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Microwave -Assisted Synthesis of N -2'- Substituted –A, B-(9, 10- Dihydro Anthracene -9, 10-Diyl) Succinimide -Ethane-1'-Oic Acids and the Role of Carboxylic Group in Controlling the Conformation about Nsp^2-Csp^3 Bond

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ABSTRACT

Microwave-Assisted Organic Synthesis (MAOS) of N-(2'- substituted acetic acid)-α, β- (dihydroanthracene-9,10-diyl) succinimides has been achieved by reaction of anthracene-maleic anhydride Diels-Alder adduct with different amino acids. Synthesis by microwave irradiation gave the desired compounds in higher yields and in shorter reaction times than those obtained by conventional method. The carboxyl group in these derivatives remains in *anti* orientation and does not exhibit hydrogen bonding with the carbonyls of the succinimide. In case of serine and threonine a six membered intra-molecular hydrogen bonded puckered cyclic structure between –OH group and –C=O of –COOH in *anti*-conformation has been proposed.

Keywords: Diels-Alder adduct, conformation, microwave irradiation, intra-molecular hydrogen bonding

INTRODUCTION

Microwave (MW) irradiation is well known to induce reduction in time of various reactions, yield enhancement and cleaner chemistry. Recently, this irradiation has been widely used as an alternative to conventional heating to a number of research programmes and development processes, whereby microwave-assisted organic synthesis (MAOS) becomes a fashion in organic chemistry.[1-7] Under this MAOS programme an attempt has been made to condense Diels-Alder adduct of anthracene- maleic anhydride with amino acids. Synthesis of these compounds is of interest as the magnetic asymmetry of the cage is diagnostic in demonstrating the finer details of the molecules. Restricted rotation and non-planar conformations about N-C (phenyl) bond in *ortho* substituted anilides in system **(1)** have been reported with the help of asymmetric cage moietes[8-10]. A preferred non- planar conformation about N-C bond due to intramolecular hydrogen bonding between 2'-OH and one of the carbonyls of the succinimidyl ring and a intramolecular hydrogen bonded seven membered puckered cyclic structure in the preferred *anti* orientation has been demonstrated in α, β-(9,10-dihydroanthracene 9,10-diyl)- N- (*o*-hydroxy phenyl) succinimide **(2)**[11]. The existence of an intramolecular hydrogen bonded cyclic structure was inferred from non-magnetic equivalence of α and β–protons and the appearance of 6'- proton at a shielded position. A preferred non- planar conformation about N-C bond and a six membered intramolecular hydrogen bonded cyclic structure in 1,3-diol compounds **(3)**[12] has been demonstrated.

In the present study we report a comparative study of the MAOS and conventional heating for the synthesis of α,β-(dihydroanthracene-9,10-diyl) succinimido-N-acetic acids and the role of a carboxylic group in controlling the conformation about Nsp^2-Csp^3 bond which has also a tendency to form intramolecular hydrogen bonding. For this purpose a series of compounds **(6a-f)** have been prepared and their conformations have been studied by ^{1}H NMR spectroscopy.

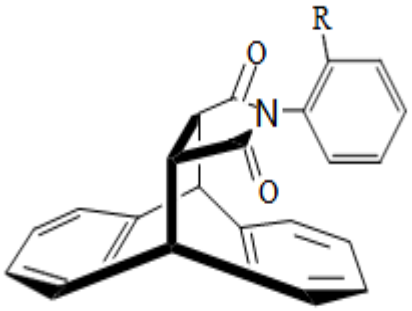
RESULTS AND DISCUSSION

Microwave irradiation of anthracene-maleic anhydride adduct **(4)** with different amino acids **(5)** (i.e. glycine, alanine, valine, phenylalanine, serine, threonine) in Microwave oven for 3-8 min. gave N-(2'- substituted acetic acid)- α, β-(9,10-dihydroanthracene-9,10-diyl) succinimides **6a-f** with high yields (Scheme 1, Table 1). Conventional oil bath

heating for the synthesis of compounds (6a-f) required half an hour at 180-185^0 C, followed by refluxing with an excess of acetic acid for 3hr.[13] Microwave irradiation completed the reactions in one step in one pot comparatively with high yields within minutes. The structures of all the synthesized compounds **6a-f** have been elucidated from their spectral analyses.

