KINETIC VS THERMODYNAMIC PRODUCT DISTRIBUTIONS OF MACROCYCLIC TETRAPYRROLE CYCLIZATION PRODUCTS FROM 1,19-DISUBSTITUTED A,C-BILADIENE SALTS§

Kevin R. Gerzevske, Jack J. Lin, and Kevin M. Smith*

Department of Chemistry, University of California, Davis, California 95616, U.S.A.

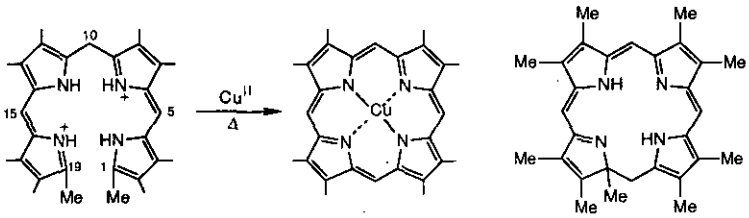
Abstract - Chromium(III) promoted oxidative cyclization reactions of a,c-biladiene hydrobromides bearing bulky 1- and 19-substituents to give macrocyclic products are partially reversible; depending upon the reaction temperature, kinetic or thermodynamic products are formed and identified.

One of the most useful and generalized procedures for the preparation of porphyrins involves the oxidative cyclization of 1,19-dimethyl-a,c-biladiene salts. First discovered by Johnson and Kay in 1961,[1] cyclizations of tetrapyrrolic substrates (**1**) to porphyrins (**2**) have evolved considerably[2] in recent years. Though a variety of metal oxidants[3] and even anodic oxidation[4] have been investigated, copper(II) has historically been the preferred oxidant for cyclizations; however, the harsh conditions for subsequent metal removal (H_2SO_4/TFA for copper) have limited its usefulness. One of the more useful metallic catalysts has been chromium(III)[5] which has the advantage that it yields metal-free porphyrins. When nickel(II) and cobalt(II) were used as alternative oxidizing agents, metallated tetradehydrocorrin salts were formed.[6] Although much work has been devoted to cyclization methodologies, little work has been centered on mechanistic studies involving isolated intermediates from cyclizations of a,c-biladiene salts.

Investigations of the mechanistic pathway for a,c-biladiene cyclizations have been of recent interest in our group. In our study of electrochemical cyclization of decamethly-a,c-biladiene (**1**), we discovered a "valley" intermediate (**3**), which allowed us to propose a mechanistic pathway for the cyclization.[4] This mechanism was generalized to

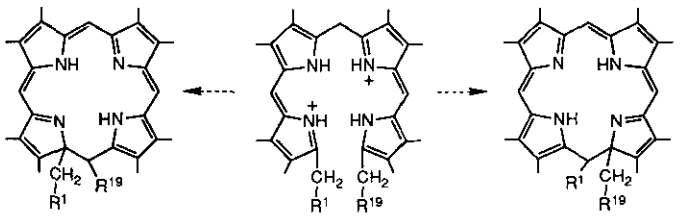
§ Dedicated to Professor Alan R. Katritzky, FRS, on the occasion of his 65th birthday.

copper(II) promoted cyclizations by isolating copper(II) "valley" intermediates from a,c-biladienes with bulky 1,19-substituents. Clezy has made broadly similar observations in the copper(II) promoted cyclizations of b-bilenes.[2,7]



1 2 3

When groups such as ethoxycarbonylmethyl, which are chemically more reactive than methyl, were attached to either the 1- or 19-positions, subsequent cyclizations of the resulting a,c-biladienes copper(II) acetate afforded a variety of copper "valley" intermediates as well as homoporphyrins.[8] As a result, we decided to explore metal catalyzed cyclization of such reactive a,c-biladienes more closely. Using a modification of the chromium(III) catalyzed cyclization methodology developed by Boschi *et al.*,[5] we have investigated the cyclization of several unsymmetrical a,c-biladienes to produce free base "valley" intermediates; our results lead directly to important conclusions regarding the relative reactivities of substituents in the 1- and 19- positions of the a,c-biladiene substrates.

