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Stereoelectronic effects in the Stereoselectivity of the Diels-Alder Reactions: Reactions of Aminoanthracenes with N-phenylmaleimide

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ABSTRACT

Diels-Alder reaction of aminoanthracenes with N-phenylmaleimide gives two stereoisomeric adducts syn (~70%) and anti (~30%) irrespective of the amino group being at 1- or 2- positions of anthracene. The results indicate that electronic effect is dominating in deciding the isomer ratio. The configuration of the adducts syn and anti have been established with the help of spectroscopic data of the adducts and the corresponding N-diacetamido derivatives. Whereas free rotation about the aryl C(2) - N bond is observed in 2-diacetamido derivative, there is hindered rotation and non-planar conformation about the aryl C(1)-N bond in the 1-diacetamido derivative.

Keywords: aminoanthracene, stereoelectronic effects, stereoselectivity, hindered rotation, non-planar conformation.

INTRODUCTION

The Diels-Alder reaction, one of the most useful synthetic reactions in organic chemistry, belongs to the general class of cycloaddition reaction usually called a [4 + 2] cycloaddition reaction involving a conjugated 4π-electron system called the *diene* and a 2π electron system called *dienophile*. It was correctly formulated by two German chemists, Otto Diels and Kurt Alder (1950 Nobel prize winners in chemistry) in 1928 and since then it has become one of the most fundamental and useful reactions in the armamentarum of the synthetic organic reactions. It is a concerted process in which two new σ-bonds and a new π-bond are formed at the expense of three π-bonds in the starting materials [1 - 6].

In general the reaction takes place simply by mixing the components at room temperature or by gently warming in a suitable solvent, although in some cases with unreactive dienes or dienophiles more vigorous conditions may be necessary. The Diels-Alder reaction is reversible and many adducts dissociate into their components at quite low temperatures. In these cases heating is disadvantageous and the forward reaction is facilitated and better yields are obtained by using an excess of one of the components, or a solvent from which the adduct separates readily. Lewis acid catalysts [7-9] accelerate many Diels-Alder reactions. In a few cases high pressures have been used to facilitate reactions which otherwise take place only slowly or not at all at room temperature [10].

In the terminology of the orbital symmetry classification, the Diels-Alder reaction is [4π + 2π] supra - supra cycloaddition, an allowed process [11]. The stereochemistry of both the diene and the dienophile is retained in the cyclization process. The transition state for a concerted reaction requires that the diene adopts the *cisoid* conformation [12]. The diene and the dienophile approach each other in parallel planes. The symmetry properties of the π-orbital permit stabilizing interaction between C-1 and C-4 of the dienes and the two carbons of the dienophile. Usually the strongest interaction is between the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile [13] rather than the interactions between HOMO of the dienophile and LUMO of the diene even though both the interactions are allowed processes. Electron releasing groups in the diene raises the energy of the HOMO and electron withdrawing groups in the dienophile lowers the energy of the LUMO thereby enhancing the rate of the reaction [14,15].

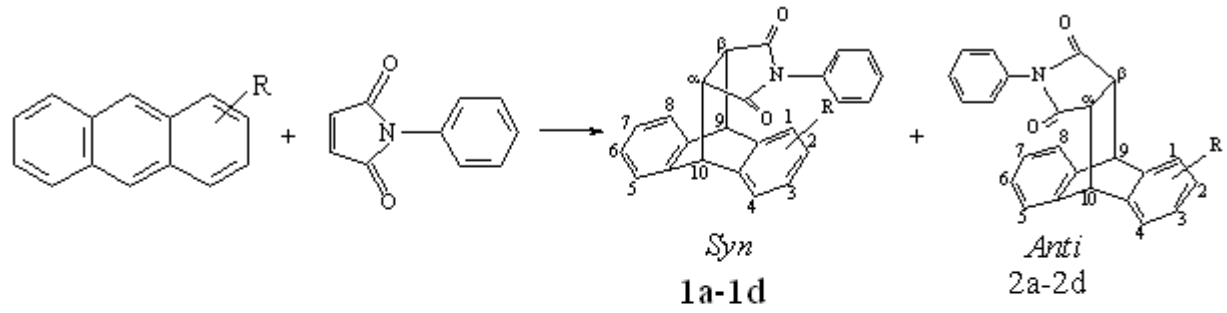
The usefulness of the Diels-Alder reaction in synthesis arises from its versatility and from its remarkable stereoselectivity. By varying the nature of the diene and the dienophile many different types of ring structures can be built up. In the majority of case, all the six atoms involved in forming the new ring are carbon atoms but this is not necessary and the ring closure may also take place at atom other than carbon, giving rise to heterocyclic compound. It is very frequently found, however, that the reaction is controlled by stereoelectronic effects of the substituents [16].