^{1}H NMR of the compound **6b** shows a doublet at δ 0.82 (3H) for the methyl protons and a quartet at δ 4.06 (1H) for C*H*COOH proton along with other resonances. A shielded singlet for the methyl protons suggested that there is a preferred conformation about Nsp^2-Csp^3 bond. The preference of only one conformation having carboxylic group in *anti* orientation clearly indicates that the high torsional barrier about N-C bond has resulted from the strong electrostatic repulsion of the carboxylic group with the cage phenyl ring and tries to be in *anti*-orientation. The magnetic equivalence of α & β protons in **6b** eliminates the possibility of intramolecular hydrogen bond of the –COOH group with one of the carbonyls of the succinimidyl ring.

^{1}H NMR of compound **6c** is quite characteristic in demonstrating the conformational preference about Nsp^2-Csp^3 bond. The spectrum shows the following resonances: δ 0.24, 0.83 (dd, 6H) for the isopropyl methyl protons, δ 2.24 (m, 1H) for isopropyl methine proton, δ 3.30 (t, 2H) for α, β protons, δ 4.14 (d, 1H) for C*H*COOH proton with other resonances.



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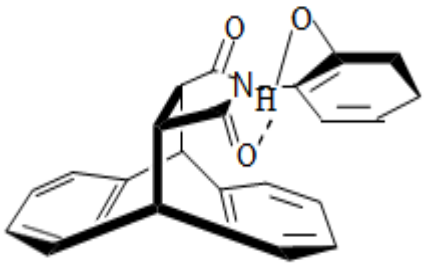

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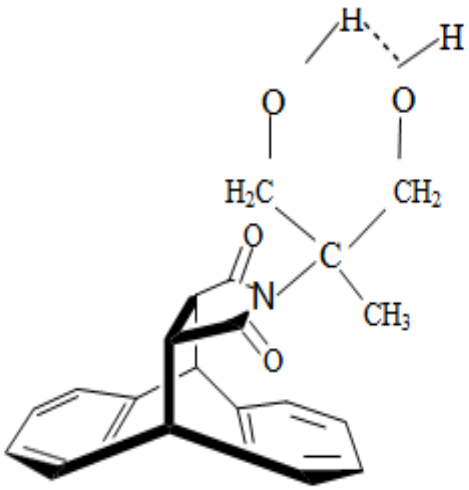

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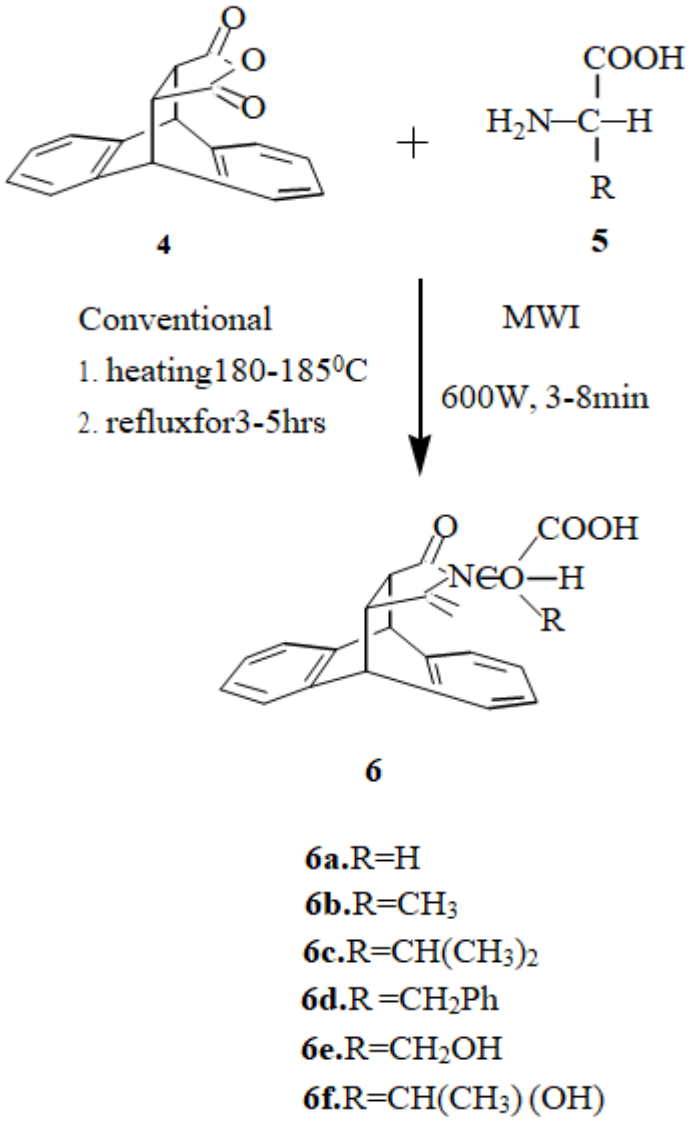
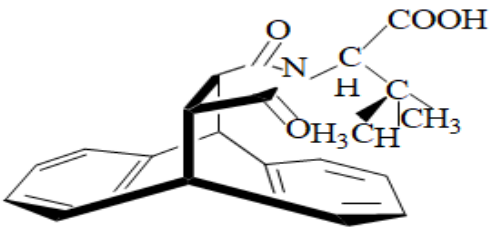


