ester. Nevertheless, both esters qualitatively and quantitatively undergo the same reactions.

In our initial experiments, reactions of TCNE with protoporphyrin di-*tert*-butyl ester were shown by silica gel TLC (chloroform/ether, 40:1, or chloroform/acetone, 40:1)

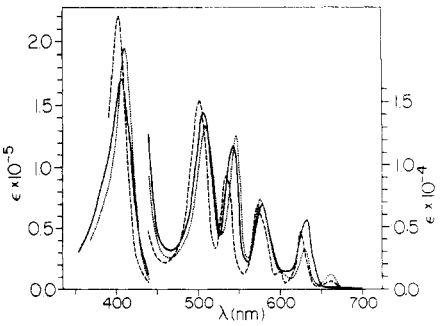
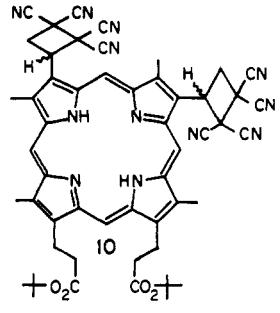
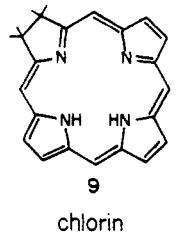


Figure 1. Visible spectra of protoporphyrin di-*tert*-butyl ester (**2**) (—) and its mono (···) and bis (- - -) TCNE adducts (**20** and **10**).

to give three major products. Furthermore, the product distribution changed little between reaction times of 2 and 48 h, obviating the necessity for the longer reaction time reported by Callot et al.[6] Refluxing protoporphyrin di-*tert*-butyl ester with 5.25 equiv of TCNE for 2–4 h in chloroform gave inter alia an insoluble brick-red material which was crystallized from acetone/petroleum ether. The electronic spectrum showed that this material was a porphyrin with an etio-type[12] visible spectrum (Figure 1). Chromatography on silica gel of the chloroform-soluble products from the above reaction, which were green, gave two compounds whose visible spectra were consistent with those of chlorins (**9**) or isobacteriochlorins (**3**). Elemental analyses of all three compounds showed them to be bis(TCNE) adducts of the porphyrin diester.



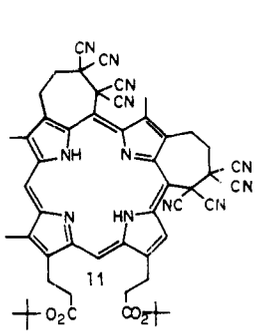


chlorin

Analytical chromatography (acetone/petroleum ether, 14:5, or chloroform acetone, 2:1) of the porphyrin component from the chloroform reaction revealed that two compounds were present. The two porphyrins were too unstable to be completely separated and purified by preparative chromatography, but they could be purified by fractional crystallization. Their visible spectra were nearly identical, while NMR spectroscopy of both compounds revealed no vinyl protons, two protons in the region δ 7–7.5, four protons in the region δ 4–5 (partially superimposed on the α-propionate protons), and *four* meso protons.

Three possible *porphyrin* structures suggest themselves for the bis(TCNE) adduct; they are the [2 + 2] cycloadduct containing two cyclobutane rings (**10**), a system containing two seven-membered rings (**11**), and the acyclic adduct **12**. Only structure **10** is consistent with the observed NMR spectra. The [2 + 2] cycloadditions of two TCNE molecules with protoporphyrin will give two diasteriomeric pairs

(5) C. K. Chang, *Biochemistry*, **19**, 1971 (1980).
(6) H. J. Callot, A. W. Johnson, and A. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1424 (1973).
(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1971.
(8) P. D. Bartlett, *Q. Rev., Chem. Soc.*, **24**, 473 (1970).
(9) R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).
(10) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).
(11) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967); **5**, 211 (1966).
(12) In an "etio type" electronic spectrum the highest energy visible band (IV) is more intense than band III (the next highest in energy). In "rhodo type" electronic spectra, which occur when the porphyrin 2- and 4-substituents have markedly different electron-withdrawing properties, band III is more intense than band IV.[13]
(13) M. Gouterman in "The Porphyrins", Vol. III, D. Dolphin, Ed., Academic Press, New York, 1978, Chapter 1.



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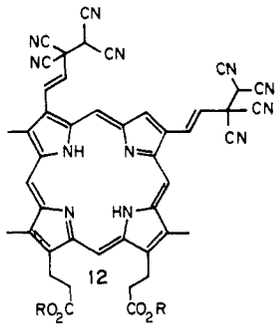
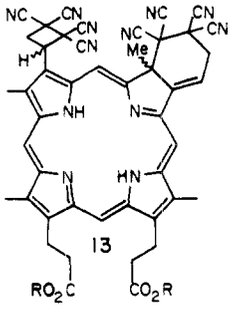


12

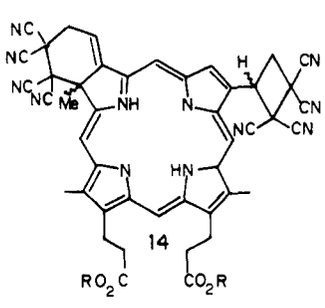
(each containing two enantiomers), and it is the diastereomers which were separated by fractional crystallization and TLC.

The 270-MHz NMR spectrum of the more mobile enantiomeric pair of **10** reveals two separate resonances at δ 6.93 and 7.12 each integrating for one proton (each a triplet) corresponding to the two unique cyclobutane methine protons. The less mobile enantiomeric pair of **10** exhibited a multiplet at δ 6.48 for the two cyclobutane methine protons which apparently exhibit very similar chemical shifts.

Although the visible spectra (see Figure 2 for an example) of the green bis(TCNE) adducts by themselves left the chlorins **13** and **14** and the isobacteriochlorin **5** (as a

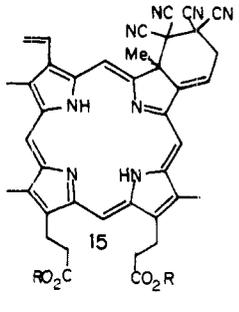


13



14

pair of diastereomers) as possible structures, further data favored the first two structures, **13** and **14**. Loss of 1 mol of TCNE (from the green bis(TCNE) adducts) gave products which were clearly chlorins, the [4 + 2] monoadducts **15** and **16** (see Figure 2 for an example). The more



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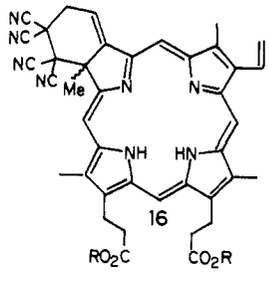


16

mobile green bis(TCNE) adduct of **13** and **14** showed only one spot on silica gel TLC (chloroform/acetone, 30:1), but the less mobile partner chromatographed as two poorly resolved spots. Each of the chlorins **13** and **14** will be formed as pairs of diastereomers, but only in the latter case have we been able to develop a chromatographic system that begins to resolve the pairs of diastereomers. Nevertheless, both of the green bis(TCNE) adducts showed more than four but less than eight separate meso protons and more than four but less than eight separate pyrrole ring methyl groups in their NMR spectra. These data are consistent with both **13** and **14** being diastereomeric mixtures. In addition, and in both cases, the unambiguous

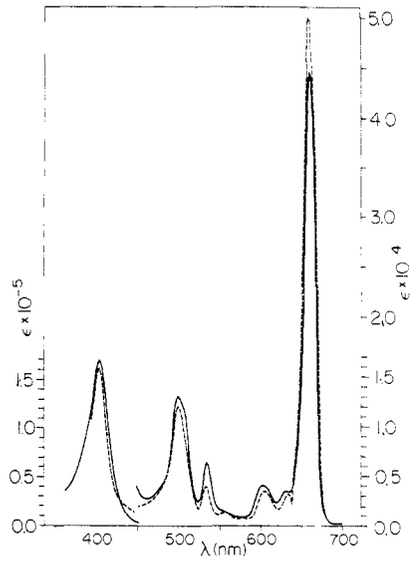


Figure 2. Visible spectra of a [4 + 2]/[2 + 2] TCNE monoadduct (---) (**13** or **14**, isomer 2) and a mono [4 + 2] TCNE adduct (—) (**15** or **16**, isomer 2) of protoporphyrin di-*tert*-butyl ester.

observation of a single cyclobutane methine proton and two aliphatic methyl groups (one for each diastereomer and each integrating to 1.5 protons) confirms their structures as **13** and **14**.