The characteristic feature of anthracene behaving as a diene and its ability to undergo Diels-Alder reaction with various dienophiles have been well documented. Substitutions in the diene molecule (anthracene) influence the rate of the reaction both through their electronic nature and steric effects. The relative rates of reaction of some substituted anthracenes with maleic anhydride as determined under pseudo first order conditions are given below (Table -I)[17].

Table 1: Relative rates of D.A. reaction of substituted anthracenes with maleic anhydride

Compound	Rate of reaction k($Lmol^{-1}s^{-1}$)
2-Nitroanthracene	0.086×10^{-5}
Anthracene	0.014×10^{-3}
2-N,N-dimethylaminoanthracene	0.055×10^{-3}

In the present investigation, the stereoelectronic effects of the amino group on the stereoselectivity of the Diels-Alder reaction of amino substituted anthracenes and N-phenyl maleimide have been studied. The reaction gives two diastereomeric products *syn* **1** and *anti* **2** with the former as the major isomer irresepective of the amino group being at 1- or 2- positions of anthracene. The structures of the compounds have been characterized on the basis of spectroscopic data of the compounds and the corresponding N-diacetamidoderivatives **1b, 2b** and **1d, 2d** of the adducts.



1a, R= 1- NH_2 ; 2a, R= 1- NH_2

1b, R= 1- NAc_2 ; 2b, R= 1- NAc_2

1c, R= 2- NH_2 ; 2c, R= 2-NH_2

1d, R= 2- NAc_2 ; 2d, R= 2- NAc_2

EXPERIMENTAL SECTION

The melting point were recorded on 'Veego' melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu FT - IR 8400, at the Department of Chemistry, Manipur University. ^{1}H NMR spectra were recorded in deuterated chloroform ($CDCl_3$) on a Brucker ACF 300 MHz spectrometer using TMS (tetramethylsilane) as 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.

Preparation of Compounds

1-Aminoanthracene:

1-Aminoanthracene was prepared by the reduction of 1-aminoanthraquinone by zinc dust and alkali following the procedure reported earlier [18]. 1-Aminoanthraquinone (5g) was stirred with 10% sodium hydroxide (60ml) and

zinc dust (5g) at room temperature for about 30 min. It was slowly heated upto about 85-90^{o}C. Zinc dust (5g) was then introduced into the reaction mixture in two equal instalments at an interval of 30 minute each and heating was continued with constant stirring for 24h at 90^{o}C. After cooling, the solid material from the reaction mixture was collected and washed several times with water. Soxhlet extraction with acetone and then recrystallization from ethanol gave 1-aminoanthracene (3g, 70%) as greenish yellow plates, mp. 126 - 127^{o}C (lit[**18**]127^{o}C); IR (cm^{-1}): 3431, 3377, 3049, 1625, 1560, 1456.

2-Aminoanthracene:
2-Aminoantraquinone (10g) was stirred with 10% sodium hydroxide (100 ml) and zinc dust (8g) at room temperature for about 30 minutes. It was slowly heated upto about 100^{o}C. Zinc dust (10g) was then introduced into the reaction mixture in two equal instalments at an interval of about 30 min. each and heating was continued with constant stirring at about 100 - 110^{o}C for 24 h. After cooling, the solid material was collected and washed several times with water. Soxhlet extraction with acetone and then recrystallization from toluene gave 2-aminoanthracene (6g, ~70%) as yellow plates, mp. 238 - 240^{o}C (lit [**17**] mp. 238^{o}C); IR (cm^{-1}): 3428, 3365, 3043, 1637, 1556, 1454; NMR ($CDCl_3$) δ: 3.80 (2H, broad, NH_2), 6.91 - 7.34 (3H, m, Ar - H), 7.77 - 7.85 (4H, m, Ar - H), 8.20 (1H, s, 9-H), 8.30 (1H, s, 10-H)

Diels - Alder reaction of 1-aminoanthraene with N-phenylmaleimide:
A mixture of 1-aminoanthracene (0.5g) and N-phenylmaleimide (0.5g) in toluene (3ml) was refluxed for 5h. The progress of the reaction was monitored on TLC. The reaction mixture was cooled and diethyl ether was added to it. The off white solid obtained was filtered and dried. The two isomeric adducts were separated by column chromatography on silica gel. The *anti* adduct **2a** was eluted first at 15% ethyl acetate in hexane and then the *syn* adduct **1a** 16% ethyl acetate in hexane.

