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REVIEW COMMENTARIES

SWITCHING OF REACTION PATHWAYS DUE TO METHYLENE CHAIN LENGTH EFFECTS

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ABSTRACT

Reaction products of bifunctional chain molecules with structure X—$(CH_2)_n$—Y may critically depend on the chain length n. When the chain length is short ($n \leqslant 5$), reaction products particular to an intramolecular reaction can be dominant, while a process corresponding to an intermolecular reaction between X—CH_3 and H_3C—Y may take place for higher homologues having large n ($\geqslant$10). The reaction switching dependent on n is explained in terms of the encounter probability for both end groups (X and Y) with conformations pertinent to product formation. The reaction switching of this sort is discussed on the basis of a reactivity profile recorded as a function of the chain length. Similar reactivity profiles have been observed for thermal Friedel–Crafts cyclization and photo-Smiles rearrangement/photoredox reaction. It is anticipated that the magic methylene chain length of 7 may give rise to an appreciable decrease in reaction yields (e.g. 'difficulty in medium-sized ring closure') or an anomalous switching of reaction pathways due to chain length effects.

1 INTRODUCTION

When two molecules X—CH_3 and H_3C—Y undergo some reactions or interactions in the ground or excited state (electronic energy transfer, formation of electron-donor-acceptor complexes, excimers, or exciplexes), the corresponding intramolecular analogue X—$(CH_2)_n$—Y may behave like the intermolecular counterpart. However, a remarkable dependence of the reaction yield on the chain length is anticipated, since the steric constraint may have some effects on the orientation and distance with respect to the two reaction centres X and Y. In general, the reactivity of higher homologues (X—$(CH_2)_n$—Y, $n \geqslant 10$) is closely related to that

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of the intermolecular reaction between X—CH_3 and H_3C—Y. However, the conformational restriction in short chain molecules may disfavour the reaction path corresponding to that of the higher homologues. The reaction pathway which is totally absent in the intermolecular analogue may predominate in some extreme cases of short chain compounds. There have been only a limited number of papers reporting anomalous reaction switching caused by methylene chain length effects. This is partly due to the predominant idea that the combination of functional groups at both ends of the chain determines the reactivity and reaction path. The purpose of the present review is to show that the methylene chain linking the two reactive sites becomes a major factor controlling reaction pathways.

Although no clear definition has been given for methylene chain length effects, they can be regarded as influences of chain length on physical properties (e.g. spectroscopic data) and chemical reactivity. The dependence of reaction yields or rates on chain length has often been cited as a 'reactivity profile'.[1] In this review, some typical examples of reaction switching will be discussed on the basis of their reactivity profiles. We focus on the following two types of reactions:

(1) starting chain species have two reaction centres at each end;

(2) reaction intermediates derived from ring ruptures have an open-chain structure.

The reactions of bifunctional chain molecules have been extensively studied from several points of view.[1,2] Among other things, the ring closure reaction has been well investigated by synthetic chemists searching for preparative methods for perfumes (civetone, muscone, etc.) and macrolide antibiotics. Photophysical and photochemical primary processes of biochromophoric species have been elucidated by a large number of research groups.[3]

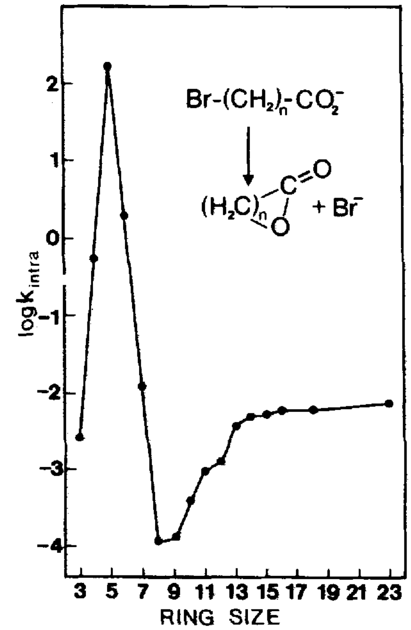


Figure 1. Reactivity profile for lactone formation of ω-bromoalkanoates. Dependence of the intramolecular rate constant k_{intra} on ring size. Data taken from Reference 1d

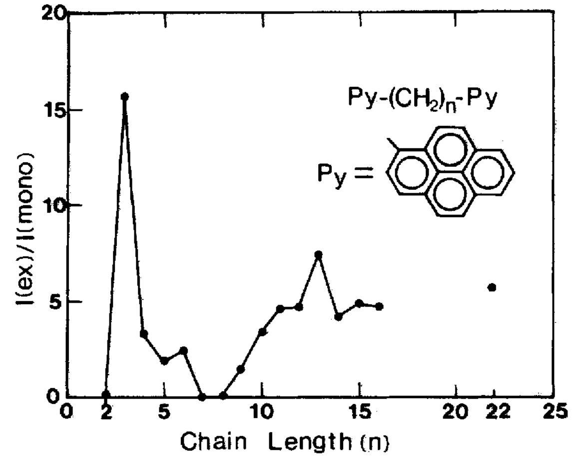


Figure 2. Dependence of the excimer to monomer emission intensity ratio $I(\mathrm{ex})/I(\mathrm{mono})$ upon chain length for a series of α,ω-di-(1-pyrenyl)alkanes. Data taken from Reference 5

2 CYCLIZATION AND INTRAMOLECULAR EXCIMER FORMATION

The product yield of a cyclization reaction recorded as a function of ring-size (m) shows three particular features: high efficiency for common rings (m = 5–7), anomalously low yield for medium-sized rings (m = 8–11), and fairly good yield for larger cyclic compounds ($m \geqslant 12$). This kind of reactivity profile has been known in, for example, the formation of cyclic ketones, imino-nitriles, and acyloins.[1a]