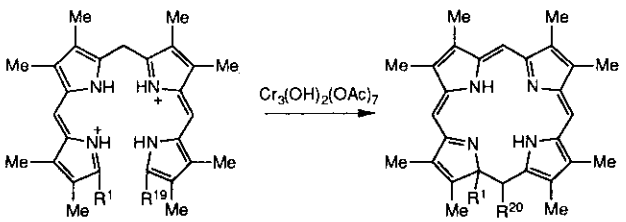


5 4 6

Use of 1,19-disubstituted a,c-biladiene salts bearing identical 1- and 19-substituents must obviously lead to a single "valley" intermediate, but if two different 1- and 19-substituents in the a,c-biladiene (**4**) are used, then depending upon kinetic and thermodynamic properties, two products (**5** and **6**) are possible. Using standard methodology from dipyrromethanes and tripyrrenes,[9] we therefore prepared several symmetrical as well as unsymmetrical 1,19-disubstituted a,c-biladiene salts, as shown in Table 1. The reactive R groups we chose to occupy the 1- and 19-positions were ethoxycarbonylmethyl (AEE) and p-tolylmethyl (PX); obviously, for mechanistic purposes each 1- and 19- R group must possess a methylene group which will eventually provide the bridging carbon atom on the products. Since the cyclization is oxidative, any observed interconversion of **5** and **6** is not strictly reversible *via* the a,c-biladiene (**4**); reversibility can only apply to the stages following the initial metal promoted oxidation. For the cyclizations, we subjected the each substrate to cyclization at an appropriate temperature in either DMF or aqueous ethanol with chromium(III) acetate hydroxide and either triethylamine or sodium acetate, respectively, as also shown in Table 1. The reactions were monitored by spectrophotometry and deemed complete upon dissapearance of one of the characteristic a,c-biladiene peaks (λ = 520 nm).

Cyclization of 1-methoxycarbonylethyl-2,3,7,8,12,13,17,18,19-nonamethyl-a,c-biladiene dihydrobromide (1-AEE,19-Me) (**7**) at room temperature or at 80°C in aqueous ethanol afforded 20-ethoxycarbonyl-1,2,3,7,8,12,13,17,18-nonamethyl-1,20-dihydroporphyrin (**8**), with the methyl occupying the "valley" position, in yields as high as 67%. When the experiment was repeated at 140°C in DMF, the product (**9**) was obtained (30%) in which an AEE instead occupied the "valley" position. Cyclization of the (1-PME,19-Me) substrate (**10**) at 100°C gave only the product (**11**) (14%) with the PME in the "valley" position .

Table 1: Structures of a,c-biladienes studied, along with reaction conditions and products.

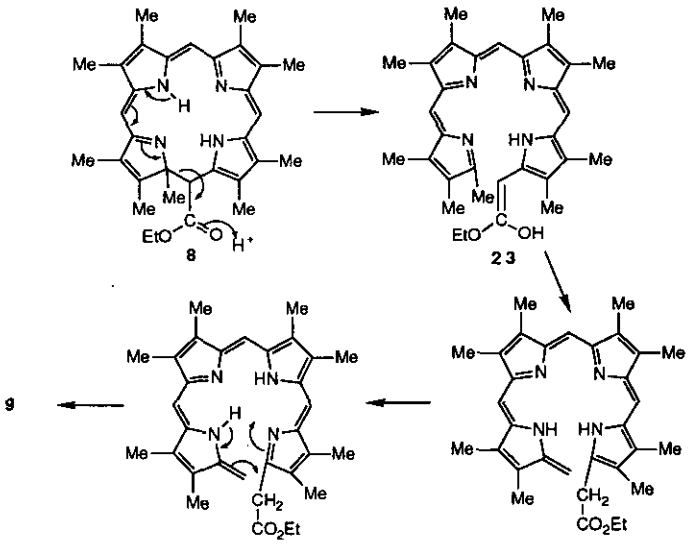


a,c-Biladiene			Reaction Conditions		Product(s)			
Compound	R^1	R^{19}	Temp.(°C)	Solvent	Compound	R^1	R^{20}	Yield(%)
7	AEE	Me	80	aq EtOH	**8**	Me	CO_2Et	67
			140	DMF	**9**	AEE	H	30
10	PME	Me	140	DMF	**11**	PME	H	14
12	AEE	PME	23	aq EtOH	**13**	PME	CO_2Et	51
			80	aq EtOH	**13**	PME	CO_2Et	24
					14	(homoporphyrin)		15
			100	DMF	**14**	(homoporphyrin)		16
15	PX	PX	100	DMF	**16**	PX	p-C_6H_4Me	50
17	PX	Me	140	DMF	**18**	Me	p-C_6H_4Me	51
			100	DMF	**18**	Me	p-C_6H_4Me	40
19	PX	PME	100	DMF	**20**	PME	p-C_6H_4Me	13
21	PX	AEE	0	aq EtOH	**22**	PX	CO_2Et	40

Upon cyclizing the 1-AEE,19-PME-a,c-biladiene substrate (**12**) at room temperature in buffered ethanol, the product (**13**) with the PME in the "valley" position was obtained exclusively (51%). However, at 80°C not only **13** (24%) but also the previously characterized[8] homoporphyrin (**14**) (15%) was obtained. At 140°C in DMF the homoporphyrin (**14**) was obtained exclusively.

