

A SYNTHETIC APPROACH TO CROWN ETHER ANALOGS
BY THE REMOTE PHOTOCYCLIZATION WITH A PAIR SYSTEM OF PHTHALIMIDE
AND METHYLTHIO GROUPS¹⁾

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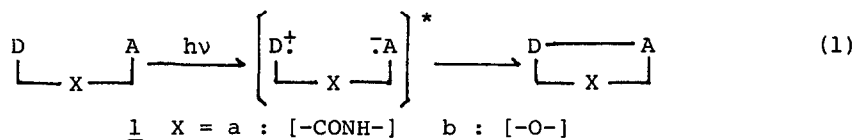
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Abstract: Upon irradiation a homologous series of certain phthalimides (2a-c) possessing a terminal sulfide function in their N-poly-ether side chain undergo regioselective remote photocyclization affording seven to fifteen-membered crown ether analogs (3a-c) in moderate yields.

Syntheses of macrocycles have recently attracted considerable attention in view of important chemical and biological applications of naturally occurring and synthetic macrocycles. Typically, crown ethers and cryptands are well known as samples of synthetic macrocyclic ligands²⁾. Although many ground-state reactions for the construction of macrocycles have been known³⁾, much less information is available for photochemical macrocyclic syntheses^{3c)}.

During the course of our systematic studies on imide photochemistry⁴⁾, we have found that phthalimides possessing a terminal sulfide function in their N-side chain undergo unusually facile photocyclization to give azathiacyclols⁵⁾. We are now extending this type of reaction to general synthesis of macrocycles on the basis of a regioselective remote photocyclization of a "pair system" which consists of, in this case, a phthalimide group and a methylthio group. With this particular pair, macrocycles of up to 16-membered⁶⁾, and cyclic peptide models of up to 21-membered⁷⁾, have been synthesized. While the phthalimide ring is a good electron acceptor (A), the sulfide is a donor (D). Therefore it is assumed that a complex formation in the excited states may facilitate the reaction, suggesting a general working hypothesis that compounds possessing certain appropriate D-A pair groups, even separated by a long chain, are capable of forming a new carbon-carbon bond on irradiation (eq.1). To see the scope and limitation of this synthetic method, examination of a structural

variation in the connecting portion (X), which combines the donor and the acceptor pair, was needed. We have already investigated the photocyclization of the phthalimides containing amide bonds (1a)^{6,7}). In the present paper, we wish to report results of the photolysis of such pair system with poly-ether bonds

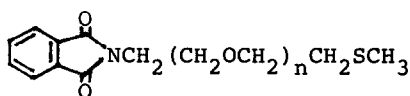
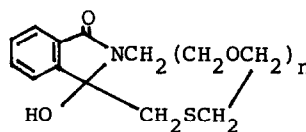
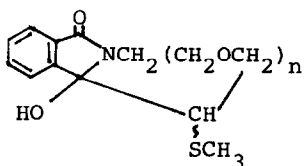
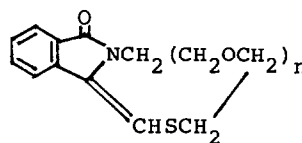


(1b) in their side chains as a connector.

Irradiation of N-[2-[2-(methylthio)ethoxy]ethyl]phthalimide 2a with 400W high pressure mercury lamp in 7.3 mM acetone solution for 0.5 hr in a stream of argon afforded a mixture of medium-sized cyclols, which were separated into 3a (mp 154-156°C, 74%) and 4a (mp 192-193°C, 6%) by silica gel column chromatography. In support of the assigned structure⁸), the cyclol 3a was readily converted into the dehydrated product 5a (mp 155-156°C) on treatment with acid. Homologous N-substituted phthalimides 2b-c containing poly-ether bonds and a ω -methylthio group were prepared, and the photolysis was performed in a similar manner (Table I)⁸). The expected heteromeric cyclols 3b (mp 143-144°C), 3c (mp 98-99°C), and 4c (mp 127-130°C), respectively, were readily obtained as a result of the C-C bond formation between the imide carbonyl group and the S-methyl (or -methylene) group through the extensive Norrish type II process^{4,6}). In a representative example, the structural assignment for 3c was based on the following reasons: (i) the presence of the cyclol moiety was confirmed by spectroscopic data [hydroxyl (ir 3240 cm⁻¹), amide (1670 cm⁻¹) and a methylene (instead of a methyl in 2c) nmr (in CDCl₃) 3.0 ppm, (d, J=14.1 Hz)]; (ii) the molecular weight values determined by a vapor-pressure method⁹) and mass spectrometry were 343 and 353, respectively, both in agreement with the monomeric