Scheme 1. Synthesis of N -2'- substituted -α, β- (9,10-dihydro anthracene -9, 10-diyl) succinimide -ethane-1'-oic acids

Table 1. Comparative data of Classical methods & MWI for the synthesis of N -2'- substituted -α, β- (9,10-dihydro anthracene -9, 10-diyl) succinimide -ethane-1'-oic acids (I-VI)

Compounds	Classical		MWI	
	Reaction time (hr)	Yield (%)	Reaction time (min)	Yield (%)
I	3	65	3	91
II	3	70	4	93
III	3	60	4	95
IV	4	62	6	84
V	5	67	8	80
VI	4	64	7	87



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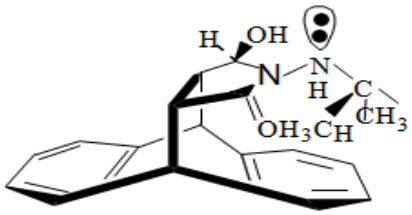

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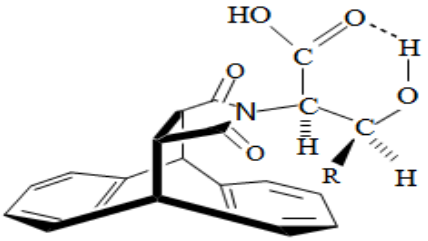

9

The spectral pattern shows that the two methyl of the isopropyl group are diastereotopic due to a chiral carbon[14] and the appearance of methyl protons at a highly shielded position suggests restricted rotation about Nsp^2-Csp^3 and Csp^3-Csp^3 bonds[15] and a preferred conformation having one of the methyl of isopropyl group held exactly over the cage phenyl ring. The spectrum of **6c** is very much similar to the N-alkyl resonances of **8** whose pyramidal geometry of the exocyclic nitrogen has been established by X-ray crystallography[16]. The magnetic equivalence of α , β– protons in **6c** eliminates the possibility of intramolecular hydrogen bonding between –COOH group and one of the carbonyls of the succinimidyl ring.

^{1}H NMR of compound **6d** is quite characteristic in demonstrating the conformational preference about Nsp^2-Csp^3 bond. The spectrum shows two multiplets at δ 2.49 (1H) and 3.19 (1H) for the benzyl methylinic protons, a double doublet at δ 4.61 (1H) for C*H*COOH proton and other normal resonances. The methylene protons are diastereotopic due to a chiral carbon and the appearance at a shielded position suggests restricted rotation and a preferred conformation having carboxylic group in *anti*-orientation. One of the highly shielded methylinic proton signal suggests it held over the cage phenyl ring, restricted rotation and a preferred conformation about Csp^3-Csp^3 bond.