The symmetrical di-PX substrate (**15**) was easily cyclized at 100°C in DMF to give the desired "valley" product (**16**) (50%) from which the products following were compared to determine their regiochemistry. Using the same protocol, the 1-PX,19-Me substrate (**17**) was cyclized to give exclusively the product (**18**) (51%) with the methyl

in the "valley" position; the regiochemistry was confirmed using proton nmr spectroscopy, with particular emphasis on the characteristic phenyl region between 6.5 and 8.0 ppm, where the chemical shift differences between "valley" and bridging phenyl protons are diagnostic (Figure 1). The bridging proton at 3.5 ppm, appearing at a chemical shift similar to that proton in **16**, established the structure beyond doubt. Heating **17** at 140°C afforded the same product. The 1-PX,19-PME substrate (**19**) was then cyclized. As could be predicted based on the previous results above, only one isomer was formed, that being the one [**20** (13%)] in which the PME was in the "valley" position. At 140°C mostly decomposition was observed. When cyclization was attempted on the 1-PX,19-AEE substrate (**21**) large amounts of side products were obtained at all temperatures except at 0°C (or below) using the aqueous ethanol method; the exclusive product (**22**) (40%), had the PX in the "valley" position.



Scheme 1: Proposed mechanism for conversion of kinetic product (**8**) from cyclization of a,c-biladiene salt (**7**) into thermodynamic product (**9**).

In all cases, it is possible to predict the structure of the kinetic product. In general, where either the AEE or PX is utilized, stabilization of the intermediate species causes this moiety to preferentially provide the bridging carbon. In the case of the kinetic 1-AEE,19-Me product (**8**) where the ester is attached to the bridging carbon, an enol (**23**) can form as shown in Scheme 1, breaking the macrocycle, and irreversibly either isomerizing to the thermodynamic "valley" AEE compound (**9**) or as in the case of compound (**13**), forming the thermodynamically favored homoporphyrin (**14**) after further oxidation. When the PX takes the bridging position, as in **18**, an enol intermediate similar to **23** is not an option; therefore once the most kinetically stable isomer is formed, the structure is irreversibly locked. Steric congestion must play a role in determing the structure for compounds such