Further study on the reaction of protoporphyrin di-*tert*-butyl ester with two molecules of TCNE showed that the [2 + 2] adduct porphyrins **10** were the kinetically favored products as short reaction times under conditions where their solubilities were limiting favored their formation. Longer reaction times under conditions where the [2 + 2] adducts remained in solution favored the formation of **13** and **14**, the thermodynamically more stable isomers. A single ambiguity remained, however, for the only bis(TCNE) adduct that we had not isolated was the isobacteriochlorin **5** which Callot et al. claimed was the only product formed in the reaction. It was finally observed that under the conditions favoring the formation of the bis(TCNE) chlorins **13** and **14**, small amounts of the mono [4 + 2] chlorins (**15** and **16**) were invariably present. Chromatographing closely behind and partially superimposed on the less mobile of the chlorins **15** and **16** (chloroform/acetone, 30:1) was a blue-green compound with an electronic spectrum consistent with that of an isobacteriochlorin (Figure 3). Separation of this compound from the less mobile of the pair **15** and **16** proved extremely difficult. Finally, it was found that chromatography on silica gel using dichloromethane/88% aqueous formic acid (100:1 v/v) caused all other TCNE addition products to be protonated and remain at the top of the column while the unprotonated bis [4 + 2] isobacteriochlorin adduct (**5**, R = $(CH_3)_3C$) was eluted with an R_f of ~0.5. The yield of **5** was low even in the presence of an eightfold excess of TCNE. Furthermore, even in the presence of such an excess of the dienophile, the [4 + 2] monoadducts **15** and **16** were always present in the reaction.

These results along with the subsequent observation that direct [4 + 2] reaction of vinyl porphyrins with TCNE was never observed indicated that rearrangement of the mono [4 + 2] and [2 + 2] chlorins **13** and **14** to the [4 + 2] diadduct **5** competed unfavorably with loss of TCNE from the tetracyanocyclobutane ring of **13** and **14**. Forcing the reaction toward the [4 + 2] diadduct by increasing the TCNE concentration was precluded by the already high TCNE concentrations employed and the limiting solubility of TCNE in chloroform.

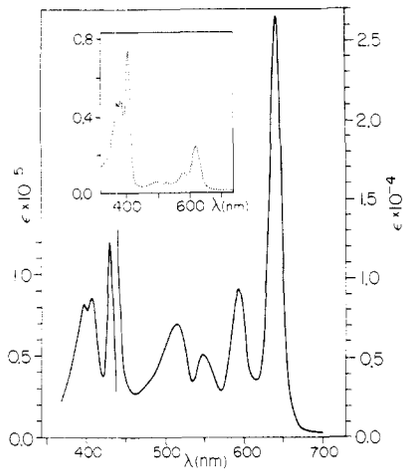
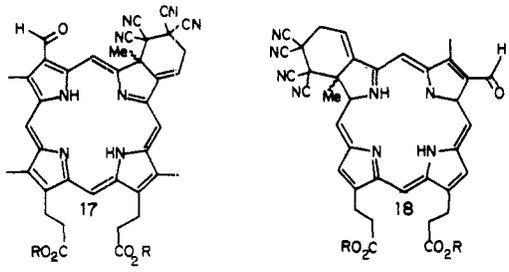


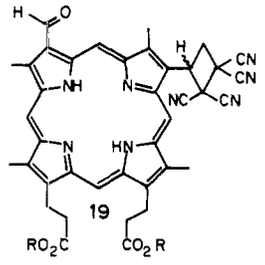
Figure 3. Visible spectra of the [4 + 2] bis(TCNE) adduct of protoporphyrin di-*tert*-butyl ester (**5**) (—) and (inset) sirohydrochlorin octamethyl ester in methanol/H_2SO_4 [M. J. Murphy and L. M. Siegel, *J. Biol. Chem.*, **248**, 6911 (1973)].

In view of the multiplicity of products obtained in the reaction of two molecules of TCNE with the protoporphyrin ester, some simpler systems were investigated in order to provide further evidence for the [2 + 2] addition of TCNE to vinyl porphyrins. Reaction of a mixture of 2-formyl-4-vinyldeuteroporphyrin and 2-vinyl-4-formyldeuteroporphyrin di-*tert*-butyl esters with excess TCNE in refluxing chloroform produced a porphyrin with an etio-type spectrum which we were unable to purify. Continued reflux resulted in conversion of this porphyrin into two chlorins whose NMR spectra were consistent with structures **17** and **18**. Experiments with the pure isomers,



2-formyl-4-vinyldeuteroporphyrin and 2-vinyl-4-formyldeuteroporphyrin as their *tert*-butyl esters, showed that the chlorin of greatest mobility on silica gel, which was orange, was **17**, the [4 + 2] TCNE adduct of the 2-vinyl-4-formyldeuteroporphyrin. The chlorin of lesser mobility on silica gel, which was green, proved to be **18**, the [4 + 2] TCNE adduct of 2-formyl-4-vinyldeuteroporphyrin.

Reaction of the 2-formyl-4-vinyldeuteroporphyrin ester with TCNE at room temperature, however, gave the pure TCNE adduct, as a porphyrin, **19**, with an etio-type visible



spectrum (Figure 4), in high yield. Isolation of the pure porphyrin was only possible in this case because it crystallized from the reaction mixture. NMR analysis of this

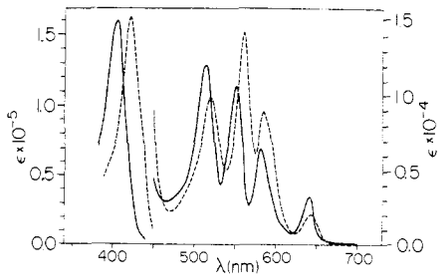
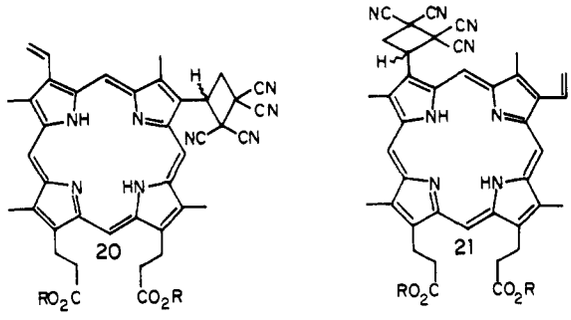


Figure 4. Visible spectra of 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester (- - -) and its [2 + 2] TCNE adduct (**19**) (—).

compound showed a doublet of doublets at δ 6.50 for the cyclobutane methine proton and four meso protons, but no vinyl protons were observed. These data are again consistent with a [2 + 2] addition to 2-formyl-4-vinyldeuteroporphyrin having occurred to give **19** which possesses a single tetracyanocyclobutane ring. The fact that this compound possesses an etio-[12] instead of a rhodo-type visible spectrum (Figure 4) indicates the tetracyanocyclobutane ring possesses appreciable "rhodofying"[12] character.

Further evidence of the rhodofying nature of the tetracyanocyclobutane ring came from the reaction of protoporphyrin di-*tert*-butyl ester with a single equivalent of TCNE. At room temperature this reaction forms an unstable porphyrin which may be isolated by direct crystallization of the reaction mixture. This compound proved to be the mixed mono [2 + 2] TCNE adducts of protoporphyrin **20** and **21**. In the case of these porphyrins,



protons of a single vinyl group were observed in the NMR spectrum. In the visible spectrum, however, band III is of about equal intensity to band IV (Figure 1). Thus the tetracyanocyclobutane ring is again shown to possess appreciable rhodofying character.

Allowing **20** and **21** to stand overnight in chloroform or refluxing protoporphyrin di-*tert*-butyl ester with a single equivalent of TCNE in chloroform for 4 h produced the expected two [4 + 2] monoadduct chlorins **15** and **16**.