N-phenyl-*syn*-α,β- (1-amino-9, 10-dihydroanthracene-9, 10-diyl) succinimide 1a:
m.p: 250 - 251^{o}C; Calculated for $C_{24}H_{18}N_2O_2$: C,78.60%; H,4.96%; Found: C,78.56%, H,4.91%; IR(cm^{-1}) : 3411, 3352, 1774, 1704; ^{1}HNMR ($CDCl_3$ δ: 3.36 (2H, d, α + β), 3.89 (2H, broad, -NH_2), 4.82 (1H, s, 9 - H), 4.92 (1H, s, 10 - H), 6.48 (12H, m, aromatic).

N-phenyl-*anti*-α,β- (1-amino-9, 10-dihydroanthracene -9, 10-diyl) succinimide 2a:
m.p.: 232 - 233^{o}C; Calculated for $C_{24}H_{18}N_2O_2$: C,78.60%; H,4.96%; Found: C,78.62%, H,4.93%; IR (cm^{-1}): 3427, 3371, 1772, 1710; ^{1}HNMR ($CDCl_3$) δ: 3.32 - 3.45 (2H, m, α + β), 3.81 (2H, broad, -NH_2), 4.82 (1H, d, 9 - H), 5.02 (1H, d, 10 - H), 6.56 - 7.42 (12H, m, aromatic).

Diels-Alder reaction of 2-Aminoanthracene with N-phenylmaleimide:
About 0.5 g of 2-aminoanthracene and 1.0 g of N-phenylmaleimide was refluxed for 8h in dry toluene (5ml). The reaction mixture was allowed to cool and the solid material was washed with 20 ml of hexane. It was treated with about 50 ml of diethylether. It was found that one of the adducts (*anti*) was soluble in ether and the other adduct (*syn*) was insoluble.

N-phenyl-*syn*-α,β (2-amino-9, 10-dihydroanthracene-9, 10-diyl) succinimide 1c (ether insoluble):
m.p: 220^{o}C ; Calculated for $C_{24}H_{18}N_2O_2$: C,78.60%; H,4.96%; Found: C,78.58%, H,4.98%; IR(cm^{-1}) : 3446, 3359, 1772, 1704 ^{1}HNMR ($CDCl_3$)δ: 3.21 - 3.31 (2H, m, α+β), 4.67-4.75 (2H, m, 9-H, 10-H), 6.38 - 6.61 (5H, m, N-phenyl group), 6.98-7.32 (7H, m, aromatic).

N-phenyl-*anti*-α,β-(2-amino-9,10-dihydroanthracene-9,10-diyl) succinimide 2c (ether soluble): m.p: 200^{o}C ; Calculated for $C_{24}H_{18}N_2O_2$: C,78.60%; H,4.96%; Found: C,78.56%, H,4.91%; IR (cm^{-1}): 3463, 3363, 1774, 1704; ^{1}HNMR ($CDCl_3$)δ: 3.37 (2H, d, α+β), 4.76-4.78 (2H, m,9-H,10-H), 6.48-6.51 (5H, m, N-phenyl group), 7.10-7.46 (7H, m, aromatic).

Preparation of diacetamido derivatives of the addusts: 1b, 2b, 1d and 2d:
The 1- and 2- diacetamidoderivatives of the adducts were obtained by acetylation of the corresponding adducts **1a, 2a** and **1c** and **2c** with acetic anhydride (refluxing the adducts with acetic anhydride for 3h). The products were recrystallized from ethylacetate and hexane mixture.

1b : mp: 183 - 185^{o}C; Calculated for $C_{28}H_{22}N_2O_4$: C,74.66%; H,7.89%; Found: C,74.70%, H,7.91%; IR (cm^{-1}) : 3066, 2956, 1780, 1710, 1596, 1496; ^{1}HNMR($CDCl_3$)δ: 2.03 (3H, s, $COCH_3$), 2.32 (3H, s, $COCH_3$), 3.32-3.46 (2H, m, α+β), 4.84 (1H, m,9-H), 4.97 (1H, m,10-H), 6.79 - 6.81 (2H, m, orthoprotons of N-phenyl), 7.03-7.43 (10 H, m, aromatic).

