# Photoreactions of Cyclic Imides. Examples of Synthetic Organic Photochemistry

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Received April 29, 1977

Photochemistry in recent years has extended the armamentarium of the organic chemist in coping with synthetic challenges.[1] Novel chromophoric systems have been developed and designed, and reactivities of excited states have been defined and utilized. The technique of selective quenching has made possible bond formation and fragmentation leading to molecular structures which would be not readily accessible by recourse to conventional reactions proceeding through ground-state paths.[1,2] Probably the most active area of organic photochemistry has been the study of systems which possess a carbonyl group.[3] As a result, a multitude of photoreactions have been extensively documented in the literature involving examples of a wide variety of carbonyl derivatives 1, in which a carbonyl is conjugated with unsaturated or heteroatom systems.[1-3] Photochemistry of an imide, a cross-conjugated carbonyl system involving a nitrogen (1, X
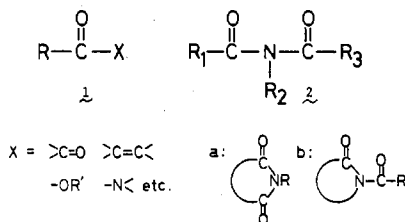
= –N(C=O)–; 2), however, has until recently been virtually ignored, while thermal reactions of imides have received much attention.[4]

As far as we are aware, no observation had been recorded about the photochemical behavior of cyclic imides 2a up to 1972,[5-7] with the exception of a vapor-phase photolysis of succinimide,[5] and only a few noncyclic imides[8] have been examined. Systematic probing into photoreactivity of a number of carbonyl derivatives led us ultimately to the discovery that N-(o-tolyl)phthalimide, upon irradiation, undergoes an unexpected cyclization to a cyclopentanol.[6] This finding provided the stimulus for a broad investigation into the synthetic potential of the excited imide carbonyl in our laboratories.[9,10] Imides are formally classified into three groups: cyclic, 2a, semicyclic, 2b, and noncyclic. Photochemistry of 2b heretofore has been unknown.[10b] The present status of the photochemistry of cyclic imides 2a is reviewed here from the viewpoint of the synthetic chemist desirous of making new nitrogen heterocycles.

Yuichi Kanaoka was born in Toyama, Japan, in 1928. He received his B.A. and Ph.D. from the University of Tokyo where he worked with Shigehiko Sugasawa. In 1956 he moved to Hokkaido University, where he has been Professor of Synthetic Pharmaceutical Chemistry since 1966. He spent the years 1959–1961 at the National Institutes of Health associated with Bernhard Witkop. His research covers the fields of both synthetic organic photochemistry, mainly related to heterocyclic chemistry, and bioorganic chemistry, including organic reactions of enzymes and proteins.

## Spectroscopic Properties and General Reactions

An isolated imide group absorbs in the far-ultraviolet (178 nm; $\epsilon \simeq 8000$), and this band is shifted to about 190–215 nm ($\epsilon \sim 13{,}000$) in succinimide and glutarimide derivatives.[11] N-Alkyl cyclic imides have a shoulder at around 240 nm, assigned to an n,π^* transition because of its molar absorptivity ($\epsilon \sim 140$) and solvent dependency.[10,12] The 254-nm emission of a low-pressure mercury lamp is convenient for exciting aliphatic imides. Wavelength dependency of the reaction showed that the range 230–270 nm is mainly effective with the maximum around 240 nm, suggestive of involvement of the n,π^* transition.[10,12]

In the initial stage of our research, electronic spectra of phthalimides, representative of aromatic cyclic imides, were examined.[9,10] N-Alkylphthalimides have a π,π^* band around 290 nm ($\epsilon \sim 2000$) which submerges a weak n,π^* band, the latter being observed in nonpolar solvents. Since simple phthalimides show no fluorescence, the lowest singlet may be the n,π^* state, at least for N-alkylphthalimides. Phosphorescence spectra of N-substituted phthalimides indicated that their triplet states are mainly of π,π^* character; lifetimes are long (0.6–0.8 s), and there is little vibrational structure.[9,10a] Regardless of the details of the reacting species, high-pressure mercury lamps were effectively used for the photoreactions of phthalimides.

The cyclic imides 2a undergo virtually all of the major photochemical reactions known for the simple carbonyl system, and several unique reactions as well.[13] As

(1) N. J. Turro, "Molecular Photochemistry", W. A. Benjamin, New York, N.Y., 1965; J. G. Calvery and J. N. Pitts, Jr., "Photochemistry", Wiley, New York, N.Y., 1966.

(2) A. Schönberg, "Preparative Organic Photochemistry", Springer-Verlag, Berlin, 1968; *Org. Photochem.*, 1–3 (1967–1973); N. J. Turro and G. Schuster, *Science*, 187, 303 (1975).

(3) J. N. Pitts, Jr., and J. Wan, "The Chemistry of the Carbonyl Group", S. Patai, Ed., Wiley, New York, N.Y., 1966, pp 823–916; *Photochemistry*, 1–8 (1970–1977).

(4) M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, 70, 439 (1970); O. H. Wheeler and O. Rosado, "The Chemistry of Amides", J. Zabicky, Ed., Wiley, New York, N.Y., 1970, p 335.

(5) G. Choudhary, A. M. Cameron, and R. A. Back, *J. Phys. Chem.*, 72, 2289 (1968).

(6) Y. Kanaoka and K. Koyama, *Tetrahedron Lett.*, 4517 (1972).

(7) Small-ring analogues such as azetidinediones apparently form a special family, which is not included in this review. See, for example, J. A. Schutyser and F. C. De Schryver, *Tetrahedron*, 32, 251 (1976).