Although ring-closure reactions have nothing to do with photochemistry, intramolecular excimer formation shows an interesting dependence on the chain length similar to that of cyclization. Cyclization yield is highest at a chain length of $n = 3$ for lactone formation from ω-bromoalkanoates.[1d] The intramolecular excimer is most easily formed for the species with $n = 3$;[4] this finding has been known as Hirayama's rule. When the chain length n is 6–9, the ring-closure efficiency exhibits a minimum. Almost no intramolecular excimer is formed for 1,7-di(1-pyrenyl)heptane or 1,8-di(1-pyrenyl)octane.[5] Cyclization yield and emission intensity of intramolecular excimers is increased for the species with $n \geqslant 12$. However, there is a tendency to level off for higher homologues. Figure 1 shows the reactivity profile for the lactone formation, whereas Figure 2 illustrates the relative emission intensity of intramolecular excimers. It should be noted that the cyclization reaction and the intramolecular excimer formation are closely related from the viewpoint of methylene chain length effects.

3 PHOTO-SMILES REARRANGEMENT AND PHOTOREDOX REACTION[6]

Photochemical reaction pathways of bichromophoric chain species, $p\text{-}\mathrm{O_2NC_6H_4}\text{—}(\mathrm{CH_2})_n\text{—}\mathrm{NHC_6H_5}$ depend on the chain length n. Short chain compounds ($n \leqslant 6$) exhibit the photo-Smiles rearrangement, while long chain molecules ($n \geqslant 8$) undergo a photoredox reaction. An intermolecular analogue consisting of *p*-nitroanisole and *N*-methylaniline yields redox reaction products, *p*-nitrosoanisole and aniline. The photo-Smiles rearrangement can be characterized as an intramolecular nucleophilic substitution reaction. However, no

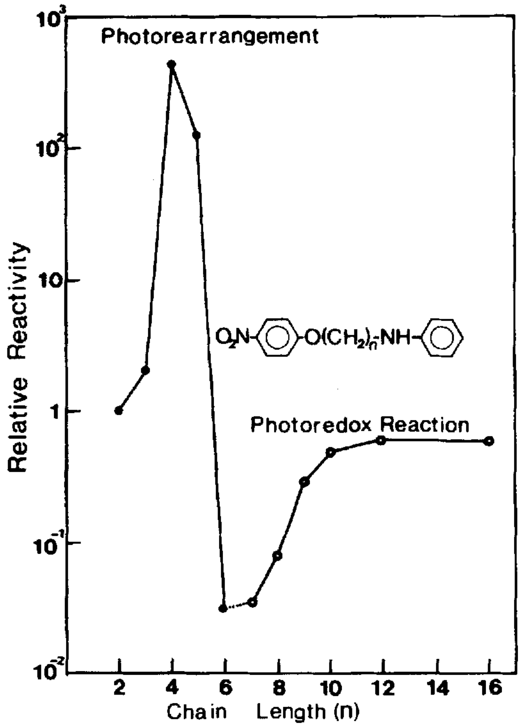
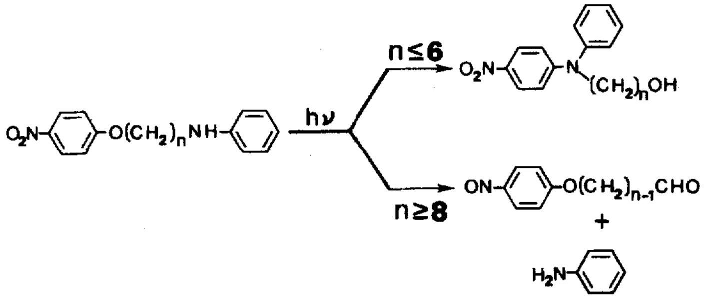


Figure 3. Dependence of the reactivity on chain length in photoreactions of *N*-[ω-(*p*-nitrophenoxy)alkyl]anilines

substitution product (*N*-methyl-*p*-nitrodiphenylamine) has been detected in the photoreaction mixture of the corresponding intermolecular reaction system. The photo-Smiles rearrangement is characteristic of an intramolecular reaction particular to the short-chain species. It is suitable to measure electronic absorption spectra of reaction mixtures in order to monitor which type of photo-reaction is taking place. The reaction mixture contains the photoproduct as well as the starting material. The absorption bands due to *p*-nitrophenoxyl, *p*-nitrosophenoxyl, and *p*-nitrodiphenylamino chromophores are easily distinguished from each other, because their absorption maxima are fairly separately located. The longest wavelength band is assigned to an allowed transition and, therefore, photoproducts are properly identified by means of absorption spectroscopy. When $n \leq 6$, the new absorption band due to a photoproduct is attributed to the *p*-nitrodiphenylamino moiety. When $n \geq 8$, the absorption band assigned to the *p*-nitrosophenoxyl group is seen in the electronic spectra of the reaction mixtures. It is noteworthy that when one type of reaction takes place, another kind of reaction completely disappears. Although reactivity at $n = 6$ or 8 is extremely low, no concurrent intramolecular reaction products have been detected by absorption spectroscopy or liquid chromatography. An intermolecular photoredox reaction occurs at $n = 7$ to some extent.

The intramolecular reactions are summarized in Scheme 1, and the reactivity profile is depicted in Figure 3. The *p*-nitrophenoxyl moiety is transformed into the *p*-nitrodiphenylamino chromophore when $n \leq 6$ and into the *p*-nitrosophenoxyl group when $n \geq$



Scheme 1

8. The photo-Smiles rearrangement involves a spiro-type Meisenheimer complex[7] (see Chart 1), and therefore, the anilino nitrogen must approach to the ring carbon at the *ipso* position with respect to the alkoxyl substituent to yield the rearrangement product. On the other hand, the nitro oxygen must be close to the methylene group adjacent to the anilino nitrogen to give the redox reaction product. The encounter probability of the two reaction centres with conformation pertinent to the product formation may critically depend on the chain length.

