Ring-Closure Reactions. 10.[1] A Kinetic Study for the Formation of Macrocyclic Aromatic Ethers. Lack of the Rigid Group Effect on Large-Ring Formation[2]

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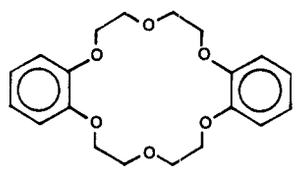
As a quantitative approach to the evaluation of the rigid group effect on large ring formation, the kinetics of the base-induced cyclization of a series of substrates $HOZO(CH_2)_{12}Br$, in which Z denotes varying phenylene and naphthylene moieties, have been studied. When allowance is made for the slightly different nucleophilicity of the anionic end in the various bifunctional compounds, the ease of ring closure turns out to be practically unaffected by the very different geometry and size of the rigid moieties. This remarkable result, which is at variance with widely accepted ideas, is discussed and compared with our previous findings in the field of many-membered ring formation.

In 1951 Baker et al.[3] suggested that the ease of ring closure of a long-chain bifunctional compound should be greatly enhanced by the presence of a number of atoms composing the chain itself held in the form of a rigid group suitable for ring closure. The *o*-phenylene unit was considered as a clean-cut example of a structural moiety fitting these requirements, since in ortho-disubstituted benzene derivatives at least four carbon atoms lie in the same plane with angles of approximately 120°.[3] Following Baker's arguments, Ziegler[4] explicitly referred to the "rigid group principle" as a general rule for many-membered ring formation.

While there is no doubt that such an effect can operate in the medium-ring region,[5,6] as to the large rings experimental evidence so far available is either scanty or even questionable. For example, the fact that compound **1** has been synthesized in far higher yield than compound **2** (80 and 1.8%, respectively)[7] was taken[8] as a clean-cut example of the rigid group effect. Such an interpretation is not very safe because the reaction conditions (base–solvent systems) as adopted for the preparation of the two compounds were not comparable with each other. Furthermore, the formation of macrocyclic monomeric (**3**) and dimeric (**4**) *o*-phthalate esters has been claimed to be facile because of the presence of the rigid group(s) OOCC=COO,[8] but the evidence for such an ease is by no means convincing.



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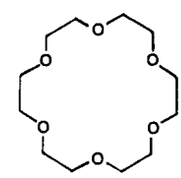

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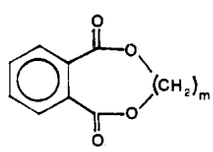

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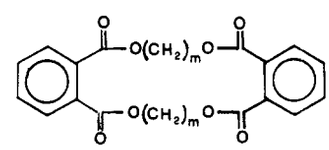

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It has been suggested[4] that the rigid group should act by restriction of the rotational freedom in the open-chained precursor and, possibly, by reduction of the strain energy due to nonbonded interactions in the ring-shaped transition states.

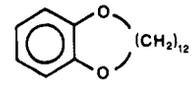
In recent studies[1,9] we have reported that both entropies and ethalpies of activation are only slightly dependent of chain length when large rings are formed, the latter being very close to the values of the strainless intermolecular counterparts. Hence, in the large-ring region little or no gain in the entropy term is expected upon reduction of the number of rotors by one unit nor any significant decrease of the strain energy upon introduction of a rigid group in an already strainless (or nearly so) transition state. In accordance with the above observations, evidence has been presented[1] that in the large-ring region ease of ring closure, as quantitatively expressed by the effective molarity, EM, is fairly insensitive to structural effects. EM values relative to five different reaction series lie well within a factor of 10, in spite of the fact that in two out of the five series a rigid group, viz., an *o*-phenylene unit, is present. It appears from these findings that the rigid group effect has a limited scope and should be either small or negligible for large rings.