^{1}H NMR spectrum of compound **6e** shows two multiplet at δ 2.92 (1H) and 3.26 (1H) for the C*H*$_2$OH protons, a multiplet at δ 4.42 (1H) for C*H*COOH proton with other normal resonances. The appearance of methylene protons at shielded position suggests restricted rotation and a preferred conformation having carboxylic group in *anti* orientation. Shielding pattern of methylene protons suggests restricted rotation and a preferred conformation about Csp^3-Csp^3 bond. The magnetic equivalence of α & β- protons in **6e** eliminates the possibility of intramolecular hydrogen bond of the –COOH group with one of the carbonyls of the succinimidyl ring. The hydroxyl group away from the cage may involve in hydrogen bonding with the carboxylic group[17] in *anti*-conformation. An intramolecular hydrogen bonded six membered cyclic structure orthogonal to the succinimidyl plane **(9)** may be proposed. The down field shift of –OH frequency (3486cm^{-1}) in IR and a down field shift of COOH in ^{1}HNMR is in agreement with the proposed structure.

^{1}H NMR spectrum of compound **6f** shows a doublet at δ 1.06 (3H, CH_3), a multiplet at δ 3.95 (1H, CHCOOH) along with other normal resonances. The appearance of methyl protons at shielded position suggests restricted rotation and a preferred conformation having carboxylic group in *anti*-orientation. Shielding signals for methylene proton and methyl protons suggest restricted rotation and a preferred conformation about Csp^3-Csp^3 bond. A similar structure **(9)** has been proposed for this compound also.

CONCLUSION

The present work describes simple, efficient and eco-friendly method for the synthesis of different α,β-(dihydroanthracene-9,10-diyl) succinimido-N-acetic acids **6a-f** employing microwave irradiation method, and compare with conventional heating method The structures of these compounds has been investigated through IR and proton NMR spectra. The carboxylic group at 2'-position is sufficient to restrict the rotation about N-C bond and remains in *anti* orientation without any intramolecular hydrogen bonding with one of the carbonyls of the succinimidyl ring. But in case of serine and threonine a six membered intramolecular hydrogen bonded puckered cyclic structure between –OH group and –C=O of –COOH in *anti*-conformation has been proposed.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as neat samples on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JOEL AL 300 FT-NMR (300 MHz) spectrometer in chloroform-d as a solvent using tetramethylsilane as an internal standard. The microwave irradiated reactions (MWI) were made in a domestic microwave oven model MS 1927C (LG). Analytical thin layer chromatography was performed using E. Merck silica gel G. Visualization was accomplished with UV light or iodine vapour. Analytical thin layer chromatography was performed using E. Merck silica gel G.

General procedure for synthesis of α, β-(9,10-Dihydroanthracene-9, 10-diyl)succinic anhydride (Anthracene-maleic anhydride adduct)

A. *Conventional method*. It was prepared according to the method of Vogel[18] by refluxing anthracene (20 g) with maleic anhydride (11 g) for 30 min. in dry oxane (200 ml) with frequent shaking. After cooling somewhat it was boiled with a pinch of animal charcoal. The hot solution was filtered and the solid which separated on cooling was dried in a vaccum desicator, (yield 75%), m.p. 261-63^0.

B. *Microwave method*[19]**.** A mixture of 2.0g of anthracene and 1.1g of maleic anhydride was ground thoroughly in a mortar and then transferred to a 100-ml beaker. After the addition of 1.0 ml of dioxane, the mixture was shaken gently. The beaker was covered with a watch glass and placed in the microwave oven. The irradiation was carried out for 2 minutes at 600W. The beaker was removed from the oven and allowed to cool at room temperature, the solid obtained was recrystallized from dioxane, yielded the adduct in 90%, m.p. 261-263^{0}C.
IR: ν_{max} 1870w, 1840w, 1790s cm^{-1}

Preparation of α, β-(9, 10-dihydroanthracene-9, 10 diyl) succinimido-N-acetic acids(6a-f)

A. *Conventional method***.** Compound **6a** was prepared by heating anthracene-maleic anhydride adduct with glycine, in equimolar proportion at 180-85^0 for half an hour. First the anhydride reacts with the amino acid and forms an acid amide, which was refluxed with an excess of acetic acid for 4 hrs. The excess of acid was distilled off and the pasty materials obtained were solidified on trituration with cold methanol and was recrystallized from ethanol. Compounds **6b-f** were prepared in the same way from alanine, valine, phenylalanine, serine and threonine respectively.