The relationship of the products and the reversibility of the reaction was investigated next. Refluxing of a mixture of the diastereomers represented by **10** in acetone resulted in the appearance of the bis(TCNE) chlorins **13** and **14** almost immediately. Smaller amounts of the TCNE porphyrins **20** and **21** and the [4 + 2] monoadduct chlorins **15** and **16** were, however, present virtually from the start of the reaction. After 12–16 h of reflux, the [4 + 2] and [2 + 2] monoadduct chlorins had disappeared from the solution. At this time, a small amount of the TCNE porphyrins **20** and **21**, a small amount of protoporphyrin di-*tert*-butyl ester, and larger amounts of the [4 + 2] monoadduct chlorins were present. After 48 h of reflux, the only porphyrinic material present was protoporphyrin di-*tert*-butyl ester (**2**). The yield of **2** in this reaction could be substantially increased by reflux in aqueous acetone (9:1) for 24 h. A more careful study of

the reverse reaction showed that heating of the more mobile bis(TCNE) chlorins (13 or 14) in acetone gave the less mobile TCNE chlorins (15 or 16), and, conversely, the less mobile bis(TCNE) chlorin (13 or 14) gave the more mobile TCNE chlorin (15 or 16). Little or no scrambling of products was observed to occur in this reaction, and no evidence for the intermediacy of the TCNE porphyrin in these reactions could be found by TLC. Hence, in these cases loss of TCNE occurs largely if not exclusively from the four-membered tetracyanocyclobutane ring. Similarly, the reaction of TCNE with the TCNE chlorins in chloroform gives their complementary bis(TCNE) chlorins. Here further reaction of the [4 + 2] monoadducts occurs almost exclusively to give [2 + 2] addition.

In refluxing acetone, each of the [2 + 2] diadduct porphyrins (the two diasteriomers of 3) rearrange to both bis(TCNE) chlorins 8 and 9, further evidence that both vinyl groups of protoporphyrin react in a similar manner with TCNE. Reflux of the mixed isomeric TCNE porphyrins 20 and 21 in acetone first produced the TCNE chlorins 15 and 16 and then protoporphyrin di-*tert*-butyl ester (2). A small amount of 2, however, was produced in parallel with the TCNE chlorins, indicating that loss of TCNE from the [2 + 2] monoadduct is competitive to a small extent with rearrangement to the [4 + 2] adduct. Reaction of the purified chlorins 15 and 16 gave 2. In this reaction, no rearrangement to the TCNE porphyrin was observed.

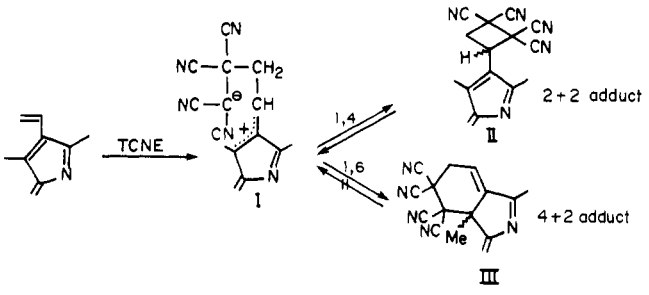
The TCNE porphyrin 19 from 2-formyl-4-vinyldeuteroporphyrin proved to be more stable than its counterpart 20 formed from 2. In acetone at room temperature a full 6 weeks was required to recover 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester. At intermediate times the [4 + 2] monoadducts of 2-formyl-4-vinyldeuteroporphyrin with TCNE could be observed in the reaction mixture. The electron-withdrawing formyl group is thus observed to increase the stability of the [2 + 2] adduct between vinyl porphyrins and TCNE.

The loss of TCNE from its adducts with vinyl-bearing porphyrins is thus observed to follow a well-defined sequence. [2 + 2] monoadducts which are porphyrins bearing the tetracyanocyclobutane ring rearrange to form [4 + 2] adducts which are chlorins. These [4 + 2] adducts then lose TCNE to reform the original porphyrin. Loss of TCNE from the [2 + 2] monoadduct does occur, but at a much slower rate than rearrangement to the [4 + 2] adduct. If the porphyrin is a [2 + 2] bis(TCNE) adduct, usually only one rearrangement occurs to form a [4 + 2]/[2 + 2] monoadduct. A small amount of the [4 + 2] bis(TCNE) adduct is formed due to a second rearrangement, but even in the presence of excess tetracyanoethylene, the reaction cannot be driven to completion. This is so because after the first [2 + 2] to [4 + 2] rearrangement occurs, a second rearrangement then competes unfavorably with loss of TCNE from the [2 + 2] adduct. Loss of TCNE from the [2 + 2]/[4 + 2] monoadduct chlorins 13 and 14 appears to occur exclusively by a retro-[2 + 2] reaction. Loss of TCNE from [4 + 2] monoadducts is, however, observed to occur by a retro-[4 + 2] reaction. Rearrangement of [4 + 2] adducts to [2 + 2] adducts is not observed to occur.

Discussion

The reaction of TCNE with vinyl-bearing porphyrins has been shown to be of interest for several reasons. It is another situation where there is apparent competition between a concerted Diels–Alder [4 + 2] cycloaddition and a stepwise [2 + 2] reaction proceeding through a dipolar intermediate. In this case the [2 + 2] adduct is apparently the kinetically favored product, and the [4 + 2] adduct is

Scheme I



favored thermodynamically. Loss of TCNE from the [4 + 2] adduct was observed to be slow. Our experiments, however, have not produced any evidence for the existence of free TCNE during the ready conversion of the [2 + 2] adducts to the [4 + 2] adducts. A tenfold excess of 9,10-dimethylanthracene, which reacts rapidly with TCNE in a [4 + 2] fashion,[11] was observed to block the reaction of protoporphyrin di-*tert*-butyl ester with TCNE in chloroform both at room temperature and at reflux. Under both sets of conditions, however, the rearrangement of the TCNE porphyrins 20 and 21 to the [4 + 2] monoadduct chlorins 15 and 16 is unaffected by the presence of 9,10-dimethylanthracene. Thus, free TCNE is not present during these rearrangements. In order that the rearrangement of the [2 + 2] cyclobutane adduct to the [4 + 2] adduct be concerted, a sterically unfavorable antarafacial [1,3]-sigmatropic rearrangement must occur. Rather than this, we assume that the dipolar intermediate I (Scheme I) is a common intermediate in these reactions and that the 1,4-closure to give the [2 + 2] adduct (II, Scheme I) is kinetically favored on steric grounds, while the 1,6-diene gives the thermodynamically favored [4 + 2] adduct III (Scheme I).

As noted above, the 2,2,3,3-tetracyanocyclobutane ring is, as one would expect, electron withdrawing, and its electronic effects are especially apparent from examination of the electronic spectra of porphyrins substituted by this functional group. Conversion of 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester into its [2 + 2] adduct (19) changes the visible spectrum from a rhodo to an etio type. A similar change is observed when 2-formyl-4-vinyldeuteroporphyrin is converted to 2,4-diformyldeuteroporphyrin. In addition, the intensity of the visible band III is markedly increased when a single vinyl group of protoporphyrin di-*tert*-butyl ester is converted to the tetracyanocyclobutane ring (as in 20 or 21). The resultant spectrum (Figure 1) is intermediate between a rhodo type and an etio type in that bands III and IV of 20 are of almost equal intensity.[12] Conversion of protoporphyrin to a monovinyl monoacrylate ester porphyrin gives similar results.[14]

Peak positions, as well as intensity, have often been used as an indication of the electron-withdrawing power of porphyrin substituents.[15,16] In the case of the bis(tetracyanocyclobutyl)porphyrin (10), λ_{max} (in $CHCl_3$) are observed at 404, 502, 534, 571, 626 nm. Those of protoporphyrin are 406.5, 506, 534, 571, and 626 nm, and those of a dialkyl porphyrin such as mesoporphyrin are at 400, 499, 533, 567, and 621 nm. Using these data, one observes that the electron-withdrawing power of the tetracyanocyclobutane ring would be between that of a vinyl group

(14) A. Hamilton, M.Sc. Thesis, University of British Columbia, 1976.
(15) J. E. Falk, "Porphyrins and Metalloporphyrins", Elsevier, Amsterdam, 1964.
(16) B. O. Saunders, A. G. Holmes-Siedler, and B. P. Stark, "Peroxides", Butterworths, Washington, DC, 1964.

and that of an ethyl group, whereas on the basis of a rhodofying effect, the electron-withdrawing power would appear to be greater than that of the vinyl group. Caughey et al., however, have shown that there is no quantitative correlation between peak position and the electron-withdrawing power of porphyrin side chains.[17,18]

[2 + 2] adducts of TCNE and vinyl-bearing porphyrins are of potential use in porphyrin chemistry as protecting groups in view of the reversibility of the reaction. Preliminary studies have shown that in refluxing aqueous acetone (1:9), the bis(TCNE) porphyrin **10** loses two molecules of tetracyanoethylene to form protoporphyrin in about 30% yield. Currently studies are underway to find more favorable conditions for this reaction, and 9,10-dimethylanthracene may prove useful in this regard. The TCNE porphyrins **20** and **21** should give protoporphyrin in much higher yield, but yields in this reaction have not as yet been quantitated.