A systematic investigation aimed at the elucidation of this problem calls for a kinetic study of the cyclization reactions of several α,ω-bifunctional compounds in which rigid groups of varying geometry and size have been incorporated. Reaction 1, in which Z denotes phenylene and naphthylene moieties, appeared to be suitable to the end under several respects. It had been extensively studied by Ziegler and Lüttringhaus[10] from the preparative point of view. Furthermore, macrocyclic aromatic ether formation via intramolecular Williamson synthesis is suitable for accurate kinetic work, as was shown by us in a series of recent papers.[1,6,11]

$$Br(CH_2)_mOZO^- \xrightarrow{k_{intra}} \overline{(CH_2)_mOZO} + Br^- \qquad (1)$$

$$MeOZO^- + BuBr \xrightarrow{k_{inter}} MeOZOBu + Br^- \qquad (2)$$

In this work we wish to report on the kinetics of the base-induced formation of macrocyclic diethers **5–9** from the



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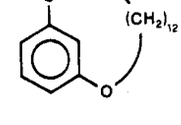

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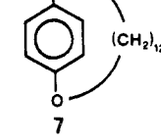

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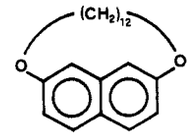

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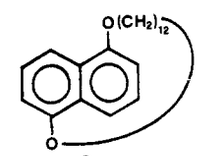

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Table I. Yields, Physical Constants, and Analytical Data for the Preparation of Mono-12-bromododecyl Ethers 11a–14a

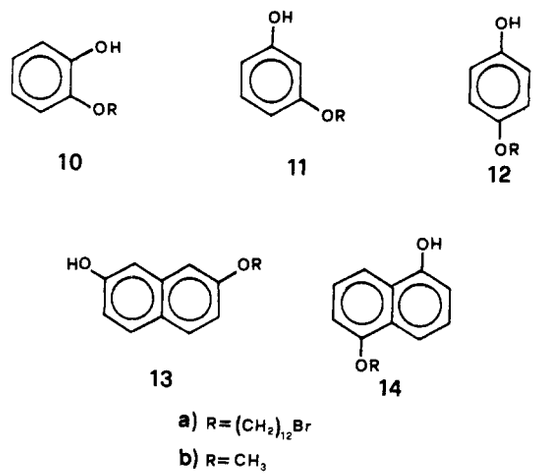
Compd	Registry no.	Yield, %	Mp, °C	Anal. Calcd, % C	H	Br	Found, % C	H	Br
11a	63163-44-0	33	55–57	60.50	8.18	22.36	60.36	8.22	22.20
12a	63163-45-1	35	80–82	60.50	8.18	22.36	60.63	8.20	22.34
13a	63163-46-2	37	93.5–95	64.86	7.67	19.61	65.01	7.64	19.72
14a	63163-47-3	26	76–77			19.61			19.24

Table II. Yields and Physical Constants of Monomethyl Ethers 10b–14b

Compd	Registry no.	Yield,%	Mp, °C, or n^{20}D	Lit. mp, °C, or n^{20}D	λ_{max}[a]	$10^{-3}\epsilon_{max}$[a]
10b	90-05-1	*b*	1.5434	1.5429[c]	280 (314)	3.0 (5.3)
11b	150-19-6	47	1.5506	1.5520[c]	278 (309)	2.3 (4.1)
12b	150-76-5	*b*	54.5–56.0	57.0[c]	297 (337)	3.3 (3.9)
13b	5060-82-2	41	113–115	117[d]	330 (374)	3.3 (5.2)
14b	3588-80-5	33	132–133 dec	140[e]	332 (364)	7.6 (12.9)

[a] UV data in Me_2SO solution. Values in parentheses refer to the corresponding anions obtained in the presence of excess KOH. [b] Commercial product. [c] "Handbook of Chemistry and Physics", Chemical Rubber Publishing Co., 50th ed, Cleveland, Ohio, 1969–1970. [d] O. Fischer and F. Hammerschmidt, *J. Prakt. Chem.*, [2] **94**, 24 (1916). [e] O. Fischer and C. Bauer, *J. Prakt. Chem.*, [2] **94**, 13 (1916).

mono-12-bromododecyl ethers of catechol, resorcinol, hydroquinone, and 2,7- and 1,5-dihydroxynaphthalene (compounds **10a–14a**, respectively). The dodecamethylene bridge



spanning the arylenedioxy groupings is a common structural unit, which ensures the above macrocycles to be essentially strainless, i.e., large rings, as shown by inspection of space-filling molecular models. In order to account for any possible difference in the nucleophilicity of the various oxide ions, the strictly analogous intermolecular reactions (eq 2) were also considered, namely the alkylation reactions with butyl bromide of the anions derived from the monomethyl ethers **10b–14b**.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer, from 2% solutions in CCl_4. Proton magnetic resonance spectra were recorded on a Jeol JNM-C60HL spectrometer, using Me_4Si as the internal reference. Ultraviolet spectra were recorded on a Beckman DB-GT instrument, fitted with a Kontron W+W 1100 recorder. Mass spectra were obtained on a AEI MS12 spectrometer. All melting and boiling points are uncorrected.