(8) R. O. Kan, and R. L. Flurey, *Tetrahedron Lett.*, 2573 (1966); Y. Kanaoka, T. Tsuji, K. Itoh and K. Koyama, *Chem. Pharm. Bull.*, 21, 453 (1973); Y. Katsuhara, N. Maruyama, Y. Shigemitsu, and Y. Odaira, *Tetrahedron Lett.*, 1323 (1973).

(9) Y. Kanaoka, *J. Soc. Org. Synth. Chem. Tokyo*, 33, 949 (1975).

(10) (a) Y. Kanaoka and Y. Hatanaka, Abstracts of Papers, Symposium on Photochemistry: Tokyo, Nov 1975, p 151; Fukuoka, Nov 1976, p 169; Sendai, Nov 1977, p 138; (b) Y. Kanaoka, Y. Hatanaka, H. Okajima, and M. Machida, in preparation. (c) Y. Kanaoka, Y. Hatanaka, and K. Yoshida, in preparation.

(11) D. W. Turner, *J. Chem. Soc.*, 4555 (1957); C. M. Lee and K. D. Kulmar, *J. Am. Chem. Soc.*, 84, 565 (1962).

(12) Y. Kanaoka and Y. Hatanaka, *J. Org. Chem.*, 41, 400 (1976).
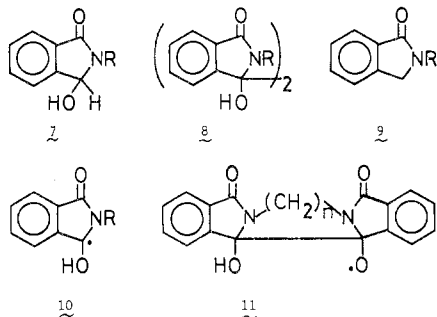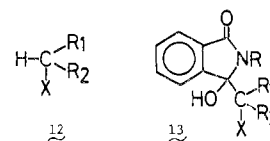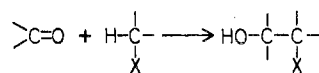
Scheme I
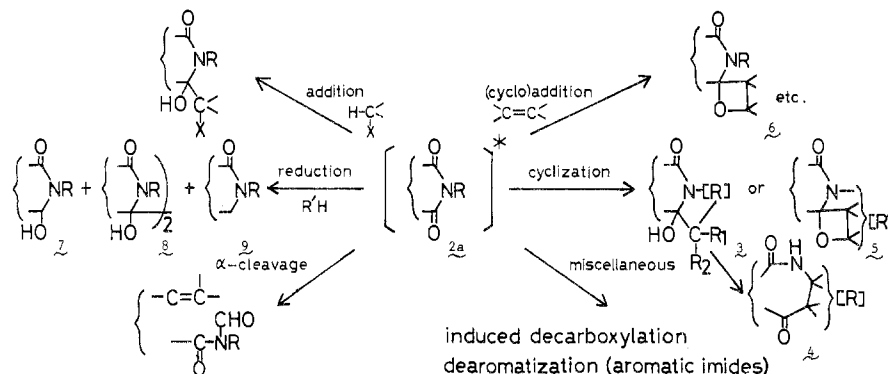
shown in Scheme I, the reactions characteristic of ketones include reduction, addition, cycloaddition, and Norrish type I and type II reactions. In addition to some special reactions induced by the imide group, such as dearomatization of the benzene moiety of phthalimides, the presence of certain functional groups in their N-substituents of phthalimides leads to unique, extended type II and other related cyclizations giving rise to a variety of new heterocycles (3, 4, and 5). Intermolecular photoadditions of olefins, represented by a typical oxetane formation, 6, also suggest new synthetic possibilities.

Photoreduction and Photoaddition of Phthalimides: Photo-Aldol Condensation and Other Additions

Compounds containing a carbonyl chromophore, upon irradiation in solvents having readily abstractable hydrogen, undergo photoreduction as one of the most common reactions. When N-alkylphthalimides were photolyzed in alcohol, the reduced products 7 were

obtained accompanied by the addition products,[6] demonstrating that the photochemical behavior of the imide carbonyl mainly parallels that of simpler ketones.[3,14] In contrast to the well-known photoreduction of benzophenone, the corresponding pinacol 8 was not detected in the above photoreduction of phthalimides. Only in the presence of better hydrogen donors such as amines was the pinacol isolated, together with the further reduced phthalimidine 9.[15] In the photolysis of N-methylenebisphthalimides in 2-propanol, the intramolecular coupling products 8 [R = -(CH$_2$)$_n$-] were obtained when the two imide moieties in the substrates

(13) All the reactions described in this article are more or less solvent-dependent. However, in general most of common solvents both protic and aprotic, such as ethanol, *tert*-butyl alcohol, acetonitrile, acetone, and benzene, can be employed as appropriate.
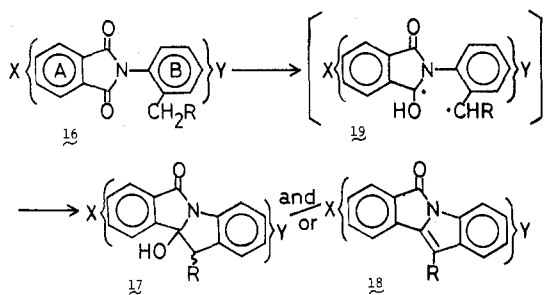(14) P. J. Wagner, *Acc. Chem. Res.*, 4, 168 (1971).
(15) Y. Kanaoka, K. Sakai, R. Murata, and Y. Hatanaka, *Heterocycles*, 3, 719 (1975).

