High stereoselectivity in the Diels-Alder reaction of substituted anthracenes: Reactions of 1-succinimidoanthracene and 1-phthalimidoanthracene with maleic anhydride

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1-Succinimidoanthracene undergoes Diels-Alder reaction with maleic anhydride to give mainly the anti adduct suggesting that the steric factors play dominant role in deciding the anti/syn stereoselectivity. 1-phthalimidoanthracene and also gives mainly the anti adduct with maleic anhydride. The configurations of the compounds have been established by preparing the corresponding imide derivatives of the anhydride adducts and observing the interactions between the imide substituent and the 1-substituent. The interactions between the 1-substituent and that on the anhydride ring of the adduct are more or less negligible in the anti-adduct.

Keywords: 1-Succinimidoanthracene, 1-phthalimidanthracene, stereoselectivity, anhydride adducts, steric factors

Substituted anthracenes provide interesting information regarding the stereoselectivity of Diels-Alder reaction with olefinic dienophiles. The symmetrical nature of the molecule except for the substituent would tend to minimize all other effects which determine the isomer ratio. The stereoselectivity of the reaction appears to be a function of the stereo-electronic factors of the substituents.

9-Substituted anthracenes give rise to regioselective products with unsymmetrical olefinic dienophiles. For instance, the reaction of 9-substituted anthracene 1 with the unsymmetrical dienophile 2 would yield two regioisomers ortho 3a and meta 3b (Scheme I). In most cases\(^1,2\), the ortho regioisomer has been found to be the major regioisomer except in a few cases where the meta regioisomer has been preferred. The regioselectivity has been attributed to kinetic reasons\(^2\). In an interesting case\(^3\), the reaction of 9-substituted anthracene with acetalimidoacrylate, the meta isomer has been found to be dominant (99%), the meta:ortho ratio of the adducts have been found to be 99:1. High diastereoselectivity in the Diels-Alder reactions of 9-substituted anthracenes with p-benzoquinone\(^4\) and N-methyl maleimide\(^5\) has also been reported.

Unsymmetrically substituted anthracenes on the other hand, give rise to stereoisomeric products. For example, 1- and 2-substituted anthracenes give the stereoisomeric adducts syn 4a and anti 4b with maleic anhydride\(^6,7\). The substitution of anthracene at the 2-position rather than the 1-position further removes any steric effect the group may exert on the reacting centers. As such, the electronic effects appear to be the dominant factors in deciding the isomer ratio (syn:anti) of the products. It has been observed that electron donating groups favour the formation of the syn adduct while electron withdrawing groups favour the formation of the anti adduct. For instance, the reaction of 2-nitroanthracene and maleic anhydride gave the syn/anti ratio of 39:61 whereas 2-N,N-dimethylaminoanthracene gave 55:45 of the syn and anti products\(^6\).

In the case of 1-substituted anthracene, since the substituent is very close to the reaction centres, the substituent would exert considerable influence on the reaction centers thereby affecting the stereoselectivity of the reaction. 1-acetamidoanthracene and maleic anhydride gave 35% and 65% of the syn and anti adducts, as reported\(^1\); while the same substituent at the 2- position gave 52% of the syn and 48% of anti adducts\(^6\). The steric effects of the substituent appear to be more dominant than the electronic factors in deciding the isomer ratio, with bulky groups favouring formation of the anti adduct in the case of 1-substituted anthracene. However, in the case of the Diels-Alder reaction of 1,4-dialkoxyanthracenes\(^8\) and
maleic anhydride, the stereoselectivity is less evident. It has been reported that methoxy- and propoxy-substituents slightly favour the \textit{anti} isomer while a small \textit{syn} preference had been observed in the case of benzyloxy substituents\(^8\). In view of these observations, it was of interest to investigate further, the stereo electronic effects of the 1-substituents towards the stereoselectivity of the Diels-Alder reaction by varying the substituents as well as the dienophiles. The present investigation aims at this objective. For the present studies, 1-succinimidoanthracene \(5\) and 1-phthalimidoanthracene \(6\) (Scheme II) have been used as the diene and maleic anhydride as the dienophile.