1,12-Dibromododecane (Fluka), resorcinol (Erba RP), hydroquinone (Erba RP), 2,7-dihydroxynaphthalene (Aldrich), and 1,5-dihydroxynaphthalene (Aldrich) were all reagent-grade commercial samples and used without further purification. Tetramethylammonium hydroxide (10% aqueous solution) was from Merck.

Mono-12-bromododecyl Ethers (10a–14a). *o*-Hydroxyphenyl 12-bromododecyl ether (**10a**) was available from a previous investigation.[12] All the other compounds were prepared according to the following general procedure. To a boiling solution of 1,12-dibromododecane (0.03 mol) and the appropriate dihydroxy compound (0.15 mol) in ethanol (70 mL) a solution of KOH (0.03 mol) in a small amount of ethanol was added in ca. 1 h. The reaction was carried out in a nitrogen atmosphere in order to prevent the oxidation of the aromatic compound in the alkaline reaction medium. The solution was refluxed until neutral (3–5 h), then most of the solvent was distilled off. Benzene was added to the residue and the last traces of solvent were removed by azeotropic distillation. The dry, solid residue obtained was finely ground in a mortar and extracted for several hours in a Soxhlet apparatus. Pentane was used as the extracting solvent in the case of compounds **11a** and **12a**, and hexane for compounds **13a** and **14a**. The desired products were obtained in a practically pure form by simply cooling the paraffinic extracts. For kinetic and analytical purposes, the compounds were further purified by elution with benzene on silica gel. Structure assignments were based on spectral data and elemental analyses. All the compounds showed strong hydroxyl absorption in the IR spectra at 3580–3600 cm^{-1}. The ^1H NMR spectra (in CCl_4 at 55 °C for **12a** and CD_3COCD_3 for **11a**, **13a**, and **14a**) were consistent with the expected structures and no extra peak was present. For all compounds common signals are present, namely those due to the $O(CH_2)_{12}Br$ grouping: δ 4.0 (br t, OCH_2), 3.5 (br t, CH_2Br), 1.3–2.0 (br m, with a prominent peak standing at δ 1.4, "central" methylene protons). The signal due to the OH group was in all cases detected as a sharp singlet, extremely variable in position. Complex multiplets were present in the aromatic proton region of the spectra of **11a**, **13a**, and **14a**, while **12a** exhibited a singlet at δ 6.7. Yields, physical constants, and analytical data of the synthesized compounds are listed in Table I.

Monomethyl Ethers (10b–14b). Guayacol (**10b**) (Merck) was purified by distillation. Hydroquinone monomethyl ether (**12b**) (Fluka) was crystallized twice from benzene. The other compounds were prepared as follows. To a stirred mixture of the appropriate dihydroxy compound (0.121 mol) and CH_3I (0.056 mol) in Me_2SO (140 mL) kept under CO_2-free nitrogen was added KOH (0.056 mol) dissolved in a small amount of EtOH. The mixture was then left at room temperature under nitrogen until neutral (2–4 h). Compound **11b** was isolated by fractional distillation of the residue obtained after aqueous workup and ether extraction. In the two other cases, isolation of the pure products was carried out as indicated above for the mono-12-bromododecyl ethers. All the compounds were further purified by elution with benzene on silica gel. IR and ^1H NMR spectra were consistent with the expected structure. Yield and physical constants are reported in Table II.