Scheme II

a, X = OH
b, X = OR
c, XR$_1$ = -C=C(CH$_2$)$_n$-
d, X = C$_6$H$_5$
e, X = NR$_2$

were separated by three or fewer methylene groups.[16] The formation of 8 can be rationalized on the basis of initial hydrogen abstraction to give a ketyl-like (semi-pinacol) radical 10 followed by a second abstraction and coupling of the resultant biradical. An alternative pathway, which involves a subsequent intramolecular radical transfer of 10 to form an alkoxy radical 11, may also be possible.

In photoaddition reactions of carbonyl compounds, referred to as "photo-aldol condensation", the methylene group activated by adjacent groups, such as double bonds or heteroatoms, is capable of addition reactions leading to carbinols (Scheme II). If a semi-pinacol radical 10, invoked as a general intermediate, is actually involved, this may well couple with the other radical formed from the solvent according to Scheme II.[15,17] In fact, a series of hydrogen donors 12, such as alcohol a,[6] ether b,[17] cycloalkene c,[17] alkylbenzene d,[15] and amine e,[15] gave rise to the corresponding carbinol 13 as a result of C–C bond formation. Thus photoreactions of phthalimides in the presence of activated methylene compounds generally include carbinol formation.

This parallelism led us to assume the principal working hypothesis that every reaction which the carbonyl system undergoes must be studied with regard to the imide group, covering all intra- and intermolecular reactions[9,10] as summarized in Scheme I. Recently Maruyama and Kubo have reported formation of intramolecular oxetanes in the photolysis of N-2-alkenyl alicyclic imides 5.[18] Further, oxetanes 6 have now been isolated in crystalline form from intermolecular photoreactions of N-methylsuccinimide and -glutarimide with 3,3-dimethyl-2-butene in acetonitrile.[10c] Whereas

(16) Y. Kanaoka and E. Sato, *Chem. Pharm. Bull.*, 26, 989 (1978).
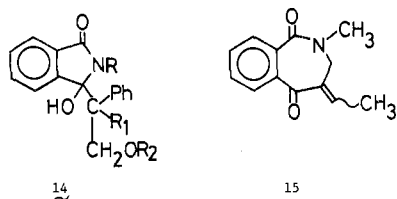(17) Y. Kanaoka and Y. Hatanaka, *Chem. Pharm. Bull.*, 22, 2205 (1974).
(18) K. Maruyama and Y. Kubo, *J. Org. Chem.*, 42, 3215 (1977).
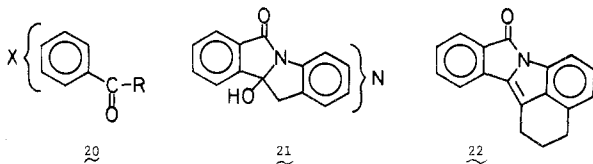
Scheme III

phthalimides undergo photoadditions with styrenes in alcohol to give solvolyzed products 14,[19] Mazzocchi et

al. have very recently observed addition of dienes, not to the carbonyl, but to the C–N bond of N-methylphthalimide producing 15.[20]

Photocyclization of N-Arylphthalimides: Synthesis of Isoindoloindole and Other Heterocyclic Systems

Participation of imides in photocyclization was first observed with the conversion of 16 (X = Y = R = H) to 17 and/or 18 (Scheme III).[6] In the hope of delineating the scope and limitation of the reaction as well as gaining an insight into the nature of the excited imide carbonyl, photolysis of a series of N-(o-tolyl)phthalimides 16 (R = H) possessing various substituents on the A or B ring was examined in $tert$-butyl alcohol or acetone.[21] Whereas photolysis of the imides with an electron-withdrawing group such as nitrile and methoxycarbonyl on the A ring afforded the cyclized products 17 and/or 18, the presence of electron-donating substituents such as methoxyl and dimethylamino inhibited this cyclization.[21] By contrast, imides possessing either electron-withdrawing or -donating group on the B ring smoothly underwent cyclization to the isoindoloindole derivatives.[21] Again, these results seem consistent with the postulated intermediacy of a biradical 19. While substituent Y influences the stability of the benzyl radical, substituent X must exhibit a direct effect on the reactivity of the excited carbonyl. It is well-known that aromatic ketones 20, with π,π^*

lowest triplets due to an electron-donating substituent X, have their reactivity substantially reduced.[1-3,14] Analogous reasoning would explain the behavior of these phthalimides. Structural variations of the B ring

Scheme IV
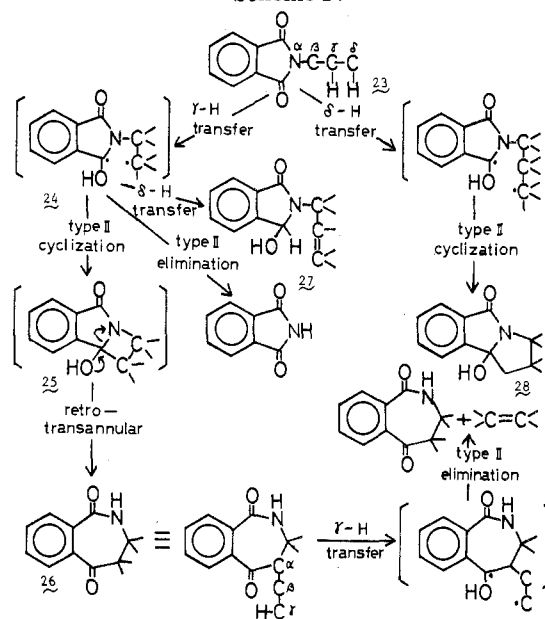
broadened the scope of synthetic applications. For example, this method was extended to the nitrogen heterocyclic analogues, and pyridopyrroloisoindoles 21 became accessible.[22] As an example of a variation for the substrate structures, replacement of the alkyl of 16 by an alicyclic methylene moiety led to a new pentacyclic ring system, 22.[23]