\textbf{Results and Discussion}

Compounds such as \(5\) and \(6\) adopt non-planar conformation about the aryl C(1)-N bond\(^7,9,10\) and the steric effects of these substituents towards the reactions at C(9)- and C(10)- position will be considerably significant. These compounds have been obtained by reaction of 1-aminoanthracene with succinic anhydride and phthalic anhydride respectively. The Diels-Alder reaction of 1-succinimidoanthracene/1-phthalimidoanthracene in boiling toluene would yield a mixture of two isomeric adducts \textit{syn} \(7\) and \textit{anti} \(8\). However, we are able to isolate only the \textit{anti} adduct; the \textit{syn} adduct being formed only in traces. The steric factors appear to play an important role in deciding the isomer ratio. The 1-succinimido and 1-phthalimido groups being bulky in size favour the formation of the \textit{anti} adducts which would be less crowding as compared to the \textit{syn} adducts. Expected non-bonding repulsions between the carbonyl moieties of the anhydride ring and that of the imide ring (R\(^1\)) may also disfavour the formation of the \textit{syn} adduct. It may also be recalled that the electron releasing factors of the imide nitrogen will be more or less neutralized by the presence of the two carbonyl groups in the imide system (in R\(^1\)).

The configurations of the adducts have been established by preparing the derivatives \(9a-c\) and \(10a-c\) and by correlation of the spectral data of the present compounds to those of the corresponding Diels-Alder adducts of 1-acetamidoanthracene. It is expected that the interactions between the two substituents (R\(^1\) and R\(^2\)) in these derivatives would be more in the \textit{syn} adduct than that in the \textit{anti} adduct. It has been observed that the interactions between the substituents R\(^1\) and R\(^2\) in these derivatives are more or less negligible thereby indicating that the products isolated in the present investigation are \textit{anti} adducts.

1-Succinimidoanthracene \(5\) adopts non-planar conformation about the aryl C (I)-N bond because of steric crowding in the planar conformation. This is evident from the fact that the methylene protons exhibited AA’ BB’ pattern in the \(^1\)H NMR spectrum, at \(\delta\) 2.85-3.12 with the signals for the aromatic protons splitting into three regions- one for the succinimido substituted ring, another for the unsubstituted ring while the C (10)-H appeared as a singlet at \(\delta\) 8.50, the signal due to C-9 proton (singlet) has been merged with the signals of the rest of the aromatic protons. Free rotation about the aryl C (I)-N bond would have rendered all the methylene protons of the succinimido ring equivalent in the NMR spectrum. The IR spectrum exhibits absorptions at 1774 and 1708 cm\(^{-1}\) showing characteristics of the imide ring system.

The adduct \(8a\) exhibits IR absorptions at 1857, 1784 and 1709 cm\(^{-1}\) characteristics of the anhydride and imide ring systems. The \(^1\)H NMR spectrum shows a multiplet at \(\delta\) 2.85-3.12 for the four methylene protons of the succinimido ring, a multiplet at \(\delta\) 3.75 (2H, looking like a singlet, but a multiplet on expansion) for the C-\(\alpha\) and C-\(\beta\) protons and two multiplets at \(\delta\) 4.80 and 4.95 for the C-9 and C-10 protons while the aromatic protons appear as a multiplet at \(\delta\) 7.0-7.50. The compound \(9a\), the \(^1\)H NMR spectrum exhibits two singlets for the methyl protons of the tolyl system, at \(\delta\) 1.03 and 2.04 due to the conformations exhibited by the tolyl system\(^7\), a multiplet at \(\delta\) 2.98-3.21 for the four methylene system of the succinimido ring, two multiplets at \(\delta\) 3.42 and 3.53 for the C-\(\alpha\) and C-\(\beta\) protons, two multiplets at \(\delta\) 4.62 and 4.95 for the C-9 and C-10 protons, a doublet at \(\delta\) 5.50 for the \textit{ortho} proton of the tolyl system and a multiplet at \(\delta\) 6.90-7.50 for the aromatic protons. The IR spectrum for this compound shows
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Scheme II
absorption around 1775 and 1709 cm\(^{-1}\) characteristics of the imide ring system.

The upfield methyl signal (\(\delta 1.03\)) of the o-tolyl group corresponds to the conformations 9a-2 where the methyl group experiences the shielding effect of the cage aromatic ring; and the downfield methyl signal (\(\delta 2.04\)) to the conformation 9a-1. From integrations of methyl signals, it has been observed that the conformation 9a-1 where the methyl group is \textit{anti} to the cage aromatic system is slightly preferred. In the conformation 9a-2, the \textit{ortho} proton of the tolyl group appears upfield (\(\delta 5.50\)) as it is under the influence of magnetic shielding of the cage aromatic system while in the conformation 9a-2, the \textit{ortho} proton resonates along with the rest of the aromatic protons. The spectral data (of R2 in particular) are more or less comparable to that of the similar derivative of unsubstituted anthracene adduct\(^9\) and that of the \textit{anti} adduct of 1-acetaamidoanthracene\(^{11}\). In the \textit{syn} adduct of 1-acetamidoanthracene\(^{11}\), the o-tolyl methyl group and also the \textit{ortho} proton suffers from the deshielding effect of 1-acetamido group, in the conformations 9a-2 and 9a-1 respectively. The fact that the 1-succinimido substituent has negligible effect on the resonances of the o-tolyl group (R\(^2\)) indicates that the present adduct is the \textit{anti} adduct.