Hydroquinone Dodecamethylene Ether (7) and 2,7-Dihydroxynaphthalene Dodecamethylene Ether (8). The present cyclization procedure is an improvement over that previously described,[12,13] in which a suspension of excess NaOH was employed. The experimental conditions were changed by the device of adding the base, Me_4NOH, in a 1:1 mole ratio with respect to the mono-12-bro-

mododecyl ethers of hydroquinone and 2,7-dihydroxynaphthalene, **12a** and **13a**, respectively. In the general procedure, the reaction was carried out in a 250-mL, three-neck flask equipped with a magnetic stirrer. The central neck was fitted with a gas inlet and outlet and the two side necks were capped with silicon rubber. The flask was charged with Me_2SO (100 mL), thoroughly fluxed with pure nitrogen, and immersed in an oil bath heated at 80 °C. A nitrogen overpressure was kept throughout. The reagents were added to the well-stirred solvent by means of two glass hypodermic syringes whose needles were inserted through the septum-capped side necks. One syringe contained 10 mL of a 0.20 M solution of Me_4NOH in 80% Me_2SO and the other 2 mmol of the bifunctional compound dissolved in the minimum amount of Me_2SO. The addition was prolonged for ca. 2 h, care being taken to add the two reagents at the same rate. To this end a trace of fluorene as a visual indicator in the reaction medium was of a great aid, since the intense red color due to the anionic form appears in the presence of a slight excess of base. After the addition was over the mixture was cooled and worked up with a standard procedure. The pure ring compounds were obtained by column chromatography on silica gel with benzene as eluent. Compound **7**, 82% yield, mp 46–47 °C, M^+ 276.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.46; H, 10.29.

Compound **8**, 95% yield, mp 111.5–113 °C, M^+ 326.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.55; H, 9.38.

The ^1H NMR spectra were found to be in accordance with the expected structures. Apart from the ethereal methylene protons, which appeared as a partially resolved triplet centered at δ 4.1, the other methylenes of **7** are shown (in CCl_4) as a broad multiplet at δ 0.8–1.9, with a prominent peak at δ 0.9. Clearly the paracyclophane structure of **7** is responsible for the significant upfield shift due to transannular interaction of the central protons of the dodecamethylene bridge with the π-electron cloud of the aromatic nucleus.[14] In compound **8**, which has a (2,7)naphthalenophane structure, the bridge lies apart from the aromatic nucleus. In the ^1H NMR spectrum (in $CDCl_3$) of this compound the central methylene protons are shown at a "normal" position, namely, as a multiplet at δ 1.3–2.2, with a prominent peak at δ 1.45.

Kinetic Measurements. The mixed solvent (99% aqueous Me_2SO, v/v) and the KOH stock solution (1.61×10^{-2} N in 93% Me_2SO) were prepared and handled as previously reported.[9] Purification of Me_2SO according to the method of Bordwell et al.[15] did not lower any further the concentration of the acidic impurities (see general part). The kinetics were followed spectrophotometrically at wavelenghts corresponding to the absorption maxima of the conjugate bases of the substrates, and the optical density of the solutions was monitored for several half-lives. The concentration of the aromatic hydroxy compounds was in the range 1.5 to 2.5×10^{-4} M in both cyclization and intermolecular reactions, the latter being run in the presence of excess butyl bromide, viz., 5×10^{-3} to 3×10^{-2} M. The experimental data were treated according to the method of Guggenheim,[16] with Δ values not less than 2 or 3 half-lives. First-order plots were linear up to 80–85% reaction for both cyclizations and intermolecular alkylations.

Results and Discussion

We have recently reported[12,13] that use of the NaOH–Me_2SO system in macrocyclic ether formation via intramolecular Williamson synthesis is very convenient as compared to the classical Ziegler and Lüttringhaus' conditions,[10] namely, K_2CO_3 in AmOH under high dilution. Our cyclization procedure, which afforded fair to good yields of cyclic products without excessively high dilution, was further improved in the present work (see Experimental Section) when applied to the cyclization of compounds **12a** and **13a**. The ring compounds **7** and **8** were obtained in very good yields, namely, 82 and 95%, respectively, which can be compared with a 79% yield previously reported[12] for the formation of **5** from **10a**. These results indicate that in Me_2SO solution these cyclization reactions are virtually free from side reactions. Therefore, the kinetics were carried out under conditions close to those of the preparative runs, namely, in 99% aqueous Me_2SO at 25 °C. The anions derived from compounds **10–14** were generated in situ by the addition of a calculated amount of a KOH stock solution, as previously reported in our kinetic work on the lactonization of ω-bromoalkanoic acids.[9] Because the phenolic