The quantum yield of the formation of 17 (X = Y = H; R = CH$_3$) was as low as $10^{-2} \sim 10^{-3}$ ($tert$-butyl alcohol, acetonitrile, benzene),[9,10] although the chemical yield of the isolated product was acceptable ($\sim$70%). A Stern–Volmer plot with $trans$-piperylene in acetonitrile as quencher is linear. These results together with the kinetic isotope effect ($\sim$5.6) observed with the deuterio derivatives of 16 suggest that the rate-limiting step may be hydrogen abstraction by the triplet imide carbonyl of largely π,π^* character.[9,10,24]

Photocyclization of N-Alkylphthalimides

Norrish Type II Reactions. Experiments with simple N-alkylphthalimides in several solvent systems followed the general pattern of the photolysis of these imides.[25] As shown in Scheme IV,[25] these results were best rationalized by considering the proposed mechanism on the basis of strictly formal analogy with the Norrish type II processes established in ketonic systems.[3,14] The substrate 23, in which the N atom is regarded as the α atom to the imide carbonyl, undergoes initial γ-hydrogen abstraction to form a biradical 24 followed either by type II elimination or by type II cyclization to an azacyclobutanol, 25. This azacyclobutanol, presumably due to ring strain, undergoes a retro-transannular ring opening leading to a benzazepinone lactam, 26. Alternatively, in some of the biradicals with δ hydrogens, a competing δ-hydrogen transfer takes place with concomitant formation of an

(19) K. Maruyama and Y. Kubo, Annual Meeting of the Chemical Society of Japan, April 1977, Tokyo. Abstracts of Papers II, p 866.

(20) O. Mazzocchi, M. J. Bowen, and N. K. Narain, *J. Am. Chem. Soc.*, 99, 7063 (1977).

(21) Y. Kanaoka, C. Nagasawa, H. Nakai, Y. Sato, H. Ogiwara, and T. Mizoguchi, *Heterocycles*, 3, 553 (1975).

(22) M. Terashima, K. Seki, K. Koyama, and Y. Kanaoka, *Chem. Pharm. Bull.*, 25, 1591 (1977).

(23) M. Terashima, K. Koyama, and Y. Kanaoka, *Chem. Pharm. Bull.*, 26, 630 (1978).

(24) Existence of radical intermediates as studied by flash photolysis was inconclusive.[10] Maruyama et al. obtained some evidence by CIDNP technique: Y. Kubo, Master's Thesis, Kyoto University, 1976.
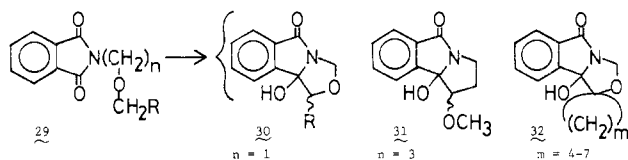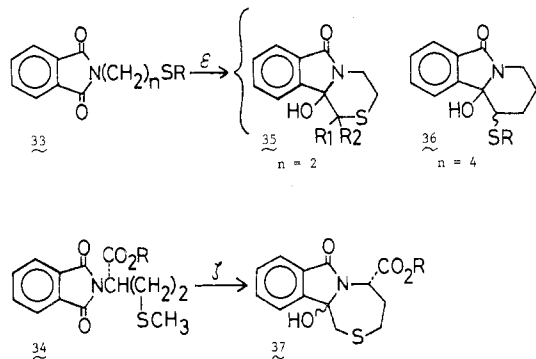
(25) Y. Kanaoka, Y. Migita, K. Koyama, Y. Sato, H. Nakai, and T. Mizoguchi, *Tetrahedron Lett.*, 1193 (1973).

Scheme V

Scheme VI

Scheme VII

Scheme VIII

unsaturated product, **27**. When **26** has a hydrogen γ to the newly formed carbonyl, hydrogen transfer and loss of olefin follow. With a substrate having a δ hydrogen, another type II cyclization affords an azacyclopentanol, **28**. This interpretation provides a rational basis for the formation and ratio of almost all the products observed.

Syntheses of Azacyclopentanol and Related Systems from Phthalimides with a Heteroatom in Their Side Chains. In a study initially designed to see the effect of a heteroatom, reactions of *N*-(ω-alkoxyalkyl)phthalimides **29** were examined (Scheme V).[26] Irradiation of **29** (R = CH_3, n = 1; R = H, n = 3) gave the products of δ-hydrogen abstraction, **30** (R = CH_3) and **31**, respectively. Extensive studies by Wagner et al. on type II processes of phenyl alkyl ketones showed that an alkoxy group activates an adjacent C–H bond.[14,27] Involvement of a quaternary carbon as a central atom is sometimes required in designing biologically active substances. For the construction of a quaternary carbon, hydrogen abstraction from a tertiary carbon followed by C–C radical coupling may be one of the attractive routes. In this manner, and with acetonitrile as solvent, heterocycles with varying spiro ring sizes, **32**, were readily synthesized.[28]

The behavior of the alkylthio analogues **33** and **34** was interesting as well as unusual in that the Norrish type II cyclization in acetone is extended even to ε- and ζ-hydrogen abstraction (Scheme VI).[29] Relatively facile δ-hydrogen abstraction was again observed to give **30** (O = S) and **31** (C = S). Formation of **35** suggested that the ε hydrogens of **33** (n = 2) are rather more reactive than the γ hydrogens. This tendency was further confirmed by facile formation of the azacyclohexanol **36**. Irradiation of *N*-phthaloyl-L-methionine ester **34** furnished, unexpectedly, an azathiacycloheptanol, **37**,

a "ζ" product, in a good yield.[29] This important "cyclophilic" character of the alkylthio-containing phthalimides was later successfully utilized for a synthesis of macrocycles.