The compound 9b exhibits IR absorption at 1775 and 1707 cm\(^{-1}\) showing characteristic of the imide ring system. The \(^1\)H NMR spectrum shows a multiplet at \(\delta 2.70\)-3.40 for the methylene protons of the succinimido ring, one singlet at \(\delta 4.26\) for the benzylmethylene protons, a multiplet at \(\delta 4.50\) for the C-\(\alpha\) and C-\(\beta\) protons, two multiplets at \(\delta 4.70\) and 5.00 for the C-9 and C-10 protons and a multiplet at 6.60-7.50 for the aromatic protons. The appearance of the benzyl methylene protons as a singlet at \(\delta 4.26\) indicates that the adduct is in the \textit{anti} form. If the adduct were in the \textit{syn} form the benzylmethylene protons should have appeared as a multiplet (or AB quartet) as in the case of the \textit{syn} adduct of 1-acetamidoanthracene\(^7\). The two protons are diastereotropic\(^{12}\) because of the asymmetric nature of the molecule. However, the degree of non-equivalence (diastereotropy) of the benzyl methylene protons will be less in the \textit{anti} adduct as they are far away from the 1-substituent and as such they appear as a singlet in the \(^1\)H NMR spectrum.

The \(^1\)H NMR spectrum of the compound 9e exhibits two doublets at \(\delta 0.84\) and 1.23 respectively for the methyl protons of the isopropyl system, a multiplet at 2.60-3.30 for the methylene protons of the succinimido ring, a multiplet at \(\delta 3.89\) (2H) for the C-\(\alpha\) and C-\(\beta\) protons, a multiplet at \(\delta 4.19\) for the methine protons of the isopropyl system while the C-9 and C-10 protons appear as multiplets at \(\delta 4.75\) and 4.90 and the aromatic protons appear as multiplets at \(\delta 7.00\)-7.40.

Because of the asymmetric cage moiety, the isopropyl methyl groups are diastereotopic, i.e., the methyl groups are non-equivalent just like the nonequivalence of methyl groups of the type --C*—CH (CH\(_3\))\(_2\) where C* stands for a stereocentre. Such nonequivalence has also been referred to as intrinsic asymmetry\(^{12\text{-}14}\). However, the non-equivalence is not so well pronounced (pair of doublets not well resolved) in the present adduct as the isopropyl group is far removed from the 1-substituent (in the \textit{anti} adduct) which is responsible for inducing asymmetry. In the case of the \textit{syn} adduct of 1-acetamidoanthracene, the isopropyl methyl doublets\(^7\) (pair of doublets) are well separated as the interacting groups R\(^1\) and R\(^2\) are close to each other.

In the spectra of the compounds 8a through 9a-c discussed above, the signals of the methylene system of the 1-succinimido ring (R\(^1\)) could serve as a reference point in establishing the \textit{syn/anti} configuration of the adducts. With change in the nature of the substituents in R\(^2\) in the anhydride ring system in the adducts, no significant change is observed in the signal of the methylene system of R\(^1\). Introduction of tolyl system or benzyl group in R\(^2\), the methylene protons (in R\(^1\)) should experience shielding effect if R\(^1\)and R\(^2\) are close as in the \textit{syn} adduct. However, the chemical shift of the methylene protons of R\(^1\) remains more or less the same as in the starting material, i.e. 1-succinimidoanthracene 5. Even in the spectrum of the anhydride adduct itself the anhydride ring has little influence on the chemical shift of the methylene protons of the 1-substituent. As such, the products obtained could be \textit{anti} adducts where the substituents R\(^1\) and R\(^2\) are well separated.

In the case of the Diels-Alder adduct 8b of 1-phthalimidoanthracene 6, it appears that the phthalamido group has negligible effect on the spectra of the various substituents (R\(^2\)) in the anhydride system 10a-c. The spectrum of the substituents (R\(^2\)) of the adducts are more or less comparable to the corresponding derivatives of the 1-succinimido adducts. For instance, the \(^1\)H NMR spectrum for the compound 10b exhibits a singlet at \(\delta 4.27\) for the benzyl methylene protons and a multiplet at \(\delta 4.53\) for the C-\(\alpha\), C-\(\beta\) protons, two singlets at \(\delta 4.70\) and 4.80
for the C-9 and C-10 protons while the aromatic protons appear at δ 6.50-7.60. Hence, it can be concluded that the Diels-Alder adduct of the 1-phthalimidoanthracene with maleic anhydride is also the anti adduct.