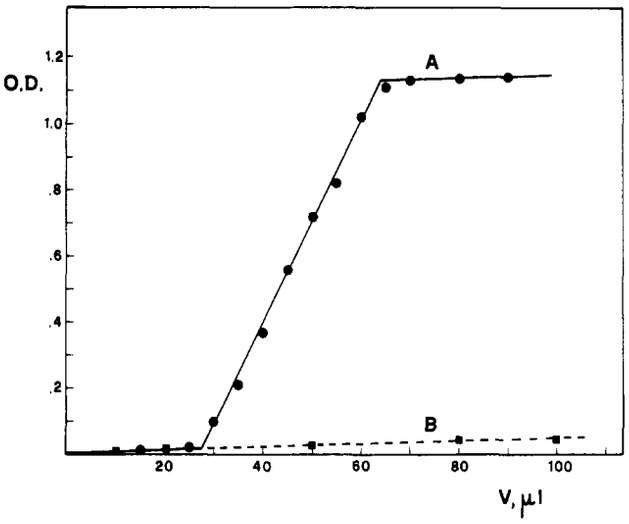


Figure 1. (A) Spectrophotometric titration at 374 nm of **13b** (2.51 mL, 2.09×10^{-4} M) in 99% Me_2SO with KOH 1.61×10^{-2} M in 93% Me_2SO. (B) Blank titration.

hydroxyl is significantly less acidic than carboxyl, the effectiveness of the KOH–99% Me_2SO system in promoting complete dissociation of the former was checked by spectrophotometric titration in some cases. A typical titration curve is reported in Figure 1. The consumption of base before the appearance of any absorption due to the anionic form of the substrate was attributed to the presence of acidic impurities in the solvent. The amount of base used up was found to be reproducible, and to correspond to an acidity of 1.80×10^{-4} N. As reported in the Experimental Section, it was not possible to reduce it any further by additional purifications of the solvent. The linearity of the titration curve indicates that in each point up to the equivalence point the amount of anionic form produced equals the total amount of added base, less that required by the blank titre. This means that the equilibrium

$$ROZOH + OH^- \rightleftharpoons ROZO^- + H_2O \qquad (3)$$

is quantitatively shifted to the right even at the low concentrations (ca. 2×10^{-4} M) used in the spectrophotometric titrations, which were similar to those in the kinetic runs. The kinetic runs were started by the fast addition of a very small volume (ca. 50–60 μL) of the KOH stock solution to a solution (2.5 mL) of the hydroxy compound. Since accuracy was poor in this operation, and any excess of base was undesirable, the latter was added in defect. Judging from the absorption of the solutions immediately after the addition of base, 50–90% of the starting hydroxy compound was neutralized. Under the given conditions, clean first-order behavior was obtained for the cyclization reactions with no effect of higher order contributions due to the polymerization reaction.[17]

The kinetic results are collected in Table III for both intra- and intermolecular reactions. The k_{intra} values span a factor of <6, indicating that the ease of ring closure is only slightly affected by the marked changes in geometry of the bifunctional substrates. In fact, most of the observed rate differences may be explained in terms of the varying nucleophilicity of the anionic end of the bifunctional substrate, as shown by the fact that k_{inter} values turn out to be sensitive to structural effects in much the same way as k_{intra} values. Thus, the differences in k_{intra} values largely disappear in the corresponding EM values, which are found to lie within a factor of 2. These results clearly indicate that the ease of ring closure to the examined large-ring diethers, as quantitatively expressed by the related EM values, is largely independent of the geometry and

Table III. Kinetic Data for the Cyclization Reaction (1) and for the Corresponding Intermolecular Model Reaction (2) in 99% Aqueous Me_2SO at 25.0 ± 0.2 °C