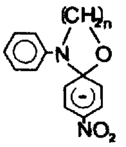


Chart1

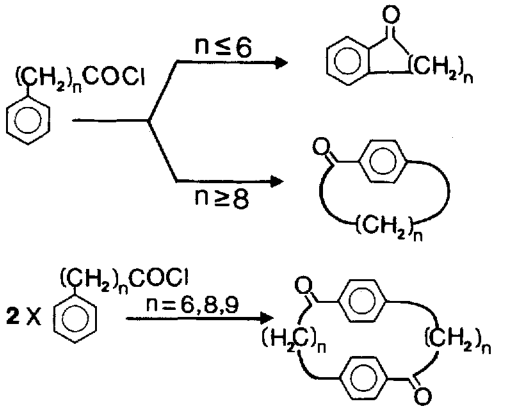
Another important factor is the stability of the cyclic Meisenheimer intermediate. It is well known that the formation of a 9- to 12-membered ring is very difficult, and therefore it is anticipated that the formation of $(n + 3)$-membered Meisenheimer complex is highly unfavourable for the chain molecules with $n = 6$–9. Consequently, another type of reaction closely related to the intermolecular process becomes dominant when n is sufficiently large. Essentially the same type of reaction switching is observed between $n = 6$ and 8 for naphthalene analogues, *N*-[ω-(4-nitro-1-naphthoxy)alkyl]anilines.

4 INTRAMOLECULAR FRIEDEL–CRAFTS ACYLATION

Ring formation of phenyl derivatives[8]

Cyclic ketones are obtained from internal Friedel–Crafts acylation of ω-phenylalkanoyl chlorides in carbon disulphide under the influence of aluminium chloride. When the chain length n is less than 5, ortho-substituted ketones are formed, while *para*-cyclization takes place for higher homologues ($n \geq 8$). Reactivity at $n = 6$ or 7 is extremely low.

Intermolecular acetylation of toluene with $AlCl_3$ yields methylacetophenones with the following product distribution:[9] *ortho* (1·17%), *meta* (1·26%), and *para* (97·6%). High reactivity at the *ortho*-position for the lower homologue is particular to the intramolecular acylation. The reaction is described in Scheme 2, and the reactivity profile is shown in Figure



Scheme 2

4. When $n = 6$, even under high dilution conditions an intermolecular acylation takes place, the cyclic dimer ketone is obtained in low yield (5–6%).[8b,c] Cyclic dimer ketones are also observed for the species with $n = 8$ and 9 in low yield (3 and 0·7%, respectively).[8c,d]

Formation of *para*-substituted dimer ketones clearly shows that the intermolecular acylation reactivity is higher at the *para*-position than at the *ortho*-position. The absorption spectrum of the nine-membered *ortho*-ketone shows a conspicuous blue shift and decrease in molar extinction coefficient in comparison with the reference spectra for the cyclic dimer ketone or strain-free *p*-methylacetophenone. This fact indicates that the dihedral angle between the carbonyl moiety and the phenyl plane is fairly large, i.e. the conjugate interaction between two chromophores is appreciably decreased. The reactivity profile is similar to that of the photo-Smiles rearrangement and photoredox reaction.

The initial chain molecule may be described as (substrate)—$(CH_2)_n$—(reagent). The reactivity dependence on n can be explained in terms of the encounter probability of the two reactive sites in the substrate and the reagent, with a particular conformation leading to formation of the respective end product. When the chain length is short, the acid chloride moiety can approach the *ortho*-position and cannot interact with the benzene ring at the

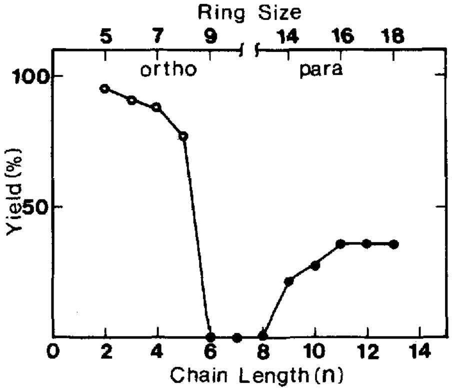


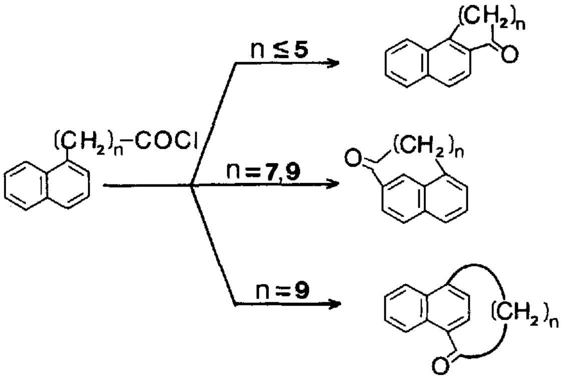
Figure 4. Dependence of the reaction yield on chain length for intramolecular Friedel–Crafts cyclization of ω-phenylalkanoyl chlorides. Data taken from Reference 8a

para-site. On the other hand, the situation is reversed for the long chain molecules. A similar phenomenon has been observed for *N*-[ω-(*p*-nitrophenoxy)-alkyl]anilines. Electron transfer takes place from the nucleophilic reagent to the nitro-aromatic chromophore in the photo-Smiles and photoredox reactions, while it occurs from the phenyl moiety to the electrophilic reagent in Friedel–Crafts acylation. In spite of these differences, reactivity profiles for these two unlike, intramolecular reactions show features commonly observed for cyclization or intramolecular excimer formation. In addition, intermolecular processes appear when the chain length is highly unfavourable for intramolecular reactions. The photo-Smiles rearrangement involves spiro-type cyclic Meisenheimer intermediate, and therefore, the reactivity partly shows dependence on the chain length similar to ring-closure.