Experimental Section

The melting points were recorded on 'Veego' melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu FT-IR and melting point apparatus and are uncorrected. IR eluent, UV radiation or iodine or KMnO₄ were used plates using ethyl acetate and petroleum ether as the compounds were checked by TLC on silica gel crystallization from different solvents. The purity of and ethyl acetate as solvent mixture, followed by chromatography on silica gel using petroleum ether multiplet. The compounds were purified by column plicities are as follows: s, singlet; d, doublet; m, multiplet. The abbreviations for NMR multi-

δ

ppm (parts per million) relative to internal standard. Chemical shifts (δ) are given in ppm (parts per million) relative to internal standard tetramethylsilane. Abbreviations for NMR multiplicities are as follows: s, singlet; d, doublet; m, multiplet. The compounds were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as solvent mixture, followed by crystallization from different solvents. The purity of the compounds were checked by TLC on silica gel plates using ethyl acetate and petroleum ether as eluent, UV radiation or iodine or KMnO₄ were used as visualizing agents.

Preparation of 1-aminoanthracene

1-Aminoanthracene was prepared by the reduction of 1-aminoanthraquinone by zinc-dust and alkali following the procedure reported earlier.

Preparation of 1-succinimidoanthracene 5

1-Aminoanthracene (2 g, 10.3 mmoles) was thoroughly mixed with 4 g (40 mmoles) of succinic anhydride and heated under reflux in dry toluene (5 mL) for about 6 hr. The pale yellow solid material formed was collected and recrystallized from ethanol. Yield: 70%; m.p. 242-44°C. ¹H NMR: δ 3.09 (4H, m), 7.0-7.4 (7H, m). Anal. Calcd. for C₁₈H₁₃NO₂: C, 78.53; H, 4.76. Found: C, 78.83; H, 4.92%.

Preparation of 1-succinimido-9,10-dihydroanthracene-9,10-endo-α,β-succinimide anhydride 8a

1-Succinimidoanthracene 3 (0.5 g) and maleic anhydride (1 g) were mixed thoroughly and gently refluxed in dry toluene with constant stirring for 5 hr. The adduct appeared as off-white insoluble substance in toluene, while the excess maleic anhydride went into the solution. The solid material was collected (~0.6 g) and traces of maleic anhydride were removed by sublimation at 110°C. The solid substance was subjected to fractional crystallization from acetone and ethanol mixture (2:1 v/v). Yield: 80%; m.p. >293°C. ¹H NMR: δ 3.04 (4H, m), 3.75 (2H, s, α+β), 4.80 (1H, s), 4.95 (1H, s), 7.0-7.5 (7H, m). Anal. Calcd. for C₂₂H₁₈N₂O₄: C, 70.77; H, 4.04. Found: C, 70.55; H, 4.34%.

Preparation of 1-succinimido-9,10-dihydroanthracene-9,10-endo-α,β-(N-tolyl)-succinimide 9a

0.21 g (2 mmoles) of the compound 8a was mixed thoroughly with one and half times its equimolar amount of o-toluidine and heated at 110-20°C for about 4 hr. The product obtained was cooled, washed with ether and recrystallized from ethanol. Yield: 54%; m.p. >285°C. ¹H NMR: δ 1.03 (1.35H, s), 2.04 (1.65H, s), 3.06 (4H, m), 3.4 and 3.53 (2H, m, α+β), 4.62 (1H, m), 4.95 (1H, m), 5.51 (0.55H, d), 6.90-7.5 (10.45H, m). Anal. Calcd. for C₂₉H₂₂N₂O₄: C, 75.30; H, 4.79. Found: C, 75.68; H, 4.95%.

Preparation of 1-succinimido-9,10-dihydroanthracene-9,10-endo-α,β-(N-benzyl)-succinimide 9b

The compound 9b was prepared by treating (0.31 g, 1 mmoles) of compound 8a with an excess of benzyl amine (0.21 g, 2 mmoles). The mixture was gently heated at 110-20°C for about 2 hr. The product obtained was cooled, washed with ether and recrystallized from chloroform-benzene mixture (2:3 v/v). Upon crystallization from chloroform-benzene, the needle shaped colourless crystals appeared. Yield: 55%; m. p.255-57°C. ¹H NMR: δ 2.7-3.4 (4H, m), 4.26 (2H, s, -CH₂-C₆H₅), 4.5 (2H, m, α+β), 4.70 (1H, m), 5.0 (1H, m), 6.63 (5H, m), 7.5 (7H, m). Anal. Calcd. for C₂₉H₂₂N₂O₄: C, 75.30; H, 4.79. Found: C, 75.43; H, 5.01%.