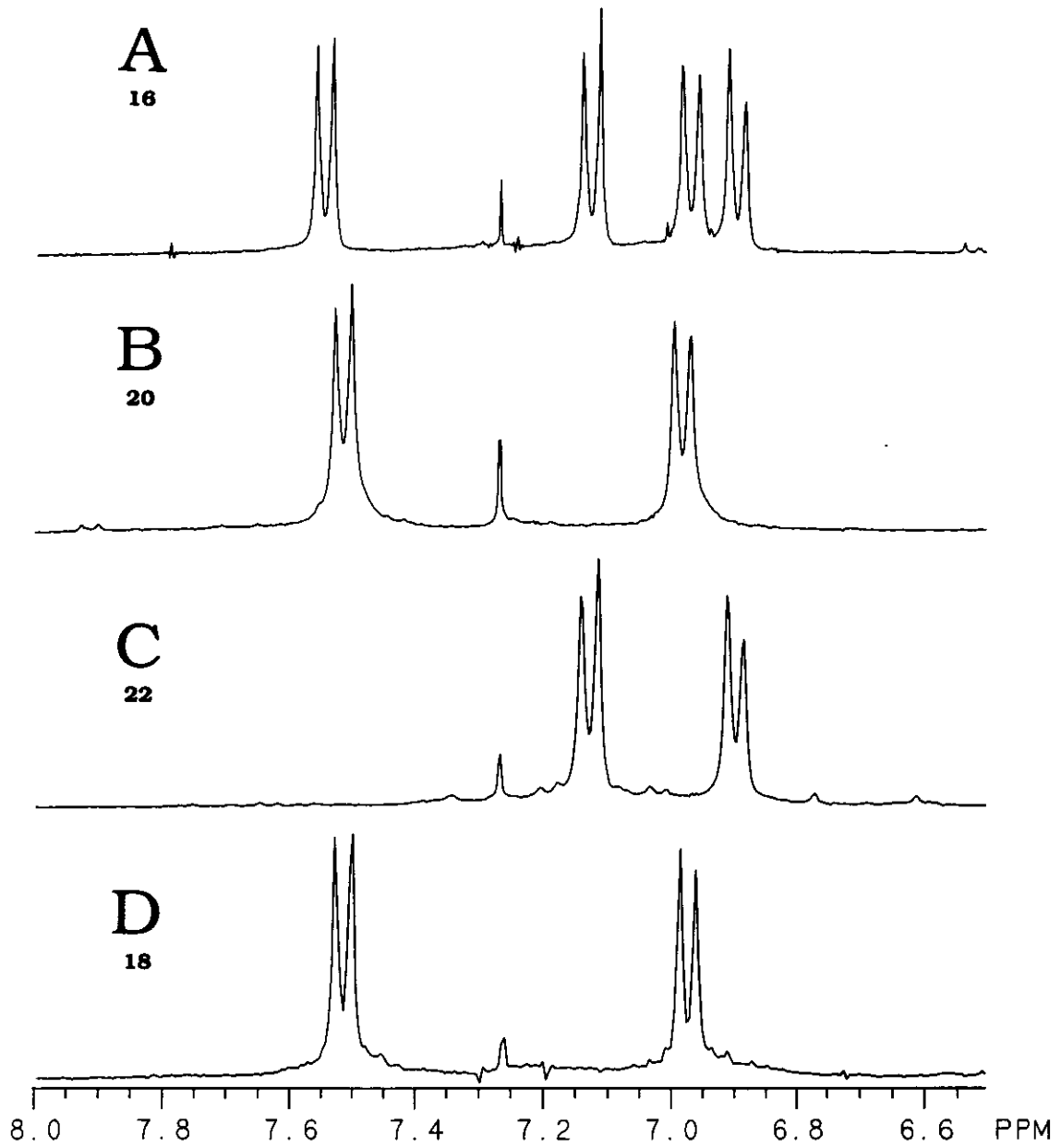


Figure 1: Phenyl region in the 300 MHz proton nmr spectra, in $CDCl_3$, of A, PX/p-C_4H_4Me "valley" compound (**16**); B, PME/p-C_4H_4Me "valley" compound (**20**); C, PX/CO_2Et "valley" compound (**22**); and D, Me/p-C_4H_4Me "valley" compound (**18**). The peak at about 7.25 ppm in each spectrum is assigned to residual $C\underline{H}Cl_3$ in the solvent.

as **11**. From the above discussion, we can conclude that the propensity for 1- or 19-substituents to provide the macrocyclic bridging carbon in the metal assisted cyclization of 1,19-disubstituted a,c-biladienes is:

$$-CH_2CO_2Et > -PX > -Me > -CH_2CH_2CO_2Me$$

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (HL-22252) and the National Science Foundation (CHE-93-05577). We thank Dr. Paul A. Liddell for helpful preliminary experiments. Mass spectrometric analyses were performed by the UCSF Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

REFERENCES

1. A. W. Johnson and I. T. Kay, *J. Chem. Soc. C*, 1961, 2418.
2. Recent review: P. S. Clezy, *Aust. J. Chem.*, 1991, **44**, 1163.
3. K. M. Smith and O. M. Minnetian, *J. Chem. Soc., Perkin Trans. 1*, 1986, 277.
4. (a) K. L. Swanson, K. M. Snow, and K. M. Smith, *Tetrahedron*, 1991, **47**, 685. (b) D. Jeyakumar, K. M. Snow and K. M. Smith, *J. Am. Chem. Soc.*, 1988, **110** , 8562.
5. T. Boschi, R. Paolesse, and P. Tagliatesta, *Inorg. Chim. Acta*, 1991, **168**, 83.
6. A. W. Johnson, D. Dolphin, R. L. N. Harris, J. L. Huppatz, and I. T. Kay, *J. Chem. Soc., C*, 1966, 30.
7. P. S. Clezy, B. N. Ravi, and L. V. Thuc, *Aust. J. Chem.*, 1986, **39**, 419. E. J. Atkinson, J. J. Brophy, and P. S. Clezy, *Aust. J. Chem.*, 1990, **43**, 383.
8. P. A. Liddell, M. M. Olmstead, and K. M. Smith, *J. Am. Chem. Soc.*, 1990, **112**, 2038. P. A. Liddell, K. R. Gerzevske, J. J. Lin, M. M. Olmstead, and K. M. Smith, *J. Org. Chem.*, in press.
9. J. A. P. B. de Almeida, G. W. Kenner, J. Rimmer, and K. M. Smith, *Tetrahedron*, 1976, **32**, 1793. K. M. Smith and G. W. Craig, *J. Org. Chem.*, 1983, **48**, 4302.

Received, 26th July, 1993