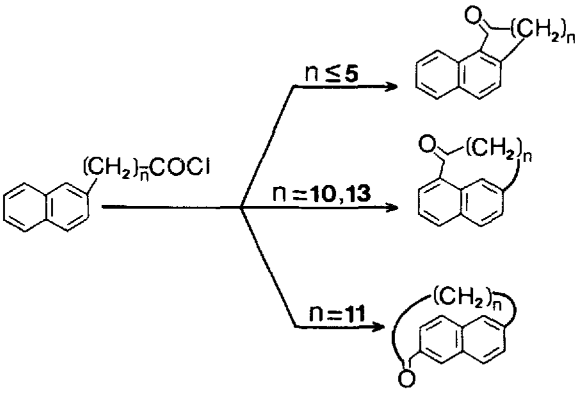
Cyclization of naphthyl derivatives[10,11]

ω-(1-Naphthyl)alkanoyl chlorides yield three kinds of product in intramolecular Friedel–Crafts acylation (see Scheme 3). Intermolecular acetylation of 1-methylnaphthalene exhibits the reactivity order of position 4 >> 3–2,[12] and therefore the intramolecular acylation at the 7 position represents an anomalous orientation. The long chain species undergo processes similar to that of the intermolecular reaction.

Scheme 4 shows that three different type of cyclic ketones are formed from ω-(2-naphthyl)alkanoyl chlorides depending upon the chain length. The reactivity order in the



Scheme 3



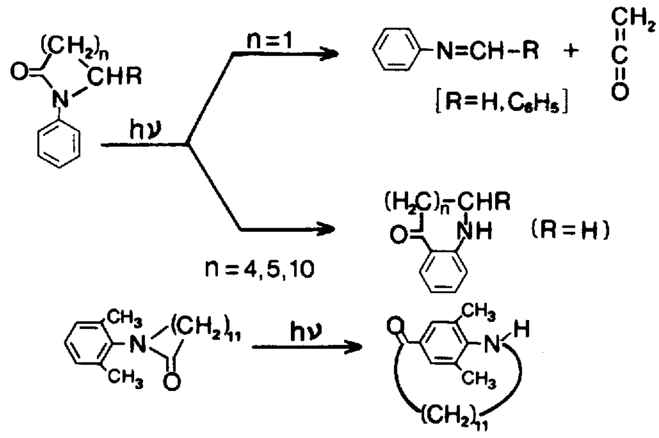
Scheme 4

intermolecular acetylation of 2-methylnaphthalene has been reported to be 1 > 8 > 6 ≫ 4–5–7.[12] In this case, no unusual acylation particular to the intramolecular process has been observed. The long chain molecule reacts at the remote site of 6.

5 PHOTOCHEMISTRY OF *N*-PHENYLLACTAMS[13]

The photochemical behaviour of *N*-phenyllactams depends on the ring-size as is shown in Scheme 5. Some cyclic anilides undergo the C—N bond cleavage in the excited singlet state, producing a biradical intermediate, $O{=}\dot{C}{-}(CH_2)_n{-}\dot{N}C_6H_5$. The photo-Fries rearrangement involves the ring-opening and re-cyclization processes and the photoproducts are characterized as *ortho*-amino cyclic ketones. The photo-Fries rearrangement is observed for 7-, 8-, and 13-membered lactams with quantum yields of 0·07, 0·11, and 0·08, respectively. The four-membered lactam undergoes two bond rupture, i.e. ring-opening, which yields ketene and anil (azomethine compound). *N*-Phenylpyrrole is obtained from photoreaction of *N*-phenylpyrrolidone (5-membered ring). *N*-Phenylpiperidone (6-membered ring) yields an unstable product, which has not been identified.

Photo-Fries Rearrangement



Scheme 5

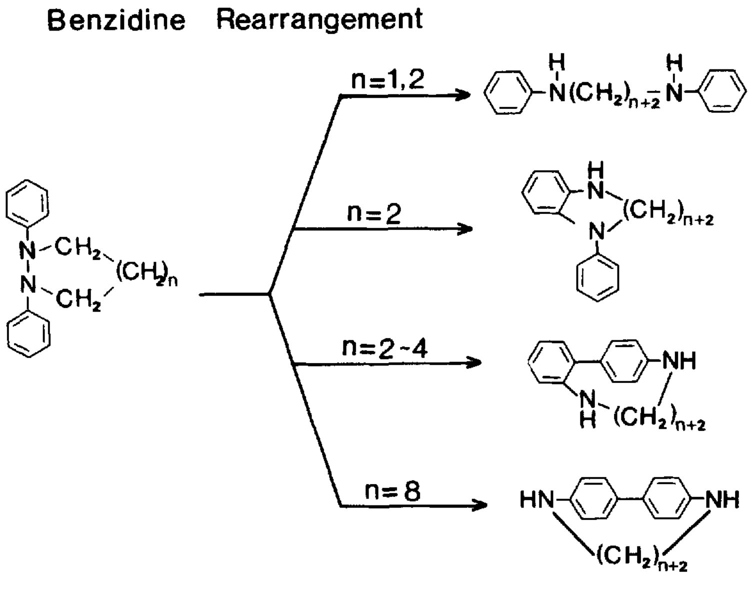
The nine- and ten-membered *ortho*-amino ketones show electronic absorption spectra completely different from that of the 15-membered compound. When non-cyclic strain-free *o*-*N*-methylaminoacetophenone is taken as a standard, the absorption spectrum of the 15-membered amino-ketone is very similar to that of the standard. On the other hand, the electronic spectra for the 9- and 10-membered rings exhibit conspicuous blue shifts. These facts suggest that the dihedral angle between the carbonyl moiety and the phenyl ring is fairly large. It would be worthwhile to investigate the formation process for these strained-species.