In phthalimides having sulfur or nitrogen in their alkyl side chains, either elimination or cyclization can take place depending on the reaction conditions.[9,10] Recently Roth et al. reported photocyclization of pertinent Mannich bases to **38**.[30a,b] They examined also some photoadditions.[30b,c]

Synthesis of Multicyclic Benzazepines from N-Alicyclic Phthalimides. One interesting feature of type II cyclizations is the behavior of N-alicyclic phthalimides.[31] Photolysis of *N*-cyclopentyl- and *N*-cyclohexylphthalimides **39** (n = 3, 4) in ethanol mainly gave azepinones **40**, the normal cyclization products, accompanied by their reduced products **41**. However, *N*-cycloheptyl compound **39** (n = 5) afforded a novel bridged cyclobutane system, **42**, whose structure was established by X-ray analysis by Karle et al.[32] The formation of **42** and **43**, the latter being a minor product from **39** (n = 4), is perfectly consistent with the general pattern (Scheme IV) as amplified in Scheme VII;[31] at the benzazepinone stage, it is again the γ hydrogen which is abstracted, and the cyclobutanol is formed presumably via a biradical, **44**.

Norrish Type II Cyclization of Alicyclic Imides: A Novel Ring-Expansion Reaction

The first example of a novel ring-expansion reaction of alicyclic imides was found with the unsubstituted
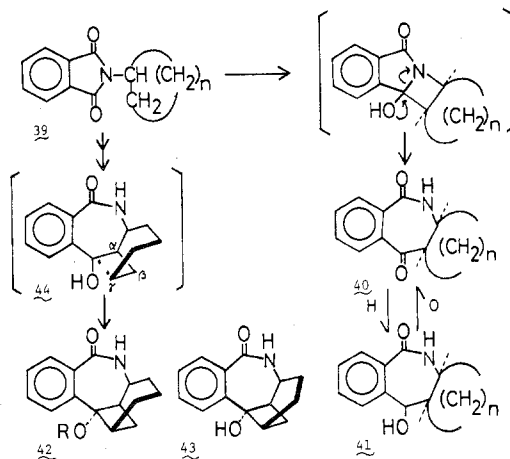
(26) Y. Kanaoka, Y. Migita, Y. Sato, and H. Nakai, *Tetrahedron Lett.*, 51 (1973).

(27) P. J. Wagner, P. A. Kelso, A. E. Kempainen and R. G. Zepp, *J. Am. Chem. Soc.*, **94**, 7500 (1972); P. J. Wagner, P. A. Kelso, A. E. Kempainen, J. M. McGrath, H. N. Schott, and R. G. Zepp, *ibid.*, **94**, 7506 (1972), and papers cited therein.
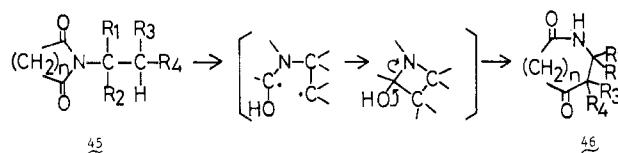
(28) H. Nakai, Y. Sato, H. Ogiwara, T. Mizoguchi, and Y. Kanaoka, *Heterocycles*, **2**, 621 (1974).

(29) Y. Sato, H. Nakai, H. Ogiwata, T. Mizoguchi, Y. Migita, and Y. Kanaoka, *Tetrahedron Lett.*, 4565 (1973).

(30) (a) H. J. Roth and D. Schwarz, *Arch. Pharm.*, **308**, 218 (1975); (b) *ibid.*, **308**, 631 (1975); (c) *ibid.*, **309**, 52 (1976); (d) H. J. Roth and G. Hudeshagen, *ibid.*, **309**, 58 (1976).

(31) Y. Kanaoka, K. Koyama, J. L. Flippen, I. L. Karle, and B. Witkop, *J. Am. Chem. Soc.*, **96**, 4719 (1974).

(32) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

Table I
Photoproducts from Alicyclic Imides 45[12,a]

	R₁	R₂	R₃	R₄	46 yield, %
			45		
	R_1	R_2	R_3	R_4	
			n = 2		
a	H	H	H	H	45
b	H	H	CH₃	H	42
c	H	CH₃	H	H	56
d	H	H	CH₃	CH₃	33
e	CH₃	CH₃	H	H	49
			n = 3		
f	H	H	H	H	37
g	H	H	CH₃	H	52

a 10 mM solution in acetonitrile, 60-W low-pressure mercury lamp, 30 min.

parent compound 45a of this family. A series of succinimides and glutarimides were examined as listed in Table I.[12] The principal feature of the Norrish type II processes of the alicyclic imides is that cyclization is rather dominant in contrast to that of the keto system,[14,27] leading to keto lactams 46 with ring enlargement by the two-carbon unit derived from the side chain (Scheme VIII).[12] The quantum yield of the formation of 46a was 0.64 (in acetonitrile), notably larger than that for the reaction of the aromatic counterparts 16 by a factor of 100, indicating practical application of this reaction on a preparative scale. Variation of the N-substituents, including heteroatoms and carbocycles, may lead to a wide variety of products. In view of their multifunctionality, these photoproducts will be further used as synthetic intermediates. By activation due to introduction of heteroatoms into the side chain, type II processes seem possible involving also δ-hydrogen abstraction.[12,33] The ring size of the imides (*n*) can be increased beyond three.[10] In addition, the imide ring may carry substituents including heteroatoms as well as cycloalkanes as desired.[12,34]