Addition of an electron-withdrawing group to a vinylporphyrin greatly increases the stability of its TCNE adduct as evidenced by the long reaction times necessary to form 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester from its [2 + 2] TCNE adduct. Syntheses in which the vinyl group of a porphyrin such as 2-formyl-4-vinyldeuteroporphyrin is protected by TCNE while the formyl group is modified to a less electron-withdrawing substituent with subsequent regeneration of the vinyl functionality are thus a possibility.

Use of [4 + 2] adducts of vinyl-bearing porphyrins as aids in separating isomers of 2(4)-vinyl-4(2)-X-deuteroporphyrins (where X is a functionality other than vinyl) would seem to be advantageous in many cases. The easy separation of photoprotoporphyrin isomers in the synthesis of 2-formyl-4-vinyl- and 2-vinyl-4-formyldeuteroporphyrins indicates that the nonplanarity of these chlorin derivatives aids in their separation. This hypothesis is substantiated by the easy separation of the formyl chlorins **11** and **13** and the vinyl chlorins **15** and **16**. The direct separation of 2-formyl-4-vinyldeuteroporphyrin dimethyl esters has been reported, although it is difficult and must be done by TLC.[19] Separation of isomeric [4 + 2] TCNE adducts of mono vinylporphyrins followed by removal of TCNE by retro-"Diels–Alder" reaction appears to be a general method of separating such porphyrin isomers.

Finally, [4 + 2] cycloadditions of suitable dienophiles with vinylporphyrins can be used to synthesize macrocycles having a chlorin chromophore which will not be susceptible to oxidation or rearrangement, as is the case when the chlorin bears hydrogen atoms at the β and β' positions. Moreover, [4 + 2] reactions at rings A and B can, as we have shown, generate the isobacteriochlorin chromophore of sirohydrochlorin (**1**), and we expect that judicious choice of the porphyrinic diene and dienophile in studies which are currently in progress in our laboratory will give sirohydrochlorin itself.

Experimental Section

General Methods. Dichloromethane, methanol, and *tert*-butyl alcohol were dried by distillation from calcium hydride. All other chemicals were reagent grade or the best commercially available grade. Silica gel for column chromatography was obtained from ICN Pharmaceuticals (catalog no. 402747). Silica gel thin-layer plates (250-μm layer) were obtained from Analtech Inc.

Protoporphyrin IX. Protoporphyrin was prepared from hematoporphyrin dihydrochloride by the method of DiNello and Chang.[19] Occasionally the product oiled out of the formic acid solution upon addition of ethyl ether. If this was the case, the solution was decanted from the oil and the porphyrin precipitated by trituration with water.

Protoporphyrin IX Di-*tert*-butyl Ester (2, R = $(CH_3)_3C$). Protoporphyrin free acid (7.5 g) was suspended in dry dichloromethane and the solvent brought to reflux. Oxalyl chloride (25 g) was carefully added and the solution again brought to reflux. After 15 min at reflux the solution was cooled, and the solvent and excess oxalyl chloride were removed in vacuo. The residue was redissolved in a small amount of dry dichloromethane and the solvent again removed in vacuo. The residue was then redissolved in dry dichloromethane (450 mL) and the mixture heated to reflux under a condenser fitted with a drying tube. Dry *tert*-butyl alcohol (50 mL) was added and the solution refluxed for 45 min. At the end of this time, additional dry *tert*-butyl alcohol (50 mL) was added and refluxing continued for an additional 45 min. At the end of this time, solvent and excess *tert*-butyl alcohol were removed in vacuo, and the residue was dissolved in chloroform (1 L). The chloroform solution was extracted once with water (500 mL), stirred vigorously with the addition of saturated $NaHCO_3$ until carbon dioxide evolution ceased, and then extracted twice more with water. The chloroform solution was then dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude protoporphyrin di-*tert*-butyl ester (**2**) was taken up in a minimum volume of chloroform and chromatographed on silica gel (grade IV, 1 kg) with chloroform–diethyl ether (100:1 v/v) as the eluting solvent. The fractions containing the product were taken to dryness and crystallized from benzene (about 10 mL/g). The mother liquors were concentrated, and a second crop was obtained. The combined yield was 6.3 g (70%).

An analytical sample was recrystallized from benzene: mp 228–229 °C dec; λ_{max} ($CHCl_3$) 406.5 nm (ϵ 167), 506 (14.2), 540.5 (11.6), 575.5 (6.9), 630 (5.5); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.40 (s, 18 H, *t*-Bu), 3.16 (t, J = 8 Hz, 4 H, β-propionate), 3.22 (s, 3 H, ring methyl), 3.24 (s, 6 H, ring methyls), 3.28 (s, 3 H, ring methyl), 4.18 (t, J = 8 Hz, 4 H, α-propionate), 6.04 (dd, J_1 = 12 Hz, J_2 = 2 Hz, 2 H, vinyl), 6.14 (dd, J_1 = 18 Hz, J_2 = 2 Hz, 2 H, vinyl), 8.15 (dd, J_1 = 18 Hz, J_2 = 12 Hz, 2 H vinyl), 9.66 (s, 1 H, meso), 9.72 (s, 1 H, meso), 9.85 (s, 2 H, meso); mass spectrum, m/e (relative intensity) 674 (M^+, 100), 618 (20), 562 (26). Anal. Calcd for $C_{42}H_{50}N_4O_4$: C, 74.75; H, 7.47; N, 8.30. Found: C, 74.76; H, 7.59; N, 8.09.

2-Formyl-4-vinyl- and 2-Vinyl-4-formyldeuteroporphyrin Di-*tert*-butyl Esters. The isomeric (rings A and B) photoprotoporphyrin di-*tert*-butyl esters (**7**) (isomer 1 = 3-hydroxy-4-devinyl-4-formylethylideneprotoporphyrin, isomer 2 = 1-hydroxyl-2-devinyl-2-formylethyldeneprotoporphyrin) were prepared according to the method of Inhoffen et al.[20] Photolysis of **2** (R = $(CH_3)_3C$, 2 g/L of solvent) was carried out in methylene chloride/pyridine (9:1 v/v) in bright Vancouver sunlight for 2 days or for a shorter period of time with a high-intensity tungsten–iodine visible lamp. Separation of the isomers was accomplished on silica gel grade IV with dichloromethane–ether (20:1) as the eluting solvent.

Photoprotoporphyrin isomer 1 or 2 (325 mg) was dissolved in dry dichloromethane (150 mL). $NaBH_4$ (325 mg) dissolved in dry methanol (4 mL) was added and the solution stirred at room temperature for 1 h. Silica gel TLC (dichloromethane–ether, 10:1 v/v) at the end of this time revealed that the green aldehyde had been completely replaced by the less mobile gray alcohol [1-(3)-hydroxy-2(4)-devinyl-2(4)-(hydroxymethyl)ethylidineprotoporphyrin diester]. Acetic acid was then added dropwise to the reaction mixture until hydrogen evolution ceased. The reaction mixture was poured into water (300 mL) and extracted with chloroform (200 mL). The chloroform layer was washed three times with water, dried over sodium sulfate, and taken to dryness in vacuo.