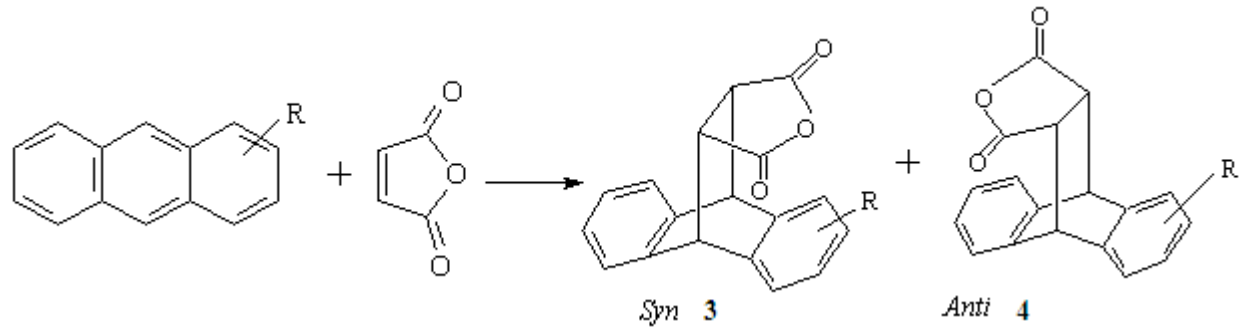
2b : mp: 221 – 224^{0}C; Calculated for $C_{28}H_{22}N_2O_4$: C,74.66%; H,7.89%; Found: C,74.60%, H,7.86%; IR(cm^{-1}) : 3068, 2952, 1778, 1712, 1596, 1500; ^{1}HNMR($CDCl_3$)δ: 1.79(3H, s, $COCH_3$), 2.75 (3H, s, $COCH_3$), 3.36 - 3.45 (2H, m, α+β), 4.73(1H, d, 9 - H), 4.97 (1H, d, 10-H), 6.47-6.50(2H, m, orthoprotons of N-phenyl), 6.98-7.50 (10H, m, aromatic).

1d : mp: 234-235^{o}C; Calculated for $C_{28}H_{22}N_2O_4$: C,74.66%; H,7.89%; Found: C,74.62%, H,7.85%; IR(cm^{-1}): 3045, 2956, 1774, 1708, 1492, 1380; ^{1}HNMR($CDCl_3$)δ: 1.94(6H, s, $N(COCH_3)_2$), 3.21-3.27 (2H, m, α+β), 4.74(1H, d, 9-H), 4.80 (1H, d, 10-H), 6.62 (2H, m, orthoprotons of N-phenyl), 6.83-7.26 (10H, m, aromatic).

2d: mp: 125-127^{o}C; Calculated for $C_{28}H_{22}N_2O_4$: C,74.66%; H,7.89%; Found: C,74.70%, H,7.90%; IR(cm^{-1}): 3050, 2960, 1776, 1714, 1494, 1367; ^{1}HNMR($CDCl_3$)δ: 2.13(6H, s, $N(COCH_3)_2$), 3.28(2H, m, α+β), 4.76(1H, d, 9-H), 4.82(1H,d, 10-H), 6.34-6.37(2H, m, orthoprotons of N-phenyl), 6.85-7.21(10H, m, aromatic).

RESULTS AND DISCUSSION

Substituted anthracenes are interesting targets for the study of stereoselectivity of the Diels-Alder reaction with olefinic dienophiles. Since the molecule is highly symmetrical the stereoselectivity of the reaction depends only on the stereoelectronic nature of the substituents. 9-Substituted anthracenes lead to the formation of regioselective adducts [19- 23] with unsymmetrical olefinic dienophiles. On the other hand, unsymmetrically substituted anthracenes give rise to seteroisomeric adducts *syn* 3 and *anti* 4 with maleic anhydride(Scheme-1).