It is also to be noted that although eleven methylene groups in the 13-membered lactam can yield a strain-free ketone of the *para*-cyclophane structure, only the *ortho*-ketone is obtained. The *para*-reactivity is observed when the two *ortho* positions are occupied by two methyl substituents. The *photo*-Fries rearrangement of acetanilide produces both the *ortho* and *para* ketones with the relative yield of Φ (*para*)/Φ (*ortho*) = 0·8–0·9 in several organic solvents.[14]

The reason for this behaviour, which is different from the intramolecular process, has not been explained. The findings for the *N*-phenyllactams are in contrast with the fact that internal Friedel–Crafts acylation does not yield 9- or 10-membered *ortho* ketone, and that the *para*-cyclization is favoured by long-chain species. This suggests that the reactivity profile for photochemistry of cyclic anilide is completely different from that for the intramolecular Friedel–Crafts cyclization.

6 THERMAL REARRANGEMENT OF CYCLIC HYDRAZOBENZENES[15]

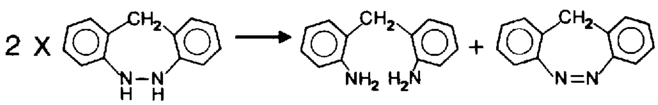
Cyclic hydrazobenzenes show different behaviour depending on the ring size (see Scheme 6). N,N′-Trimethylenehydrazobenzene in 2N hydrochloric acid undergoes reductive N—N bond cleavage to 1,3-dianilinopropane (41%). The tetramethylene analogue in 50% hydrochloric acid yields 1,4-dianilinobutane (26%), tetramethylene-*o*-semidine (16%), and tetramethyldiphenylene (20%). The oxidation process coupled with the reductive scission has not been reported. From seven- and eight-membered cyclic hydrazobenzenes, penta- and hexamethylenediphenylenes are obtained in good yield (70 and 77%, respectively). In these ring compounds, the methylene chains are too short to form the benzidine structure by union at 4,4′-positions.



Scheme 6

The N,N′-decamethylenebenzidine is obtained from N,N′-decamethylenehydrazaobenzene in very low yield (4%). The major portion (71%) of the decamethylene species is transformed into basic resins. The absorption spectrum of N,N′-decamethylenebenzidine is similar to that of strain-free N,N′-dimethylbenzidine except for a slight blue shift of an absorption band and a small decrease in the molar extinction coefficient. However, it appreciably differs from that of *N*-methylaniline, which can be regarded as a model compound for a completely twisted benzidine. Therefore, the ten methylene groups connecting the two nitrogen atoms at *p,p'*-positions have no large effect on the mesomeric interaction between the two phenyl moieties.

It is interesting to note that 2,2'-hydrazodiphenylmethane undergoes almost quantitative disproportionation into di(2-aminophenyl)methane and 2,2'-azodiphenylmethane[15c] (see Scheme 7). It can be concluded that when the chain length is extremely short, the intramolecular reaction becomes forbidden, and only the intermolecular process may be allowed. In this connection it can be noted that the excimer emission from 1,2-di(1-pyrenyl)-ethane is very weak, and therefore the monomer emission is dominant at lower concentrations.[5]

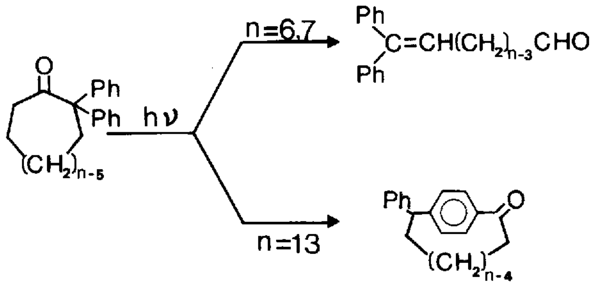


Scheme 7

7 PHOTOCHEMISTRY OF 2-SUBSTITUTED CYCLOALKANONES

Photochemistry of 2,2-diphenylcyloalkanones[16]

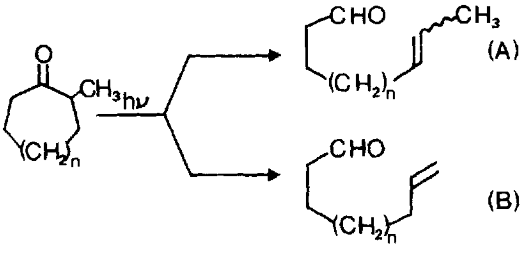
Cyclic ketones containing two phenyl groups at the 2 position undergo bond cleavage in the *n*π* excited triplet state. The reaction intermediate produced by the Norrish type I cleavage has a structure of $O{=}\dot{C}{-}(CH_2)_n{-}\dot{C}(C_6H_5)_2$. The 6- and 7-membered ketones yields open-chain products. On the other hand, a *para*-cyclophane type ketone is obtained from the 13-membered alkanone. The structure of photoproducts is depicted in Scheme 8. Turro and co-workers[17] have reported similar photochemistry of 2-phenylcycloalkanone and 2,*n*-diphenylcycloalkanone (*n*-membered ring).