The residue was dissolved in 1,4-dioxane (150 mL) and a boiling hot solution[21] of $NaIO_4$ (600 mg) in water (1.1 mL) added followed

(17) W. S. Caughey, W. J. Fujimoto, and B. P. Johnson, *Biochemistry*, **5**, 3830 (1966).
(18) D. H. O'Keefe, Ph.D. Thesis, Arizona State University, Tempe, AZ, 1974.
(19) R. K. DiNello and C. K. Chang, in "The Porphyrins", Vol. I, D. Dolphin, Ed., Academic Press, New York, 1978, Chapter 7.
(20) H. H. Inhoffen, H. Brockmann, and K. M. Bliesener, *Justus Liebigs Ann. Chem.*, **730**, 173 (1969).

rapidly by concentrated sulfuric acid (1.00 mL). After being stirred for 2 h at room temperature, the solution was poured into 5% sodium chloride (300 mL), and methylene chloride (300 mL) was added. The solution was stirred vigorously while enough saturated sodium bicarbonate solution was added to destroy any remaining sulfuric acid. The layers were separated, and the organic layer was washed with water three times, dried over Na_2SO_4, filtered, and taken to dryness in vacuo. The residue was dissolved in a minimum volume of chloroform and chromatographed on silica gel grade IV (250 g) with chloroform–ether (20:1 v/v) as the eluent. The porphyrin was recrystallized from chloroform–petroleum ether (bp 30–60 °C) to give 248 mg (80%) of product.

2-Formyl-4-vinyldeuteroporphyrin Di-*tert*-butyl Ester. An analytical sample was recrystallized from chloroform–petroleum ether (bp 30–60 °C): mp 228–229 °C dec; λ_{max} ($CHCl_3$) 420 nm (ϵ 162), 519 (10.6), 560 (14.2), 584 (9.55), 643 (2.13); ^1H NMR ($CHCl_3$, 100 MHz) δ 1.50 (s, 18 H, *t*-Bu), 3.18 (t, J = 8 Hz, 4 H, β-propionate), 3.5 (s, 12 H, ring methyls), 4.20 (t, J = 8 Hz, 4 H, α-propionate), 6.20 (m, 4 H, vinyl), 8.00 (m, 2 H, vinyl), 9.30, 9.67, 9.71, 10.15 (all s, 4 H, meso), 11.00 (s, 1 H, aldehyde); mass spectrum, *m/e* (relative intensity) 676 (M^+ 58), 620 (41), 564 (100), 505 (46), 446 (17). Anal. Calcd for $C_{41}H_{48}N_4O_5$: C, 72.76; H, 7.15; N, 8.28. Found: C, 72.87; H, 7.30; N, 8.21.

2-Vinyl-4-formyldeuteroporphyrin Di-*tert*-butyl Ester. An analytical sample was recrystallized from chloroform–petroleum ether (bp 30–60 °C): mp 228–229 °C dec; λ_{max} ($CHCl_3$) 420 nm (ϵ 167.6), 519 (10.7), 560 (15.0), 584 (9.33), 643 (1.94); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.48 (s, 18 H, *t*-Bu), 3.14 (t, J = 8 Hz, 4 H, β-propionate), 3.38, 3.44, 3.50, 3.54 (all s, 12 H, ring methyls), 4.18 (m, 4 H, α-propionate), 6.08 (m, 2 H, vinyl CH_2), 7.86 (dd, 1 H, vinyl CH), 9.28, 9.50, 9.62, 10.41 (all s, 4 H, meso), 11.09 (s, 1 H, aldehyde); mass spectrum, *m/e* (relative intensity) 676 (M^+ 60), 620 (40), 564 (100), 505 (60), 446 (30). Anal. Calcd for $C_{41}H_{48}N_4O_5$: C, 72.76; H, 7.15; N, 8.28. Found: C, 72.61; H, 7.05; N, 8.35.

2,4-Bis(2,2,3,3-tetracyanocyclobutyl)deuteroporphyrin Di-*tert*-butyl Esters (10). Protoporphyrin di-*tert*-butyl ester (**2**; 500 mg, 0.74 mmol) and TCNE (500 mg, 3.0 mmol) were dissolved in chloroform (10 mL) and allowed to stand at room temperature for 4 h. The product was isolated by filtration, and the filtrate was treated as described below to recover the [2 + 2]/[4 + 2] TCNE monoadduct chlorins **13** and **14**. Traces of these chlorins were removed from the [2 + 2] diadduct by crystallization from acetone–petroleum ether (bp 30–60 °C). Two or three crystllizations were necessary to remove all traces of the 660-nm band characteristic of the mixed bis(TCNE) chlorins **13** and **14**. The yield of the [2 + 2] diadduct porphyrins **10** was 312.8 mg (45.3%). It was necessary to work at or below room temperature during the recrystallizations to minimize decomposition of **10**.

Separation of the diastereomeric bis(TCNE) adduct porphyrins was accomplished by fractional crystallization as above. Partial solution of the porphyrins in acetone left the more insoluble isomer 2 [with lower mobility on silica gel with acetone–petroleum ether (5:14) or chloroform–acetone (2:1) as the developing solvent] undissolved. Although the two isomers were easily separated on thin-layer plates, decomposition was evident on a preparative scale.

An analytical sample of the mixed diastereomers was recrystallized from acetone–petroleum ether (bp 30–60 °C): mp 178–180 °C dec; λ_{max} (acetone) 404 nm (ϵ 214), 502 (15.1), 534 (9.20), 571 (6.88), 626 (4.65); mass spectrum, *m/e* 128 (120 °C, TCNE), 674 (170 °C, protoporphyrin di-*tert*-butyl ester). For isomer 1: ^1H NMR (acetone, 270 MHz) δ 1.28 (s, 18 H, *t*-Bu), 3.21 (2 t superimposed, J = 9 Hz, 4 H, β-propionate), 3.55, 3.66, 3.77, 4.04 (all s, 12 H, ring methyls), 4.22 (t, 2 H, α-propionate, J = 9 Hz), 4.34 (m, 3 H, α-propionate and 1 cyclobutane CH_2), 4.46 (dd, 1 H, cyclobutane CH_2, J_1 = 11 Hz, J_2 = 12 Hz), 4.98 (t, J = 12 Hz, 1 H, cyclobutane CH_2), 5.15 (t, J = 11 Hz, 1 H, cyclobutane CH_2), 6.93 (t, J = 11 Hz, 1 H, cyclobutane methine), 7.12 (t, J = 11 Hz, 1 H, cyclobutane methine), 10.15, 10.21, 10.30, 10.33 (all s, 4 H, meso). For isomer 2: ^1H NMR (CD_2Cl_2, 10% TFA, 100 MHz) δ 1.45, 1.48, 1.57 (all s, 18 H, $(CH_3)_3C$ groups from mono- and diesters), 3.06 and 3.26 (m, 4 H, β-propionate), 3.68 (s, 6 H, ring methyls), 3.90 (s, 6 H, ring methyls), 4.50, 4.76, and 4.80 (all m, α-propionate and cyclobutane CH_2), 6.48 (dd, 2 H, cyclobutane methine), 9.7 (s, 1 H, meso), 9.82 (s, 2 H, meso), 10.02 (s, 1 H, meso). Anal. Calcd for $C_{54}H_{50}N_{12}O_4$: C, 69.66; H, 5.41; N, 18.13. Found: C, 69.28; H, 5.56; N, 17.64.

2(4)-(2,2,3,3-Tetracyanocyclobutyl-4(2)-vinyldeuteroporphyrin Di-*tert*-butyl Esters. Protoporphyrin di-*tert*-butyl ester (**2**; 100 mg, 0.15 mmol) and TCNE (19 mg, 0.15 mmol) were dissolved in $CHCl_3$ (2.5 mL), and the mixture was allowed to stand for 15 min to complete the reaction. At the end of this time methanol (20 mL) was added and the product recrystallized from the reaction solution. The crystals were recovered by vacuum filtration, washed with methanol and ether, and air-dried to give 78 mg (65.5%) of product. An analytical sample was recrystallized from chloroform–methanol: λ_{max} ($CHCl_3$) 409.5 nm (ϵ 194), 508 (13.1), 545 (12.5), 574 (7.29), 629 (2.33); ^1H NMR (CD_2Cl_2, 10% TFA, 100 MHz) δ 1.45, 1.48, 1.57 (all s, 18 H, *t*-Bu of mono- and diesters), 3.26 (t, J = 8 Hz, 4 H, β-propionate) 3.66, 3.70, 3.75, 3.88, 3.91 (all s, 12 H, ring methyls), 4.15, 4.48, 4.78 (all m, 8 H, α-propionate and cyclobutane CH_2), 6.45 (m, 3 H, vinyl CH_2 and cyclobutane methine), 8.19 (dd, 1 H, vinyl CH), 9.70 (m, 4 H, meso). Anal. Calcd for $C_{48}H_{50}O_4N_8$: C, 71.80; H, 6.28; N, 13.95. Found: C, 71.20; H, 6.30; N, 13.34.