Scheme-1

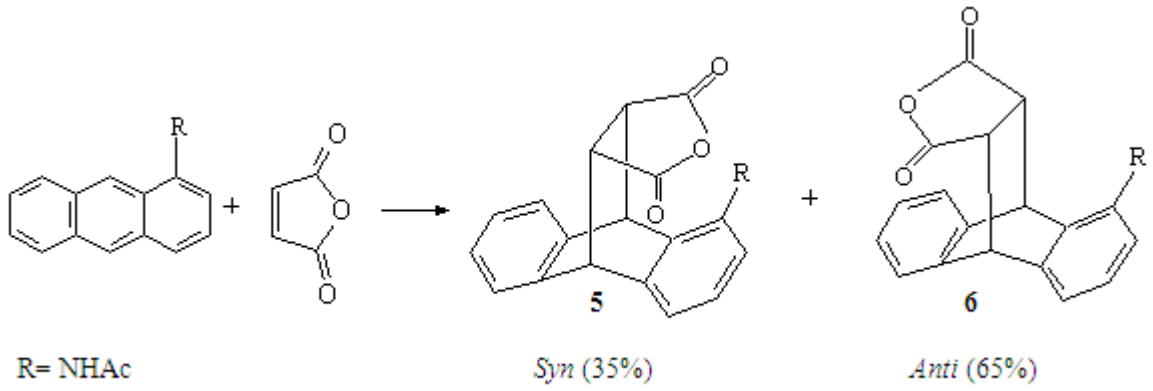
The isomeric ratio (*syn:anti*) depends on the stereoelectronic effects of the substituent. The distribution of the isomeric adducts in the case of some 2-substituted anthracenes is given below (Table -2)[17].

Table 2: Isomeric distribution of the reaction adducts of 2-substituted anthracene with maleic-anhydride.

Substituent	% syn	% anti
2-NO_2	39±1	61±1
2-NHAc	52±1	48±1
2NMe_2	55±1	45±1

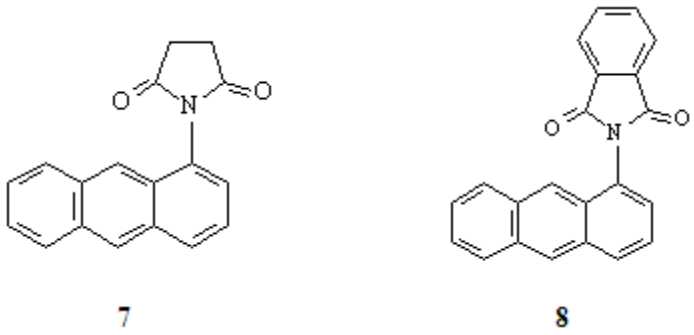
The substitution of anthracene in the 2-positions, further removes any steric effect the group may have on the reacting centres. As such, the electronic effects appear to control the stereoselectivity - electron donating groups favouring the formation of the *syn* adduct and electron withdrawing groups favouring the *anti* adduct as indicated in Table-2. The above observation of isomer ratio shows that the transition state containing the maleic anhydride fragment above the electron-rich aromatic ring is more stable than the other possiblity.

However, when the substituent is at the 1-position, since the group is very close to the reaction centre, the steric effect of the substituent on the stereoselectivity of the reaction will be considerably significant. This has been observed in the reaction of 1-acetamidoanthracene with maleic anhydride (Scheme-2)[18].



Scheme-2

Even though the acetamido group is electron donating, the reaction favours the formation of the *anti* adduct(65%), while the same substitution is at the 2-position, where the steric factor is negligible, the stereoselectivity is less significant as the product ratio is 52 : 48 (*syn : anti*). The steric factors appear to be more dominant than the electronic factor when the substituent is at the 1-position. This has been supported by the fact that only the *anti* adduct have been isolated as the major adducts in the reactions of 1-succinimidoanthracene **7** and 1-phthalimidoanthracene **8** with maleic anhydride [24].



However, in the case of the Diels-Alder reaction of 1, 4-dialkoxyanthracenes and maleic anhydride the stereoselectivity is less evident (Table - 3) [25].