Since these cyclic imides are starting materials which can be prepared relatively easily, this method provides a novel versatile synthetic entry to various medium-sized and other heterocyclic systems. Some illustrative examples hitherto synthesized are shown (47–57; in acetonitrile).[12,33,34]
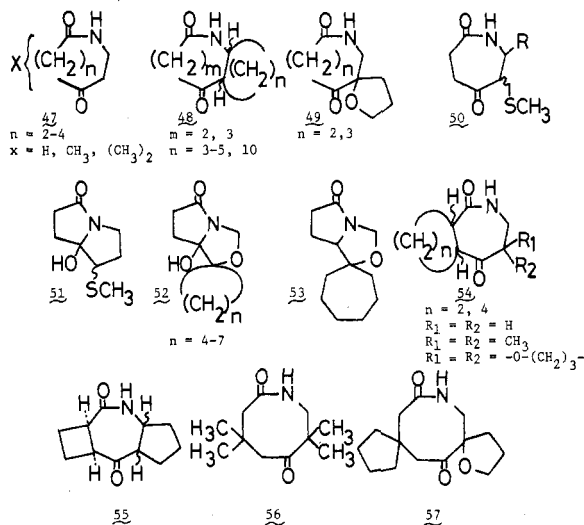
(33) H. Nakai, Y. Sato, T. Mizoguchi, M. Yamazaki, and Y. Kanaoka, *Heterocycles*, 8, 345 (1977).
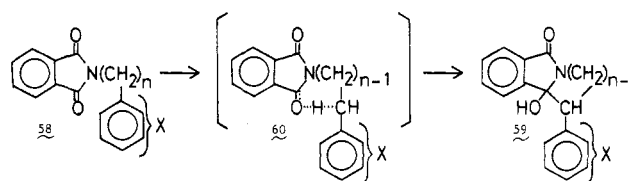(34) Y. Kanaoka, H. Okajima, and Y. Hatanaka, *Heterocycles*, 8, 339 (1977).

Scheme IX

Table II
Photoproducts from Methylthio Phthalimides 61[36,a]

61	*n*	yield, % 62	63	relative efficiency
a	5	78	6	
b	6	58	10	1.0
c	8	45	3	0.3
d	9	29	0	0.3
e	10	26	4	0.3
f	12	25	4	0.2

a 10 mM solution in acetone, 400-W high-pressure mercury lamp, 1–2 h.

Possible Examples of Synthetic Control

Photocyclization of *N*-(Aralkyl)phthalimides. Attempts to subject *N*-(aralkyl)phthalimides 58 to cyclization uncovered some interesting new aspects of the photochemistry of bichromophoric systems.[35] In the photolysis of 58 (*n* = 3–6) in acetonitrile, cyclization to 59 was maximized when *n* equaled 4, i.e., when the usually unfavorable 8-membered transition state 60 (*n* = 4) could be formed (Scheme IX).[35] Apparently the 7- and 6-membered analogues of 60 formed with relatively less ease. In addition, electron-donating substituents X, such as methyl and methoxyl, distinctly promoted the reaction.[35] Thus a special mechanism must be involved which may be associated with some interaction between the imide and the benzylic methylene. Since the phthalimide moiety is a good electron acceptor and therefore capable of forming a donor–acceptor complex with other electron donors,[36] it seems reasonable to assume that cyclization is a result of enhanced hydrogen abstraction from the methylene which is held in close proximity to the excited imide carbonyl through intramolecular complex formation. Charge-transfer complexes in photoreductions of ketones with amines have been well documented.[37,38] A weak charge-transfer band was indeed observed in the ultraviolet spectrum of an ethanol solution of *N*-methylphthalimide and anisole. Furthermore, new fluorescence peaks appeared in the spectra of both the solutions of *N*-butylphthalimide and anisole and of 58 (*n* = 4; X = *p*-CH₃O), in hexane and ethanol, suggesting the existence of inter- and intramolecular exciplexes, respectively.[9,10]

Regioselective Remote Photocyclization of Sulfide-Containing Phthalimides: A Novel Photochemical Macrocyclic Synthesis. The previously noted "cyclophilic" nature of certain phthalimides possessing a terminal sulfide function in their *N*-alkyl side chain[29] has been extensively applied to a facile
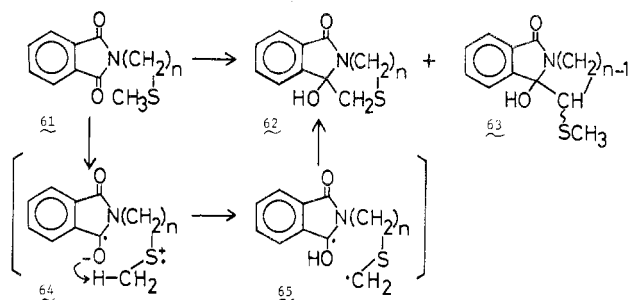
(35) Y. Kanaoka and Y. Migita, *Tetrahedron Lett.*, 3693 (1974).
(36) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka, and Y. Kanaoka, *J. Am. Chem. Soc.*, 98, 2349 (1976).
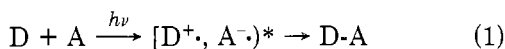(37) S. G. Cohen, A. Parole, and G. H. Parsons, *Chem. Rev.*, 73, 141 (1973).
(38) P. J. Wagner and D. A. Ersfeld, *J. Am. Chem. Soc.*, 98, 4515 (1976); P. J. Wagner and B. J. Scheve, *ibid.*, 99, 1858 (1977).