[2 + 2]/[4 + 2] TCNE Monoadducts of Protoporphyrin Di-*tert*-butyl Esters 13 and 14. Protoporphyrin di-*tert*-butyl ester (200 mg, 0.3 mmol) and TCNE (200 mg, 1.56 mmol) were dissolved in chloroform (25 mL), and the mixture was refluxed for 2.5 h under nitrogen. At the end of this time, the [2 + 2] bis(TCNE) adduct porphyrins were removed by filtration and purified as described above. TCNE (50 mg, 0.39 mmol) was added to the filtrate and refluxing continued for 1.5 h. The solution was then taken to dryness, dissolved in a minimal amount of chloroform, and chromatographed on silica gel (grade IV, 250 g) with chloroform–acetone (30:1 v/v) as the eluting solvent until the more mobile chlorin (isomer 1) was eluted. Chlorin isomer 2 was removed with chloroform–acetone (10:1 v/v). The fractions containing each bis(TCNE) chlorin were taken to dryness in vacuo, dissolved in a minimal amount of chloroform, and precipitated with petroleum ether. The yield of isomer 1 (**13** and **14**) was 69 mg (25%) and that of isomer 2 (**13** and **14**) was 84 mg (30.5%). The [2 + 2] diadduct porphyrin **5** (36 mg, 13%) was also obtained from this reaction.

An analytical sample of isomer 1 (**13** or **14**) was recrystallized from dichloromethane–petroleum ether: mp 175 °C dec; mass spectrum, *m/e* 128 (115 °C, TCNE), 674 (160 °C, protoporphyrin di-*tert*-butyl ester); λ_{max} ($CHCl_3$) 403 nm (ϵ 210), 497 (14.6), 530.5 (2.98), 553 (1.59), 603 (5.07), 627 (4.02), 657.5 (57.5); ^1H NMR (acetone-d_6, 270 MHz and 100 MHz) δ 1.32 (s, 18 H, *t*-Bu), 2.32 (m, 2 H, β-propionate), 2.49, 2.54 (both s, 3 H, aliphatic ring methyl), 2.60 (m, 2 H, β-propionate), 3.03, 3.49, 3.78, 4.02, 4.06 (all s, 9 H, 3 ring methyls), 3.86 (m, 2 H, 1 α-propionate CH_2), 4.67 (m, 4 H, 1 α-propionate and exocyclic ring CH_2), 5.14 and 5.21 (2 t, J = 11.5 Hz, 2 H, cyclobutane CH_2), 6.80 and 6.86 (2 t, J = 11.5 Hz, 1 H, cyclobutane methine), 7.90 (m, 1 H, exocyclic double bond CH), 9.54, 9.56, 9.61, 9.65, and 9.82 (all s, 4 H, meso). Anal. Calcd for $C_{54}N_{50}N_{12}O_4$: C, 69.66; H, 5.41; N, 18.13. Found: C, 69.40; H, 5.22; N, 17.63.

An analytical sample of isomer 2 (**13** or **14**) was recrystallized from dichloromethane–petroleum ether: mp 175 °C dec; λ_{max} ($CHCl_3$) 402 nm (ϵ 160), 499 (11.9), 532.5 (3.98), 556 (1.17), 605 (3.56), 632 (3.17), 662.5 (50.1); ^1H NMR (acetone-d_6, 270 Hz) δ 1.31 (s, 18 H, *t*-Bu), 2.48 and 2.52 (both s, 3 H, aliphatic ring methyl), 3.08 (t, J = 8 Hz, 2 H, β-kpropionate), 3.20 (t, J = 8 Hz, 2 H, β-propionate), 3.38, 3.62, 3.73, 3.76 (all s, 9 H, ring methyls), 4.06 (t, J = 8 Hz, 2 H, α-propionate), 4.30 (t, J = 8 Hz, 2 H, α-propionate), 4.44 (d, J = 6 Hz, 1 H, exocyclic ring CH_2), 4.56 (d, J = 4 Hz, 1 H, exocyclic ring CH_2), 4.78 and 4.93 (both t, J = 11 Hz, 2 H, cyclobutane CH_2), 6.63 and 6.77 (both t, J = 11 Hz, 1 H for both, cyclobutane methine), 7.74 (dd, J_1 = 4 Hz, J_2 = 6 Hz, 1 H, cyclohexene ring), 9.56, 9.62, 9.68, 9.72, 9.75, and 9.88 (all s, 4 H, meso). Anal. Calcd for $C_{54}H_{50}N_{12}O_4$: C, 69.66; H, 5.41; N, 18.13. Found: C, 68.93; H, 5.42; N, 17.50.

[4 + 2] Bis(TCNE) Adduct of Protoporphyrin Di-*tert*-butyl Ester (5, R = $(CH_3)_3C$). Protoporphyrin di-*tert*-butyl ester (300 mg, 0.45 mmol) and TCNE (400 mg, 3.1 mmol) were dissolved in chloroform (75 mL), and the solution was refluxed for 14 h. At the end of this time the chloroform was removed in vacuo and

(21) The periodate solution must be added boiling hot or the yield is only about 25%. Our most recent results indicate the reaction takes much less time than 2 h.

the residue dissolved in a minimum of dichloromethane containing 1% by volume of 88% formic acid. Chromatography on silica gel (grade IV) with the same solvent gave the dichroic (red at high concentration, green at low concentration) bis [4 + 2] diadduct **5** as the only mobile compound. The [4 + 2]/[2 + 2] TCNE diadducts and the [4 + 2] TCNE monoadducts are all protonated by the above treatment and have no mobility on silica gel.

The fractions containing the [4 + 2] diadduct were extracted with 5% bicarbonate solution and then water, dried over Na_2SO_4, and taken to dryness in vacuo. The [4 + 2] diadduct was dissolved in a minimum of dichloromethane and crystallized by the addition of petroleum ether (bp 30–60 °C) to give 16 mg (4%) of product.

An analytical sample was recrystallized from dichloromethane–petroleum ether: mp dec >150 °C; mass spectrum, no high-mass peaks at 170 °C; λ_{max} 397 nm (ϵ 84.6), 407 (88.6), 430.2 (124), 515 (7.25), 547.5 (5.30), 593 (9.41), 639.5 (26.6); ^{1}H NMR (acetone-d_6, 100 MHz) δ 1.27 and 1.30 (both s, 18 H, *t*-Bu), 2.10, 2.19, and 2.23 (all s, 6 H, aliphatic ring methyl), 2.86 (*t*, J = 8 Hz, 2 H, β-propionate, 2.99, 3.28, and 3.74 (all s, 6 H, ring methyls) 3.06 (t, J = 8 Hz, 2 H, β-propionate), 3.55 (t, J = 8 Hz, 2 H, α-propionate), 4.17 (t, J = 8 Hz, 2 H, α-propionate), 4.26, 4.32 (both d, J = 6 Hz, 2 H, exocyclic ring CH_2), 4.46 and 4.52 (both d, J = 4 Hz, 2 H, exocyclic ring CH_2), 7.44 and 7.49 (2 dd, J_1 = 4 Hz, J_2 = 6 Hz, 2 H, exocyclic double bond CH), 8.82, 8.84, 8.98, 9.02, and 9.45 (all s, 4 H, meso). Anal. Calcd for $C_{54}H_{50}N_{12}O_4$: C, 69.66; H, 5.41; N, 18.13. Found: C, 65.99; H, 5.73; N, 17.66.