Table I. Photoproducts from the Poly-ether Substrates

Substrate <u>2</u>		Condition			Product (yield)			
Entry	n	Weight g (mmol)	Concent'n. mM	Time min	<u>3</u> (%)	Ring size	<u>4</u> (%)	Ring size
a	1	2.5 (9.4)	7.3	30	74	9	6	7
b	2	2.0 (6.5)	5.0	70	58	12		
c	3	2.0 (5.7)	4.4	45	35	15	24	13

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value (353); (iii) on the treatment with *p*-toluenesulfonic acid, 3c similarly afforded the dehydrated compound 5c [mp 137-138°C, nmr 6.65 ppm, (1H, s, olefinic proton)].

It is well known that an alkoxy group enhances the reactivity of the adjacent C-H bond for excited carbonyl group in the Norrish type II processes¹⁰). Analogously, we have observed that phthalimides with an ether moiety in their N-substituent also undergo facile δ -hydrogen abstraction¹¹). In view of the methodology of the photochemical macrocyclic syntheses, therefore, it is noteworthy that the substrates 2 having several potentially reactive sites such as the ether bonds still undergo this selective remote cyclization at the thiomethyl group. The heteromeric cyclic ethers thus prepared are up to a fifteen membered 3c, which is nearly equivalent in size to that of 15-crown-5²). Since the ligand capacity of crown type compounds are highly dependent on the nature and arrangements of the component hetero atoms²), "mixed" crowns like 3-5 will provide an interesting candidates for a new family in the host-guest chemistry. Further possible utilities of this approach (donor-acceptor pair system) as well as the detailed cyclization mechanism are under investigation.

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References and Notes.

- 1) a) Photochemistry of the Phthalimide System. 25. Part 24: M. Machida, K. Oda and Y. Kanaoka, *Heterocycles*, 18, 211 (1982). b) Photoinduced Reactions. 53. For Part 52: see ref. 1a).
- 2) a) D. J. Cram and J. M. Cram, *Science*, 183, 803 (1974); b) *Idem.*, *Accounts Chem. Res.* 11, 8 (1978); c) J. -M. Lehn, *ibid.*, 11, 49 (1978); d) H. Dugas and C. Penny "Bioorganic Chemistry", by R. Frost, Springer-Verlag, New York, 1981, p.255.
- 3) a) J. S. Bradshaw and P. E. Stott, *Tetrahedron*, 36, 461 (1980); b) G. Illuminati and L. Mandolini, *Accounts Chem. Res.*, 14, 95 (1981); c) M. A. Winnik, *Chem. Rev.*, 81, 491 (1981).
- 4) Y. Kanaoka, *Accounts Chem. Res.*, 11, 407 (1978).
- 5) a) Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi, Y. Migita and Y. Kanaoka, *Tetrahedron Lett.*, 1973, 4565; b) Y. Sato, H. Nakai, T. Mizoguchi, M. Kawanishi, Y. Hatanaka and Y. Kanaoka, *Chem. Pharm. Bull.*, 30, (1982) in press.
- 6) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka and Y. Kanaoka, *J. Am. Chem. Soc.*, 98, 2349 (1976).
- 7) Y. Sato, H. Nakai, T. Mizoguchi and Y. Kanaoka, *Tetrahedron Lett.*, 1976, 1889.
- 8) All the new compounds gave satisfactory elemental analyses and their structures were supported by spectral (uv, ir, nmr, mass) data.
- 9) Hitachi-Perkin molecular weight measuring apparatus Model 115; in methanol.
- 10) P. J. Wagner and A. E. Kemppainen, *J. Am. Chem. Soc.*, 94, 7495 (1972).
- 11) a) Y. Kanaoka, Y. Migita, Y. Sato and H. Nakai, *Tetrahedron Lett.*, 1973, 51; b) H. Nakai, Y. Sato, H. Ogiwara, T. Mizoguchi and Y. Kanaoka, *Heterocycles*, 2, 621 (1974); c) Y. Sato, H. Nakai, M. Wada, H. Ogiwara, T. Mizoguchi, Y. Migita, Y. Hatanaka and Y. Kanaoka, *Chem. Pharm. Bull.*, 30, (1982) in press.

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