Scheme X

synthesis of medium- to large-size ring systems. A homologous series of the phthalimides **61** with varying side chains, $n = 5$–12, afforded mainly the macrocyclic system **62**, up to 16-membered, as a result of C–C bond formation between the imide carbonyl and the terminal methylthio group (Table II).[36]

Although "remote" photoreactions are infrequently encountered, much attention has recently been focused on "biomimetic chemistry",[39] cyclization theory,[40] and the general behavior of nonconjugated bichromophoric systems.[41] Generally in the cyclization of long-chain substrates, the flexibility of the chain accounts for a broad distribution of reaction sites, although Breslow et al. achieved an elegant selective remote functionalization by employing a rigid steroid system.[39] On the basis of the studies of chain-length-dependent phenomena, Winnik has recently proposed photochemical probes of hydrocarbon chain conformations in solution.[40] It is therefore remarkable that, in a flexible system such as **61**, the medium and large rings are formed with unusual facility and regioselectivity. In view of the fact that relative efficiencies of the cyclization do not vary much in going to large rings (Table II), there seems no critical limitation to the size of macrocycles to be constructed. Tentatively remote photocyclizations may be rationalized by electron transfer followed by rapid proton transfer from the radical-cation methylthio group with entropy factors favorable by virtue of charge-transfer complex formation in the excited state (**64** → **65**; Scheme X).[36] This assumption, coupled with the results from the (aralkyl)- and (anilinoalkyl)phthalimides, strongly encourages applications of the common working hypothesis, "photolysis of donor–acceptor pair systems", for general synthetic purposes (eq 1). Such an approach may provide a good model for "synthetic control"[42] or selectivity in synthetic chemistry, in which intermolecular association plays an important role.[42b] Photocomplexes and exciplexes assume the role of neighboring group effects known in the ground states[43]

$$D + A \xrightarrow{h\nu} [D^+\cdot, A^-\cdot]^* \rightarrow D\text{-}A \qquad (1)$$

Scheme XI

Scheme XII

and may accelerate reaction rates with practical consequences for preparative purposes. During the last decade the widespread involvement of charge-transfer complexes or exciplexes in photoreactions has been recognized and analyzed.[44] However, development and design of synthetically truly useful pair systems still present a major challenge.

The new method was immediately employed for the synthesis of cyclic peptide analogues.[45] Besides their well-known biological activities represented by antibiotics and hormones, cyclic and "cylindrical" peptides have become useful for the understanding of the general physicochemical behavior of proteins.[46] For a typical example, the phthalimides with a long side-chain containing two amides, **66**, was cyclized bringing about a 21-membered ring, **68** (5 mM in acetone, 15 min, 60%), which is nearly equivalent in size to that of a cyclic heptapeptide.[45]

Other Candidates of the Bichromophoric Systems. *N*-(Anilinoalkyl)phthalimides. It has been known that there are intramolecular interactions in compounds in which a phthalimide and another chromophore are separated by methylene groups.[47] On the basis of this information and the above-mentioned common working hypothesis, photolysis of *N*-(anilinoalkyl)phthalimides **69** was performed. Indeed the

(39) R. Breslow, *Chem. Soc. Rev.*, 1, 553 (1972); R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.*, 95, 3251 (1973).
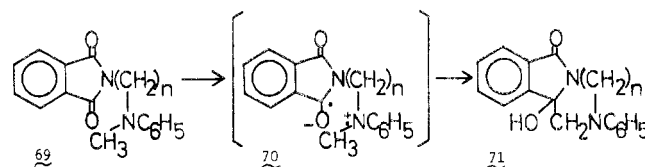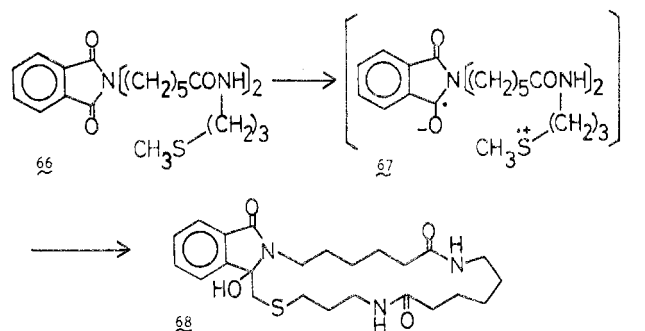
(40) M. A. Winnik, *Acc. Chem. Res.*, 10, 173 (1977).

(41) F. C. DeSchryver, N. Boens, and J. Put, *Adv. Photochem.*, 10, 359 (1977).
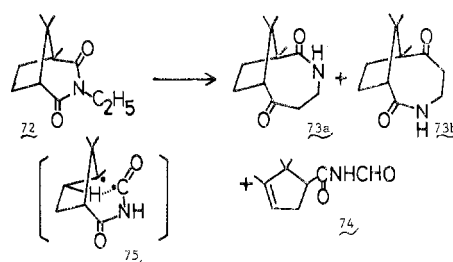
(42) (a) T. Mukaiyama, T. Endo, Y. Kojima, and T. Sato, *J. Am. Chem. Soc.*, 94, 7575 (1972); (b) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Nashimoto, and T. Ishigami, *Nature (London)*, 268, 74 (1977).

(43) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969; M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Interscience-Wiley, New York, N.Y., 1971, p 351.