[4 + 2] TCNE Monoadducts of Protoporphyrin Di-*tert*-butyl Esters 15 and 16. Protoporphyrin di-*tert*-butyl ester (**2**, R = $(CH_3)_3C$; 400 mg, 0.59 mmol) and TCNE (76 mg, 0.59 mmol) were dissolved in chloroform (15 mL), and the mixture was refluxed for 30 min. Additional TCNE (7 mg 0.05 mmol) was added and the solution refluxed for an additional 90 min. At the end of this time the reaction was taken to dryness in vacuo. The residue was dissolved in chloroform and chromatographed on silica gel (grade V, 250 g) with chloroform/ether (50:1 v/v) as the eluant. The fractions containing the pure more mobile isomer 1 were collected and taken to dryness in vacuo to give 126 mg (26%) of product. Fractions in which isomer 2 (the less mobile partner) predominated were taken to dryness in vacuo and rechromatographed as above to give 44 mg (9%) of pure isomer 2. The mixed fractions from the first column yielded 75 mg of mixed isomers 1 and 2.

An analytical sample of isomer 1 was recrystallized from dichloromethane–petroleum ether: mp dec >150 °C; mass spectrum, m/e 128 (120 °C, TCNE), no high-mass peaks at 170 °C; λ_{max} ($CHCl_3$) 404 nm (ϵ 183), 500.5 (13.9), 535.5 (7.31), 602.5 (4.25), 631 (3.55), 660 (48.9); ^{1}H NMR (acetone-d_6, 100 MHz) δ 1.32 (s, 18 H, *t*-Bu), 2.46 (s, 3 H, aliphatic methyl), 2.97 (t, J = 8 Hz, 2 H, β-propionate), 3.15 (s and t superimposed, 5 H, ring methyl and β-propionate), 3.56, 3.60, and 3.73 (s, 6 H, ring methyls), 3.87 (t, J = 8 Hz, 2 H, α-propionate), 4.28 (t, J = 8 Hz, 2 H, α-propionate), 4.20 (d, J = 6 Hz, 1 H, exocyclic ring CH_2), 4.32 (d, J = 4 Hz, 1 H, exocyclic ring CH_2), 6.10 (dd, J_1 = 12 Hz, J_2 < 1 Hz), 6.28 (dd, J_1 = 18 Hz J_2 < 1 Hz, 1 H, vinyl CH_2), 7.66 (dd, J_1 = 4 Hz, J_2 = 6 Hz, exocyclic double bond CH), 8.14 (dd, 1 H, vinyl CH), 9.52, 9.68, and 9.80 (s, 4 H, meso). Anal. Calcd for $C_{48}H_{50}O_4N_8$: C, 71.80; H, 6.28; N, 13.95. Found: C, 71.23; H, 6.20; N, 13.80.

An analytical sample of isomer 2 was recrystallized from dichloromethane–petroleum ether: mp dec >150 °C; mass spectrum, m/e 128 (129 °C, TCNE), no high-mass peaks at 170 °C; λ_{max} ($CHCl_3$) 403.5 nm (ϵ 169), 499.5 (13.2), 534.5 (6.54), 602 (4.17), 630.5 (3.56), 660 (46.2); ^{1}H NMR (acetone-d_6, 100 MHz) δ 1.28 and 1.30 (both s, 18 H, *t*-Bu), 2.24 (s, 3 H, aliphatic methyl) 3.06 (2 t superimposed, 4 H, β-propionate), 3.34, 3.53, 3.68, and 3.74 (all s, 9 H, ring methyls), 3.98 (t, J = 8 Hz, 2 H, α-propionate), 4.24 (t, J = 8 Hz, 2 H, α-propionate), 4.36 (d, J = 6 Hz, 1 H, exocyclic ring CH_2), 4.50 (d, J = 4 Hz, 1 H, exocyclic ring CH_2), 6.25 (dd, J_1 = 12 Hz, J_2 = 2 Hz, 1 H, vinyl CH_2), 6.49 (dd, J_1 = 18 Hz, J_2 = 2 Hz, 1 H, vinyl CH_2), 7.84 (dd, J_1 = 4 Hz, J_2 = 6 Hz, 1 H, exocyclic double bond CH), 8.32 (dd, J_1 = 18 Hz, J_2 = 12 Hz, 1 H, vinyl CH), 9.60, 9.64, 9.84, and 9.98 (all s, 4 H, meso). Anal. Calcd for $C_{48}H_{50}O_4N_8$: C, 71.80; H, 6.28; N, 13.95. Found: C, 71.40; H, 6.32; N, 13.37.

2-Formyl-4-(2,2,3,3-tetracyanocytobutyl)deuteroporphyrin Di-*tert*-butyl Ester (19). 2-Formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester (100 mg, 0.15 mmol) and TCNE (100 mg, 0.78 mmol) were dissolved in chloroform (5 mL), and the mixture was allowed to stand for 2 h at room temperature. During this time, the [2 + 2] TCNE adduct crystallized from solution as maroon microcrystals which were recovered by vacuum filtration, washed with chloroform, methanol, and ether, and air-dried to give 76 mg (63.9%) of product. The filtrate yielded a small amount of the related [4 + 2] adduct chlorin which was purified as described below. A portion of the product that crystallized inter alia was used as an analytical sample: mp dec >175 °C; mass spectrum, m/e 128 (150 °C, TCNE), 676 (300 °C, 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester); λ_{max} (acetone) 413 nm (ϵ 159), 511 (12.1), 548 (10.6), 579 (6.58), 637 (3.31); ^{1}H NMR (CD_2Cl_2, 10% TFA, 100 MHz) δ 1.45, 1.48, 1.57 (all s, 18 H, *t*-Bu from mono- and diesters), 3.07 and 3.26 (both t, J = 8 Hz, 4 H, β-propionate), 3.66, 3.70, 3.90, and 4.14 (all s, 12 H, ring methyls), 4.46 (m, 6 H, cyclobutane CH_2 and α-propionate CH_2), 6.50 (dd, 1 H, cyclobutane methine), 10.61, 10.87, 10.98, and 11.49 (all s, 4 H, meso), 11.56 (s, 1 H aldehyde). Anal. Calcd for $C_{47}H_{50}N_8O_5$: C, 70.14; H, 6.00; N, 13.92. Found: C, 70.33; H, 5.94; N, 13.59.

[4 + 2] TCNE Adducts of 2-Formyl-4-vinyl- and 2-Vinyl-4-formyldeuteroporphyrin Di-*tert*-butyl Esters (17 and 18). The mixed 2(4)-formyl-4(2)-vinyldeuteroporphyrin di-*tert*-butyl esters (41 mg, 0.06 mmol) and TCNE (41 mg, 0.32 mmol) were dissolved in chloroform (50 mL), and the solution was brought to reflux. In this case, the isomeric [2 + 2] TCNE adduct porphyrins do not precipitate but are converted into the corresponding [4 + 2] adducts. After 16 h the solution was taken to dryness, and the residue was dissolved in a minimum of chloroform and chromatographed on silica gel (grade IV) with chloroform–ether (40:1 v/v) as the eluting solvent. The chlorin eluted first (isomer 1) was orange and later was shown to be related to 2-vinyl-4-formyldeuteroporphyrin di-*tert*-butyl ester, and the less mobile green chlorin (isomer 2) was later shown to be related to 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester in experiments with the pure porphyrin isomers. The fractions containing the pure chlorins were taken to dryness and the chlorins precipitated from chloroform with petroleum ether (bp 30–60 °C).

The yield of isomer 1 was 7 mg (14.4%) and of isomer 2 was 6 mg (12.3%). Subsequent reactions involving the pure porphyrin isomers, where separation of the chlorins was unnecessary, produced yields of 75–80% of the two chlorins.

An analytical sample of the [4 + 2] TCNE adduct of 2-vinyl-4-formyldeuteroporphyrin di-*tert*-butyl ester (18) was recrystallized from chloroform–petroleum ether: mp dec >150 °C; mass spectrum, m/e 128 (120 °C, TCNE), no high-mass peaks at 170 °C; λ_{max} ($CHCl_3$) 413 nm (ϵ 128), 508 (12.4), 544.5 (5.08), 569 (1.58), 621 (5.08), 648 (3.68), 679 (50.2); ^{1}H NMR (acetone-d_6, 100 MHz) δ 1.30 and 1.31 (s, 18 H, *t*-Bu), 2.47 (s, 3 H, aliphatic methyl), 2.82 (s and t superimposed, 5 H, ring methyl and β-propionate), 3.10 (t, J = 8 Hz, 2 H, β-propionate), 3.58 (s and t superimposed, 5 H, ring methyl and α-propionate), 3.68 and 3.72 (both s, 3 H, ring methyl), 4.20 (t, J = 8 Hz, 2 H, α-propionate), 4.42 (d, J = 5.4 Hz, 1 H, exocyclic ring CH_2), 4.54 (d, J = 4 Hz, 1 H, exocyclic ring CH_2), 7.66 (dd, J_1 = 4 Hz, J_2 = 5.4 Hz, 1 H, exocyclic ring CH), 9.38, 9.47, 9.67, and 9.82 (all s, 4 H, meso), 11.25 (s, 1 H, aldehyde). Anal. Calcd for $C_{47}H_{50}O_5N_8$; C, 70.14; H, 6.00; N, 13.92. Found: C, 69.72; H, 5.96; N, 13.61.