Scheme 8

Photochemistry of 2-methylcycloalkanone[18]

Bond cleavage of 2-methylalkanones efficiently takes place in the $^3n\pi^*$ state, thus yielding biradical intermediates with a structure of $O{=}\dot{C}{-}(CH_2)_n{-}\dot{C}HCH_3$. 2-Methylcyclopentanone and 2-methylcyclohexanone yield exclusively aldehydes with a methyl-substituted olefin moiety, while larger 2-methylcycloalknones efficiently produce alkenals with a vinyl group as is shown in Scheme 9. The distribution of the alkenal with the



Scheme 9

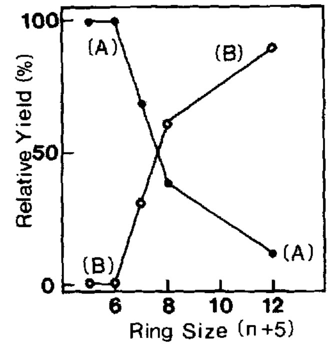


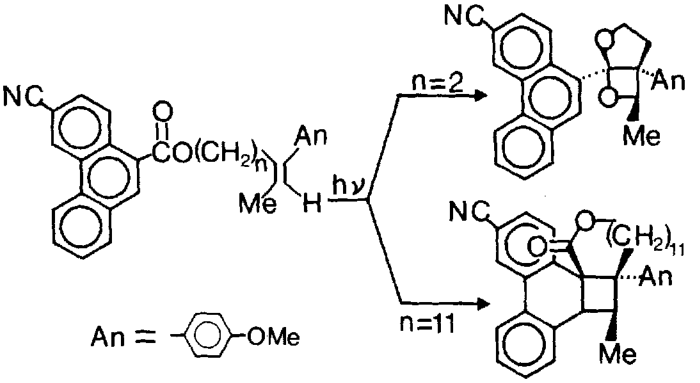
Figure 5. Dependence of the product distribution on chain length for photochemical ring opening of α-methylcycloalkanones. The reactivity profile is symmetric with respect to the line of 50% yield. Data taken from Reference 18

end group of —CH═CHCH$_3$ decreases with increasing methylene chain length. Figure 5 shows the dependence of the branching percentage on the ring size.

8 PHOTOCHEMICAL CYCLOADDITION REACTIONS

Photo-cycloaddition of phenanthrenecarboxylate and *trans*-anethole[19]

An intermolecular photo-reaction of methyl 10-phenanthrenecarboxylate and *trans*-anethole yields a cyclobutane (CB) derivative. Bifunctional chain molecules containing both aromatic

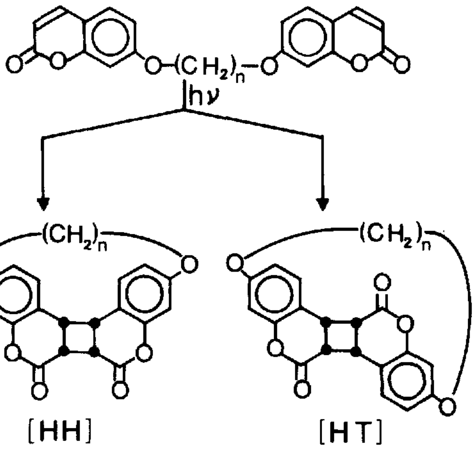


Scheme 10

chromophores undergo two different processes depending upon the chain length. When the chain length is short ($n = 2$) an oxetane compound is obtained in addition to a CB product, while the long-chain molecule ($n = 11$) yields only a CB derivative closely related to the intermolecular reaction product. Scheme 10 summarizes the observed photochemical behaviour for intermolecular reactions.

Photo-cyclization of 7,7′-polymethylenedioxycoumarins[2b,20]

An extensive study of 7,7′-polymethylenedioxycoumarins has been reported by de Schryver *et al.*[20] A cyclobutane (CB) ring is formed from the olefinic part in the lactone ring (see Scheme 11). The CB ring may have two structures, i.e. *cis*-HH (head-to-head) and *cis*-HT (head-to-tail). The HT compound predominates except for $n = 2$. The *cis*-HT dimers are also formed for intermolecular photo-cycloaddition of 7-alkoxycoumarins in the crystalline phase and micellar solutions.[21]



Scheme 11

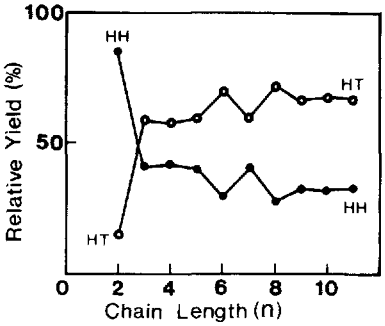


Figure 6. Dependence of the product distribution on chain length for photocycloaddition of 7,7′-polymethylenedioxycoumarins. The reactivity profile is symmetric with respect to the line of 50% yield. Data taken from Reference 2b

Reactivity profile for the photo-dimerization is shown in Figure 6. It is interesting to note that the switching chain length is much shorter than that observed for the photo-Smiles/ photoredox reactions or internal Friedel–Crafts acylation. This may be partly due to the fact that the reactive site is a small part of a large conjugate system and therefore the benzene ring serves as a linking group. When the reactive site at one end is a small aromatic moiety, the switching of reaction pathways takes place in the vicinity of $n = 7$.

9 CLASSIFICATION OF REACTIVITY PROFILES AND CHAIN MOLECULES

Reactivity profiles can be categorized into several groups. When only one reaction pathway is involved, the reaction efficiency vs. chain length has a maximum at a short chain length, and a minimum appears around $n = 6$–9. For long chain species the reactivity profiles exhibit a tendency to level off. This kind of dependence is classified as Case I and illustrated diagramatically in Figure 7. Simple ring-closure and intramolecular excimer formation may fall into this category.