B. *Microwave method*[20]**.** A mixture of anthracene-maleic anhydride adduct and glycine was ground thoroughly in a mortar and transferred into a beaker, few drops of N, N- dimethyl formamide was added to this mixture. The reaction mixture was covered with a watch glass and was irradiated at 800 W for 3 minutes in the microwave oven. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature and then water was added. The solid product was collected by filtration and recrystallized from ethanol to give compound **6a**. Compounds **6b- f** were prepared in the same way from alanine, valine, phenylalanine, serine and threonine respectively.

(6a). IR: 2938b, 1780w, 1706s, 1620w; ^{1}H NMR δ: 3.32 (t, 2H, α and β-H), 3.81 (s, 2H, -C*H*$_2$), 4.82 (t, 2H, 9 and 10-H), 7.15-7.32 (m, 8H, aromatic protons), 10.50 (bs, 1H, -COO*H*, D_2O exchangeable); Anal. Calcd. for $C_{20}H_{15}NO_4$ C, 72.06; H, 4.54; Found C, 72.01; H, 4.46.

(6b). IR: 2986b, 1773w, 1735s, 1610w; ^{1}H NMR δ: 0.82 (d, 3H, C*H*$_3$), 3.05 (t, 2H, α and β-H), 4.06 (q, 1H, -C*H*COOH), 4.81 (t, 2H, 9 and 10-H), 7.15-7.60 (m, 8H, aromatic protons), 10.35 (bs, 1H, -COO*H*, D_2O exchangeable); Anal. Calcd. for $C_{21}H_{17}NO_4$ C, 72.61; H, 4.93; Found C, 72.57; H, 4.83.

(6c). IR: 2961b, 1777w, 1749s, 1691w; ^{1}H NMR δ: 0.24, 0.83 (dd, 6H, 1:1, CH(C*H*$_3$)$_2$), 2.24 (m, 1H, C*H*(CH$_3$)$_2$) , 3.30 (t, 2H, α and β-H), 4.14 (d, 1H, -C*H*COOH), 4.82 (t, 2H, 9 and 10-H), 7.15-7.60 (m, 8H, aromatic protons), 10.47 (bs, 1H, -COOH, D_2O exchangeable); Anal. Calcd. for $C_{23}H_{21}NO_4$ C, 73.58; H, 5.64; Found C, 73.55; H, 5.58.

(6d). IR: 2968b, 1774w, 1736s, 1620w, ^{1}H NMR δ: 2.49, 3.19 (m, 2H, , 1:1, C*H*$_2$Ph), 3.04 (t, 2H, α and β–H), 4.61 (t, 2H, 9- and 10- H), 4.74 (d, 1H, C*H*COOH), 7.01-7.34 (m, 13H, aromatic protons), 10.39 (bs, 1H, -COO*H*, D_2O exchangeable); Anal. Calcd. for $C_{27}H_{21}NO_4$ C, 76.58; H, 4.99; Found C, 76.47; H, 4.91.

(6e). IR: 3486b, 2925b, 1780w, 1704s, 1631w; ^{1}H NMR δ: 2.92, 3.26 (m, 2H, 1:1, -C*H*$_2$OH), 3.28 (t, 2H, α and β-H), δ 3.29 (bs, 1H. OH, D_2O exchangeable), 4.42 (dd, 1H, -C*H*COOH), 4.78 (t, 2H, 9 and 10-H), 7.13-7.39 (m, 8H, aromatic protons), 12.37 (bs, 1H, -COO*H*, D_2O exchangeable); Anal. Calcd. for $C_{21}H_{17}NO_5$ C, 69.41; H, 4.71; Found C, 69.34; H, 4.62.

(6f). IR: 3464b, 2977b, 1742w, 1708s; ^{1}H NMR δ: 1.06 (t, 3H, -CH_3), 3.21 (t, 2H, α and β-H), 3.84 (m, 1H, -C*H*[$OHCH_3$]), 3.95 (d, 1H, -C*H*COOH), 3.99 (bs, 1H, OH, D_2O exchangeable), 4.59 (t, 2H, 9 and 10-H), 7.10-7.29 (m, 8H, aromatic protons), 12.42 (bs, 1H, -COOH, D_2O exchangeable); Anal. Calcd. for $C_{22}H_{19}NO_5$ C, 70.02; H, 5.07; Found C, 70.00; H, 5.01.

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