(44) A. Lablache-Combier, *Bull. Soc. Chim. Fr.*, 154 (1972); M. R. J. Dack, *J. Chem. Educ.*, 169, 170 (1973); M. Gordon and W. R. Ware, Ed., "The Exciplex", Academic Press, New York, N.Y., 1975; M. Ohashi, S. Suwa, and K. Tsujimoto, *J. Chem. Soc., Chem. Commun.*, 348 (1977).

(45) Y. Sato, H. Nakai, T. Mizoguchi, and Y. Kanaoka, *Tetrahedron Lett.*, 1889 (1976).

(46) C. H. Hassall and W. S. Thomas, *Chem. Brit.*, 7, 145 (1971).

(47) D. E. Breen and R. A. Keller, *J. Am. Chem. Soc.*, 90, 1935 (1968); R. S. Davidson and A. Levis, *Tetrahedron Lett.*, 61 (1974).

reaction proceeded, probably by way of an analogous electron-transfer process, **70**, to give large-size ring systems **71** ($n = 12$; acetone–petroleum ether).[48] The search for new donor–acceptor pair systems continues.[10b,49]

Type I and Other Reactions

Photolysis of *N*-ethyl-*d*-camphorimide (**72**) furnished a product, **74**, of a different pattern as well as the expected bridged keto lactams **73**.[34] The pathway leading to **74** may involve α cleavage of the photoelimination product followed by hydrogen transfer in the intermediate biradical **75**, in which a radical is stabilized on the tertiary carbon (Scheme XII).[34] This is a typical case of the type I process found in imide photochemistry.

Miscellaneous photoreactions of cyclic imides include decarboxylation of *N*-phthaloyl-α-amino acids[50] and dearomatization of 4-methylphthalimide derivatives.[51] Evidence for oxetane formation in the cyclic imide system is accumulating.[10c,18,49] Such oxetane formation, both intra- and intermolecular, is a subject of current interest. Cyclizations, probably initiated by electron transfer,[36,45,49,52] are also being pursued.

(48) M. Machida, H. Takechi, and Y. Kanaoka, *Heterocycles*, 7, 273 (1977).

(49) K. Maruyama, Symposium on Photochemistry, Sendai, Nov 1977, Abstracts of Papers, p 212.

(50) Y. Sato, H. Nakai, T. Mizoguchi, M. Kawanishi, and Y. Kanaoka, *Chem. Pharm. Bull.*, 21, 1164 (1973).

(51) Y. Kanaoka, Y. Hatanaka, E. N. Duesler, I. L. Karle, and B. Witkop, in preparation.

(52) K. Maruyama, Y. Kubo, M. Machida, K. Oda, Y. Kanaoka, and K. Fukuyama, *J. Org. Chem.*, 43, 2303 (1978).

Conclusion

One section of the still growing array of photoreactions of carbonyl derivatives is based on the diverse photochemical behavior of cyclic imides. Mechanistic studies are still in their infant stage. However, in general, the effects of nitrogen and the second carbonyl appear to compensate each other. Therefore, in a rough and simple approximation, preliminary synthetic designs would consider aliphatic imides as aliphatic ketones, and aromatic imides as aromatic ketones. Photoreactions of alicyclic imides are highly efficient. In aromatic cyclic imides, the benzenoid system behaves as a good electron acceptor, and selection of substituents would broadly vary and improve their acceptor capability of the benzenoid system and consequently their photoreactivity. The search for suitable combination of functionalized substrates in the light of the working hypothesis of the "donor–acceptor pair system" will catalyze synthetic attempts, not only in the cyclic imides but also in the field of organic reactions at large. In this Account I hope to have shown that novel features and unexpected variations in synthetic photochemistry can be introduced as a function of the complexity of molecular structures and that continued research in this area therefore is still worthwhile.

Aromatic Substitution by the S$_{RN}$1 Mechanism

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Aromatic substitution reactions have been known for a long time, at least since the first nitration of benzene by Mitscherlich[1] in 1834. Many of them are workhorses of synthetic chemistry, and most of them occur by one of a small number of extensively studied mechanisms. It is not often that a new aromatic substitution mechanism of wide scope comes onto the scene.

Such was the case, however, in my laboratory in Santa Cruz in 1970.

Actually, what we found[2] was that aromatic substitution can occur by a mechanism recognized 4 years earlier, by Nathan Kornblum[3] and Glen Russell[4] and their respective co-workers, for substitutions at certain aliphatic sites, especially for reactions of nucleophiles

with *p*-nitrobenzyl chloride and 2-chloro-2-nitropropane. My collaborators and I have found their mechanistic hypothesis to serve excellently, without any need for revision in its essential features, for prediction and interpretation of a wide range of phenomena never visualized when the mechanism was formulated in 1966.

However, I do not think that if we had set out intentionally to extend their observations to include substitutions at aromatic sites we would have been successful. We have subsequently found the nucleo-

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(1) E. Mitscherlich, *Ann. Pharm.*, 9, 39 (1834); *Ann. Phys.*, 31, 625 (1835).

(2) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, 92, 7463, 7464 (1970).

(3) (a) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, 88, 5662 (1966); (b) before 1966, R. C. Kerber, G. W. Urry, and N. Kornblum (*J. Am. Chem. Soc.*, 86, 3904 (1964); 87, 4520 (1965)) proposed a nonchain radical mechanism similar in some respects to the 1966 mechanism, significantly different in others. Their 1964–1965 hypothesis resembled a mechanism proposed by F. M. Beringer, S. A. Galton, and S. J. Huang (*ibid.*, 84, 2819 (1962)) for the phenylation of certain carbanions by diphenyliodonium ion.

(4) G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, 88, 5663 (1966); 90, 347 (1968).