Compd	10^3k_{intra}, s^{-1} [a]	$10k_{inter}$, $M^{-1}\ s^{-1}$ [b]	10^2EM, M [c]	Log EM
10	9.04 ± 0.11	2.95 ± 0.03	3.06	−1.51
11	3.56 ± 0.04	1.53 ± 0.04	2.33	−1.63
12	7.22 ± 0.13	4.68 ± 0.20	1.54	−1.81
13	1.59 ± 0.04	1.07 ± 0.06	1.49	−1.83
14	1.59 ± 0.01	0.84 ± 0.01	1.90	−1.72

[a] Average from three independent runs. [b] Average from four to six independent runs. [c] Calculated as k_{intra}/k_{inter}.

size of the rigid moiety of the reacting molecule. Furthermore, they provide additional, independent evidence on the insensitiveness to structural effects of the ease of large-ring formation in general. We have shown[1] that available EM values related to the formation of rings with more than 12 members and belonging to five different reaction series exhibit remarkable insensitiveness to structural effects. Log EM data cluster around an average value of −1.54, with a standard deviation 0.23. Table III now shows that the present values fit well into the same picture. Inclusion of these data into the existing set provides a new average value of −1.57 ± 0.22.

In conclusion, on the basis of the experimental evidence collected in this and in previous work, we believe that the operation of the rigid group effect on large-ring formation can be definitely ruled out, and that, in particular, no "magic" properties must be attributed to the *o*-phenylene unit.

Acknowledgment. Professor Illuminati's helpful suggestions are greately acknowledged.

Registry No.—7, 7125-23-7; 8, 63163-48-4; 1,12-dibromododecane, 3344-70-5; 1,3-benzenediol, 108-46-3; 1,4-benzenediol, 123-31-9; 2,7-naphthalenediol, 582-17-2; 1,5-naphthalenediol, 83-56-7.

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(17) This point can be a posteriori verified on inspection of Table III, remembering that the EM parameter is, by definition, the reactant concentration at which cyclization and polymerization occur at the same rate, and noting that concentrations in the kinetic runs are two orders of magnitude lower than the EM values.

Structural Elucidation with Nuclear Magnetic Resonance Spectroscopy. Diels–Alder Adducts of 1-Aminoanthracene and Maleic Anhydride: Restricted Rotation about the Aryl C(1)–N Bond and Intrinsic Asymmetry about the Imide (N_{sp^2}–C_{sp^3}) System

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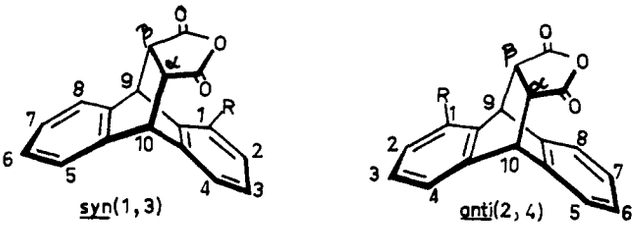
Diels–Alder reaction of 1-acetamidoanthracene and maleic anhydride yields a mixture of two isomeric adducts: syn (~35%) and anti (~65%). The configurations of both the adducts have been assigned with the help of NMR spectra of their imide derivatives. Restricted rotation and nonplanar conformation about the aryl C(1)–N bond have been demonstrated in the C(1)–$N(COCH_3)_2$ derivatives of the isomeric adducts. The steric effect of the C(1) substituent on the intrinsic asymmetry of the imide (N_{sp^2}–C_{sp^3}) system has been observed.

The characteristic feature of anthracene behaving as a diene and its ability to undergo Diels–Alder reaction with various dienophiles is a well-documented phenomenon. The Diels–Alder reaction, where there is possibility of the formation of more than one product, has been extensively investigated. The formation of two isomeric adducts syn[1a] and anti[1a] and their dependence on the nature of the 2 substituent in the Diels–Alder reaction of C(2) substituted anthracene and maleic anhydride have been demonstrated.[1b] Isolation of the two corresponding isomeric adducts in the case of C(2)-substituted anthracene and maleic anhydride and their characterization with the help of spectroscopic methods have been reported.[2] Substitution of anthracene in the 1 position, rather than the 2 position, may have a larger steric effect on the reacting centers, and the present investigations have been un-



1, 2, R = $NHCOCH_3$
3, 4, R = $N(COCH_3)_2$