An analytical sample of the [4 + 2] TCNE adduct of 2-formyl-4-vinyldeuteroporphyrin di-*tert*-butyl ester (14) was recrystallized from chloroform–petroleum ether (bp 30–60 °C); mass spectrum, m/e 128 (120 °C, TCNE), no high-mass peaks at 170 °C; λ_{max} ($CHCl_3$) 412 nm (ϵ 189), 503 (14.4), 537 (4.59), 562 (1.89), 613 (6.25), 637.5 (4.39), 668.5 (53.1); ^{1}H NMR (acetone-d_6, 100 MHz) δ 1.32 and 1.35 (both s, 18 H, *t*-Bu), 2.40 (s, 3 H, aliphatic methyl), 2.93 (t, J = 8 Hz, 2 H, β-propionate), 3.06 (t, J = 8 Hz, 2 H, β-propionate), 3.20 and 3.44 (both s, 6 H, ring methyls), 3.80 (s and t superimposed, 5 H, ring methyl and α-propionate), 4.12 (t, J = 8 Hz, 2 H, α-propionate), 4.28 (d, J = 5.6 Hz, 1 H, exocyclic ring CH_2), 4.42 (d, J = 4 Hz, 1 H, exocyclic ring CH_2), 7.54 (dd, J_1 = 4 Hz, J_2 = 5.6 Hz, 1 H, exocyclic ring CH), 9.32, 9.44, 9.74, and 10.23 (all s, 4 H, meso), 11.52 (s, 1 H, aldehyde). Anal. Calcd for $C_{47}H_{50}O_5N_8$; C, 70.14; H, 6.00; N, 13.92. Found: C, 69.17; H, 5.75; N, 13.30.

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Registry No. **2** (R = H), 553-12-8; **2** (R = $(CH_3)_3C$), 75112-37-7; **5** (R = $(CH_3)_3C$), 75125-16-5; **7** (isomer 1), 75112-38-8; **7** (isomer 2), 75112-39-9; **10** (isomer 1), 75112-40-2; **10** (isomer 2), 75112-41-3; **13** (isomer 1), 75112-42-4; **13** (isomer 2), 75125-17-6; **14** (isomer 1), 75112-43-5; **14** (isomer 2), 75125-18-7; **15**, 75112-44-6; **16**, 75112-45-7; **17**, 75112-46-8; **18**, 75112-47-9; **19**, 75112-48-0; **20**, 75112-49-1; **21**, 75112-50-4; 2-formyl-4-vinyldeuteroporphryrin di-*tert*-butyl ester, 75112-51-5; 2-vinyl-4-formyldeuteroporphryrin di-*tert*-butyl ester, 75125-19-8; TCNE, 670-54-2; *tert*-butyl alcohol, 75-65-0.

Notes

Metalation–Carboxylation of *p*- and *m*-(Trimethylsilyl)toluenes as a Convenient Route to [*p*- and *m*-(Trimethylsilyl)phenyl]acetic Acids[1a]

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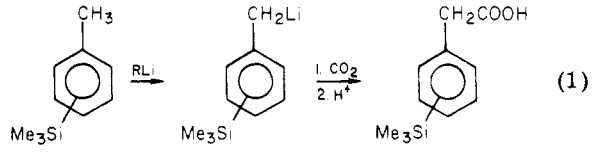
In connection with the synthesis of new anticonvulsant agents, we required moderate quantities of [*p*- and *m*-(trimethylsilyl)phenyl]acetic acids (**3a**) and (**3b**), respectively. Both of these acids have been prepared from (trimethylsilyl)toluenes **1a,b** by a classical, but circuitous, route involving benzylic bromination, displacement of bromide by cyanide, and hydrolysis of the resulting [(trimethylsilyl)phenyl]acetonitriles.[2] It occurred to us that metalation of **1a,b** to form (trimethylsilyl)benzyllithiums **2a,b**, followed by carboxylation could afford the desired acids in essentially one step (eq 1). It is well-

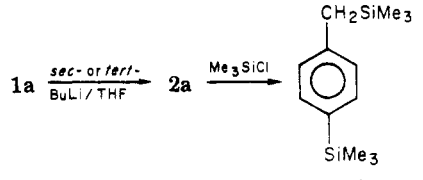


(1)

1ab **2ab** **3ab**

documented that toluene can be converted to benzyllithium by means of alkyllithium reagents, provided the metalation is conducted in the presence of Lewis bases such as TMEDA, DABCO, certain ethers, or potassium *tert*-butoxide.[3] However, examination of these studies reveals that yields of benzyllithium are highly dependent on the ratio of toluene–alkyllithium–complexing agent, as well as the nature of the complexing agent. The most satisfactory conversions involve the use of excess toluene, while reactions of various alkyllithium–Lewis base complexes with stoichiometric or substoichiometric quantities of toluene tend to give mixtures of mono-, di-, and trilithiated derivatives. In an earlier study directly related to the present work, West and Jones[4,5] found that metalation of **1a** and **1b** with a twofold excess of 4:1 *n*-butyllithium–TMEDA complex gave only 13 and 28% of **2a** and **2b**, respectively.

On the basis of the foregoing observations, it was evident that in order to use the desired metalation–carboxylation sequence for the synthesis of **3a,b**, it would be necessary to control the metalation of **1a,b** to give predominately the benzylic lithium derivatives **2a,b**, without having to employ an excess of **1a,b**. Attention was therefore focused on a study of the metalation of **1a** employing *sec*- or *tert*-butyllithium with THF as the complexing agent. The extent of metalation was determined from the ratio of [*p*-(trimethylsilyl)benzyl]trimethylsilane (**4**) to unreacted **1a** produced on quenching the reaction mixture with excess trimethylchlorosilane (eq 2).[4] Results of these experiments are shown in Table I.



(2)

4

Several conclusions can be drawn from the data in Table I. Highest yields of **4** were produced in reactions employing considerably greater than stoichiometric quantities of alkyllithium. This is apparently due to consumption of alkyllithium by the competing decomposition of THF, since those experiments employing lesser amounts of THF were most successful (expt 2 vs. 4 or expt 6 vs. 7). Some indication as to the sensitivity of metalation to the mole ratios of reactants may be gained by comparing the results of expt 5 and 8. Both experiments afforded approximately 50% of **4** based on **1a**. However, the yields of **4** based on *sec*-butyllithium consumed are quite different. In expt 5, a twofold excess of *sec*-butyllithium relative to **1a** was employed with THF as a cosolvent (method A). Under these conditions only 25% *sec*-butyllithium was converted to **2a** and eventually to **4** on quenching. In expt 8 a slight excess of **1a** relative to *sec*-butyllithium was used with a limited amount of THF (method B). In this case, about 62% of the *sec*-butyllithium was converted to **2a**. These results suggest that the rates of reaction of *sec*-butyllithium with **1a** and with THF are of similar magnitude and that

(1) (a) Supported by Grant No. NS 10197 from the National Institute of Neurological and Communicative Disorders and Stroke. (b) From the Ph.D. dissertation of M. P. Sleevi, Virginia Polytechnic Institute and State University, June 1979.

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(3) (a) For a comprehensive discussion, see: "Polyamine-Chelated Alkali Metal Compounds"; Langer, A. W., Ed.; American Chemical Society: Washington, DC, 1974. (b) Broaddus, C. D. *J. Org. Chem.* **1970**, *35*, 10. (c) Mitteilungen, K. *Chimia* **1970**, *24*, 109. (d) Schlosser, M.; Hartman, J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 508.

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