Preparation of 1-succinimido-9,10-dihydroanthracene-9,10-endo-α,β-(N-isopropyl)-succinimide 9c

0.40 g (1.44 mmoles) of compound 8a was mixed thoroughly with 0.6 mL (6.77 mmoles) of isopropyl amine and heated gently at 100-10°C for about 3 hr. The off-white solid material obtained was allowed to cool, washed with ether and then recrystallized from chloroform-benzene (2:3 v/v) mixture. Yield: 63%, m.p. 258-60°C. ¹H NMR: δ 8.4 (3H, d), 1.23 (3H, d), 2.6-3.3 (4H, m), 3.89 (2H, m), 4.19 (1H, m), 4.75 (1H, d), 4.90 (1H, d), 7.0-7.4 (7H, m). Anal. Calcd. for C₂₉H₂₂N₂O₄: C, 72.44; H, 5.35. Found: C, 72.68; H 5.51%.
Preparation of 1-phthalimidoanthracene 6

A mixture of 1-aminoanthracene (2 g) and phthalic anhydride (4 g) was heated under reflux in toluene (15 mL) for about 6 hr, with constant stirring. The adduct appeared as a light yellow insoluble substance in toluene, while the excess phthalic anhydride were removed by sublimation. The solid mass was subjected to recrystallization from ethanol. Yield: 70%; m.p. 262-64°C. Anal. Calcd. for C_{22}H_{13}NO_{2}: C, 77.63; H, 4.43. Found: C, 77.81; H, 4.49%.

Preparation of 1-phthalimido-9,10-dihydroanthracene-9,10-endo-α,α'-succinimide 10a

The anhydride adduct 8b 0.4 g was gently refluxed for 3 hr with toluene, while the excess phthalic anhydride were removed by cooling. The product obtained was cooled, washed with ether and recrystallized from chloroform-hexane (1:2 v/v). Yield: 57%; m.p.>287°C. 1H NMR: δ 1.02 (1.35H, s), 2.04 (1.65H, s), 3.59 & 3.62 (2H, m, α±β), 4.76 (1H, m), 4.99 (1H, m), 5.51 (0.55H, d), 6.8-8.1 (15.45H, m). Anal. Calcd. for C_{25}H_{22}N_{2}O_{4}: C, 77.63; H, 4.43. Found: C, 77.81; H, 4.49%.

Preparation of 1-phthalimido-9,10-dihydroanthracene-9,10-endo-α,β-(N-benzyl)-succinimide 10b

The compound 10b was prepared by refluxing the compound 8b with twice the equimolar amount of benzylamine at 120°C for about 2 hr. The solid mass thus appeared was allowed to cool, washed with ether and then recrystallized from ethanol. The colourless needle shape crystals were obtained from the concentrated solution. Yield: 87%; m.p. 197-200°C. 1H NMR: δ 4.27 (2H, s, -CH_2-C_6H_5), 4.53 (2H, m, α±β), 4.70 (1H, s), 4.80 (1H, s), 6.5-7.6 (16H, m). Anal. Calcd. for C_{29}H_{22}N_{2}O_{4}: C, 77.63; H, 4.34. Found: C, 77.73; H, 4.48%.

Preparation of 1-phthalimido-9,10-dihydroanthracene-9,10-endo-α,β-(N-isopropyl)-succinimide 10c

The above compound 10c was obtained by condensing the anhydride adduct 8b with excess of isopropyl amine at 110-20°C for 3 hr. The product was cooled, washed with ether and recrystallized from benzene-chloroform (3:2 v/v) mixture. Yield: 51%; m.p. 155-58°C. 1H NMR: δ 0.83 (3H, d), 1.15 (3H, d), 3.87 (2H, m, α+β), 4.76 (1H, m, -CH(CH_3)_2), 5.01 (1H, m), 5.20 (1H, m), 6.18-7.3 (11H, m). Anal. Calcd. for C_{29}H_{22}N_{2}O_{4}: C, 81.71; H, 4.05. Found: C, 81.83; H, 4.21%.

Conclusion

The Diels-Alder reaction of 1-succinimidoanthracene and 1-phthalimidoanthracene with maleic anhydride gives mainly the anti adduct. The steric factors appear to play dominant role in directing the stereoselectivity in the Diels-Alder reaction of the present compounds.

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