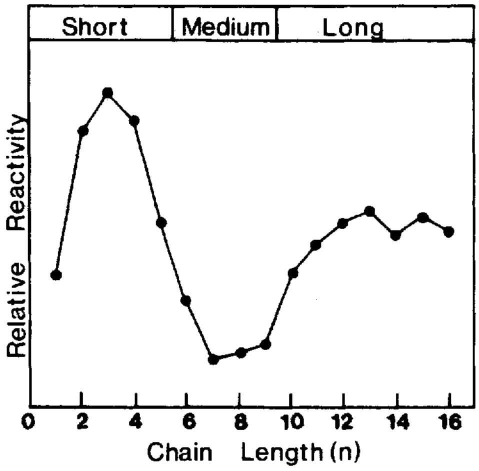


Figure 7. Diagrammatic description of reactivity profile in Case I. The chain length is classified into three groups

The case where the two competing processes are observed can be regarded as Case II. When the reaction yields for the major and minor products are slightly dependent on the chain length, the reactivity profile curves for both products may not cross. This type of dependence is classified as Case II-A. Figure 8-A shows a schematic description of Case II-A, where the reaction pathway for the major product is designated by (a) and that for the minor product by (b). When the yields for two competitive processes are considerably dependent on the chain length, both reactivity profile curves may cross at some particular chain length. This kind of dependence is referred to as Case II-B, and the reactivity profile of Case II-B is given in Figure 8-B.

The last type of Case II belongs to a rather extreme case, where the complete switching of reaction pathways occur. In such cases only one product is formed through path (a) or path (b) depending upon the chain length. This type of reactivity dependence is classified as Case II-C,

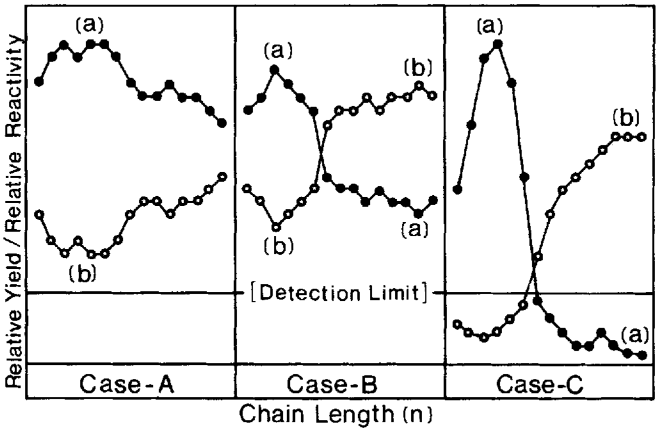


Figure 8. Schematic description of reactivity profiles in Case II. Chain length increases from the left to the right hand side in each case. The product distribution in Case A and Case B is plotted in percentage as a function of chain length, and therefore, the sum of the respective yield is equal to 100%. When the absolute total yield for path (a) and path (b) is plotted vs. chain length, the reactivity dependence on n may show a profile similar to that of Case I. Although only one reaction product due to path (a) or path (b) can be observed in Case C, the plot of the reaction yield or rate as a function of chain length may exhibit a shape similar to the reactivity profile in Case I. The hypothetical dependence of reactivity on chain length is depicted below the detection limit

and Figure 8-C illustrates the reactivity profile of Case II-C. Even if more than three reaction pathways are involved, the reactivity profile may be explained as a combination of Case I and Case II or its modifications.

It is emphasized that the classification of reactivity profile depends on the treatment of end product structures. The lactones described in Section 4 have two structures depending upon the ring size.[22] Four- to seven-membered rings have the energetically rich *cis*-configuration with respect to the C—O single bond. Large rings (ten- to sixteen-membered lactones) assume the *trans*-configuration which is commonly observed for open-chain esters. An equilibrium is adopted in the case of eight- and nine-membered ring compounds. If these structural differences are taken into account, the lactone formation may be classified as Case II-B. However, since it is more important to note the essence of chemical reactivity than to analyse the reactivity profile in detail, the lactone formation is characterized as Case I.

It has been proposed that cycloalkanes are classified into four categories on the basis of heats of combustion per methylene group:[1c] small rings (3- and 4-membered), common rings (5-, 6-, and 7-membered), medium rings (8- to 11-membered), and large rings (12-membered and larger). Chain molecules containing n methylene groups $HX—(CH_2)_n—YH$ may be obtained by reductive ring opening of the corresponding (n + 2)-membered species $\underline{X—(CH_2)_n—Y}$, and therefore, the chain length n is related to the ring size m by the equation of $n = m - 2$. On the basis of the classification for cyclic compounds, it may be useful to characterize open-chain molecules by the relationship $n = m - 2$: extremely short chain ($n = 1$ and 2), short chain ($n = 3$–5), medium chain ($n = 6$–9), and long chain ($n \geq 10$). However, it is more meaningful to define short chain as $n \leq 5$, because these three categories correspond to the three different features in Case I or Case II. According to this classification, Case II can be characterized as follows:

(1) short chain species may exhibit an unusual reactivity particular to the intramolecular reaction system;

(2) long chain compounds behave like an intermolecular analogue.

(3) Extremely low reactivity and switching of reaction pathways are observed in the range of $n = 6$–9.