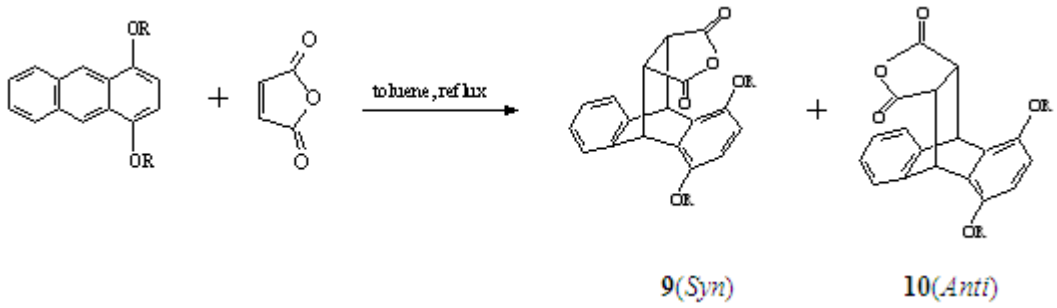


Table -3: Diels-Alder adducts of 1-alkoxyanthracenes with maleic anhydride

R	% syn	% anti
CH_3	45	55
n-Pr	43	57
CH_2Ph	57	43

In view of these observations, it will be interesting to investigate further the stereoselectively of the reaction by placing a strong electron donating group but small in size at the 1- and 2-positions of anthracene. Towards this objective we used 1- and 2- aminoanthracenes as the diene component and N-phenylmaleimide as the dienophile in the Diels-Alder reaction. In both the cases, the stereoselectivity is found to be in favour of the *syn* isomer 1 (~70%) rather than the *anti*-isomer 2(~30%) irrespective of the amino group being at 1- or 2- positions.

Our initial objective was to investigate the nature of stereoselectivity in the Diels-Alder reactions of 1- and 2-aminoanthracenes with maleic anhydride (MA). The strong electron donating character of amino group is well known but sterically it is considered very small, much smaller than a methyl group. However, the D.A. reaction of aminoanthracenes with MA cannot be clearly followed because the reaction is probably preceded by the formation of charge transfer complexes between the highly electron rich aminoanthracenes and highly electron withdrawing MA. The reaction is often accompanied by the instant formation of a highly intense orange coloured compound (insoluble in most of the organic solvents). As such the influence of the amino group at 1- and 2-position of anthracene on the nature of stereoselectivity in the D.A reaction with M.A cannot be directly studied. However the reaction of 1- and 2-aminoanthracene, with N-Phenylmaleimide occurred smoothly. As expected the *syn* adducts **1a** and **1c** are more polar and less soluble in organic solvents, and hence isolation of the adducts are not difficult. The *syn* adducts are much less soluble in diethyl ether than the *anti* adducts whereas the *anti* adducts are eluted first during column chromatography.

The IR spectra of *syn* and *anti* adducts are more or less similar except that the N-H stretching of the *syn* adducts are at slightly lower frequencies than that of the *anti* adduct because of the probability of intramolecular hydrogen bonding [26] between the N - H proton and the carbonyl groups in the succinimide moiety. However, the configuration of the adducts can be assigned from the ^{1}HNMR spectra of the adducts and the corresponding N-diacetamido derivatives of the adducts.

The IR and ^{1}HMNR spectra of **1b** and **2b** are in agreement with the *syn* and *anti* adducts of the 1-diacetamidoanthracene with N-phenylmaleimide reported earlier [27]. The *syn* and *anti* configurations of the adducts of the Diels-Alder reaction of 2-diacetamidoanthracene with N-phenylmaleimide can be convincingly assigned on the basis of proton NMR spectra.

In the ^{1}HMNR spectrum of the *syn* adduct **1d**, the acetyl methyl group appears at δ1.94 which is much more upfield than the acetyl methyl signal of the *anti* adduct **2d** (δ2.31)probably because in the former case the acetyl methyl group experiences the shielding effect of the N-phenyl group, which would be absent in the *anti* adduct. Besides, the *ortho* protons of the N-phenyl group experience deshielding effect of the acetyl group in the *syn* adduct **1d** and appears at δ 6.62 as against δ 6.34 - 6.37 of the *anti* adduct **2d**. It may be also be noted that the two N-acetyl methyl groups appears as two singlets in both the *syn* and *anti* adducts **1b** and **2b** because of hindered rotation and non-planar conformation about the aryl C(1)-N bond as the substituent is near the 9,10-bridge. However, in the case of the 2-substituted derivative since it is away formed the 9,10-bridge, there is free rotation about the aryl C(2) - N bond and hence the two acetyl groups appear as only one singlet in both the *syn* **1d** and *anti* **2d** derivatives of the 2-acetamidoderivative.

Acknowledgements
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