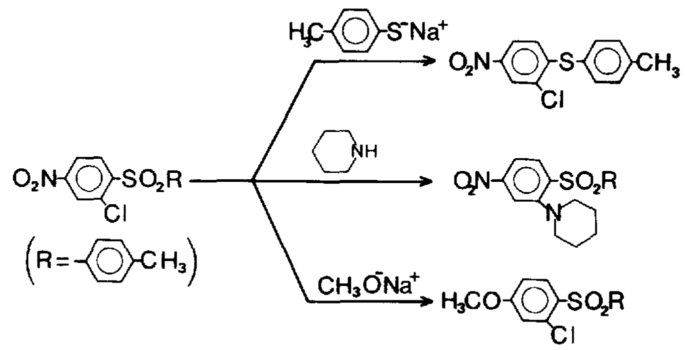
10 SWITCHING OF REACTION PATHWAYS DUE TO METHYLENE CHAIN LENGTH EFFECTS—GENERAL CONSIDERATIONS

An intermolecular reaction between X—CH_3 and H_3C—Y may be free from any geometric restriction on the orientation of the two reaction centres. In other words, the reagent can approach the most reactive site in the substrate. However, a reaction similar to the intermolecular process may not be allowed in the intramolecular case due to the conformational restriction in an X—$(CH_2)_n$—Y type molecule. Consequently, if the most reactive site is not available to the reagent, the site of the next highest reactivity can participate in the intramolecular reaction. This kind of steric effect is appreciable when the chain length is short. Thus the short chain species may exhibit reactivity completely different from that of the intermolecular counterpart. The long chain molecules ($n \geqslant 10$) behave like an intermolecular reaction system, because the conformational constraint is greatly reduced. Switching of reaction pathways due to the methylene chain length effects can then be summarized as follows:

(1) a functional group at one end X has at least two inequivalent reaction sites (Site A, Site B, etc.), e.g. *ortho/para* with respect to a substituent on a phenyl ring.

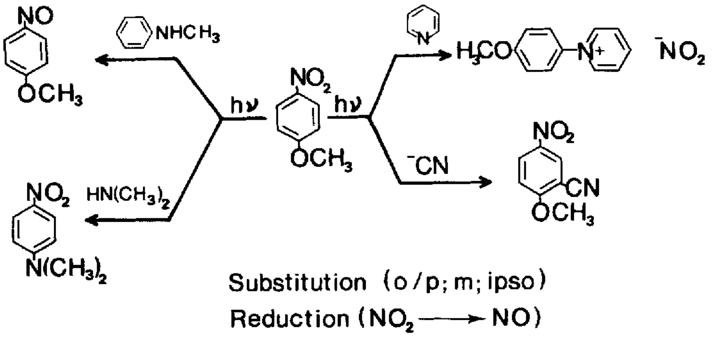
(2) dependence of reaction yield of Site A or Site B with another end group Y undergoes some change at a particular chain length n. Therefore, the structure of reaction products changes drastically before and after n.

In general, poly-substituted benzenes undergo a wide variety of thermal nucleophilic substitution reactions. One typical example is shown in Scheme 12.[23] The leaving group can be determined by the nature of nucleophilic reagents.



Scheme 12

The reactivity of photochemical nucleophilic substitutions also depends on nucleophiles. *p*-Nitroanisole undergoes at least 4 different photochemical processes, namely, substitutions at *meta*, *para*, and *ipso* positions with regard to the nitro group[24] and deoxygenation of the nitro group (see Scheme 13). An unusual reaction may appear for short chain species containing a poly-substituted phenyl chromophore, since the most dominant intramolecular reactivity is not necessarily the same as that for the intermolecular reaction. The chain length is as critical as the combination of the end groups X and Y in determining reaction pathways.



Scheme 13

11 VARIOUS FACTORS AFFECTING CHEMICAL REACTIVITY

Factors which may have some effects on chemical reactivity can be grouped into the internal and external parameters. The properties of substituents and chains linking two reactive sites and chain length are regarded as internal factors. On the other hand, catalysts and solvents are classified as external parameters. For example, there is a huge amount of knowledge about the substituent effects, which can be treated by the Hammett equation. However, this kind of structure/reactivity relationship is not expected for methylene chain length effects. Although, in principle, it is possible to evaluate quantitatively the chain length effects with the aid of elaborate calculations for conformational properties and chain dynamics,[25] it is still difficult to predict $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ explicitly as a function of chain length. Consequently the empirical rules derived from experimental results have been widely used for qualitative interpretation. Typical examples are 'difficulty in medium-sized ring formation' and the so-called '$n = 3$ rule'. It should be emphasized that the methylene chain length effects are essentially the same for both thermal and photochemical reactions, unless the linking chain is electronically excited or involved in a photoreaction. Intramolecular excimer emission is very weak at the methylene chain length corresponding to 'difficulty in medium-sized ring closure'. It is concluded that the empirical rules are applicable to cyclic transition states or cyclic reaction intermediates as well as cyclic end products. It is desirable to establish some empirical formula which involves 'difficulty in medium ring formation' and '$n = 3$ rule'. In addition, replacement of the methylene group by a moiety containing some heteroatoms (O, NH, S, etc.) may give rise to a different behaviour due to decrease in the non-bonded H—H repulsion.

Solvents and catalysts may play an important role in intramolecular reactivity. Photoredox reaction yield for *N*-[ω-(*p*-nitrophenoxy)alkyl]anilines is improved on going from acetonitrile to benzene. The reaction intermediate in this redox reaction is a biradical. Since the intersystem crossing rate between the triplet and singlet biradicals changes in the presence of an external magnetic field, the reaction yield depends on the magnetic field strength.[26] It has been reported that aluminium bromide is better than aluminium chloride as a catalyst for the internal Friedel–Crafts acylation.[8] Thus intramolecular reactions are not completely independent of the extermal parameters.

Accumulation of quantitative data on structure/reactivity relationship and analyses based upon reasonable models can clarify the importance of various factors affecting chemical reactivity. Highly selective and efficient reactions will be realized through the systematic and rational approach derived from a better understanding of chemical reactivity.

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