

## Interesting Nuclear Magnetic Resonance studies of some N, N-bis(2-methoxyethyl) substituted Benzamides

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### Abstract

DEET (*N,N* Diethyl *m*-toluamide) and DEPA (Diethyl phenyl acetamide) are synthetic compounds and proven potent insecticide and repellent respectively. In the search of effective mosquito repellent, different derivatives of DEPA or substituted benzamides were synthesized and their NMR analysis was carried out at low temperature. Sterically Crowded Bis (2-methoxyethyl) substituted Benzamides possess low rotational barrier and are floppy at room temperature. Alkyl arms attached to nitrogen become magnetically nonequivalent even at low temperature. Di ortho Substitution in benzamides enhanced hindered internal rotation and resulted splitting in methylene proton signals. The effect of substitution in benzene ring, on the splitting of methylene proton NMR is very well explained and the complete NMR data of substituted benzamides is described in this study for reference purpose.

**Keywords:** Proton NMR; Carbon NMR; Heteronuclear Single Quantum Coherence Spectroscopy (HSQC); Rotamers.

### Synopsis

Herein, Synthesis, NMR characterization of nineteen substituted benzamides at low temperature and study of formation of rotamers are reported. The results suggest that molecules are floppy in nature and form number of rotamers at room temperature. The ortho substitution on

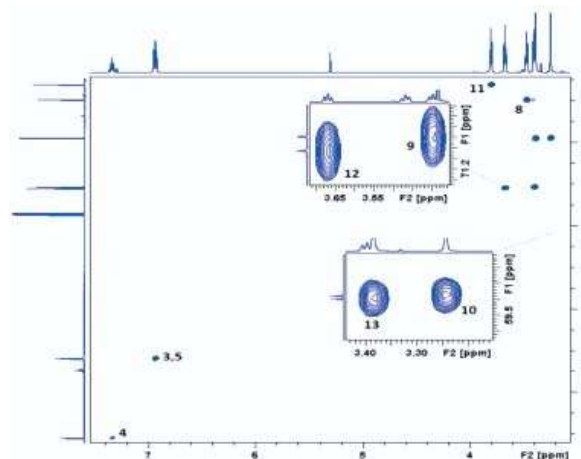
benzene ring possess restriction in rotation and reduce the formation of rotamers and causes clear splitting of methylene signals on NMR Chemical shift scale.

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## INTRODUCTION

Mosquitoes are the major source of vector borne diseases like Malaria, Dengue and Chikungunya etc. Globalization, frequent movement of travelers are one of the causes of these fast spreading diseases. In spite of lot of development in the field of insect or mosquito repellent, a mosquito free environment still a challenge for developing countries. Its complete eradication seems merely impossible and it has become a horrifying dream for scientific community.<sup>1</sup> Therefore continuous research towards the effective control of population of mosquitoes is a prime requirement of present world. Currently much emphasis is being given on the insect repellent research and taken it as an alternative of the insecticides. This is all because of the toxic effects of the latter on the human being and environment, and being a less toxic, former has potential to apply on skin and to prevent the stored products by repelling insects. In this way insect repellents effectively help to prevent and control the insect borne diseases. In recent past outbreaks of chikv fever<sup>2</sup>, yellow fever<sup>3</sup> and dengue<sup>4</sup> once again strongly fixed the requirement of mosquito repellents. So far, this field has not been explored fully, hence there is a need to develop new effective insects repellent which should be nontoxic and more environmental friendly. Various insect repellents have been discovered so far like Dimethyl phthalate (1929), Indalone (1937), military formulation 6-2-2, DEET (1953), DEPA (1990), n-methylneo decanamide (1998), 1-piperidine carboxylic acid, 2-(2-hydroxyethyl)-1-methylpropylester (Yap *et al.*, 2000). Among these DEET (N, N Diethyl m-toluamide) is a well known effective and versatile mosquito repellent. In this connection, DEPA (Diethyl phenyl acetamide)<sup>5, 6</sup> was reported as cockroach/multi insect repellent long back. Some naturally occurring sources are also reported as repellent to certain insects while they may act as insecticide for others. The natural compound 'Repel Lemon Eucalyptus' has been reported as more active in comparison to synthetic DEET, when the activity of different synthetic, chemical and herbal repellents were compared.<sup>7-9</sup> Most of the reported insect repellents are having benzamide linkages, so keeping this as target, number of benzamide derivatives were synthesized with different substitution in the benzene ring and their efficacy as mosquito repellent is under evaluation.

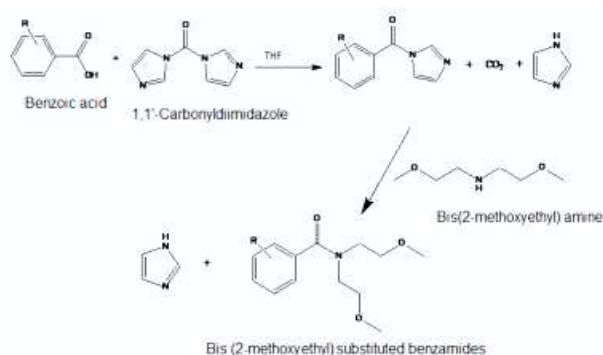
This paper describes the complete NMR structure elucidation of substituted benzamides, synthesized by simple and easy method. The <sup>1</sup>H and <sup>13</sup>C NMR

assignment of 19 benzamides, having single and double substitution in their aromatic ring presented very interesting changes in splitting pattern of methylene proton signals with substitution in benzene ring. To the best of our knowledge and literature surveyed, no unambiguous NMR assignment for both the nuclei <sup>1</sup>H and <sup>13</sup>C is available in the literature. These data obtained by a combination of 1D <sup>1</sup>H, <sup>13</sup>C and 2D <sup>1</sup>H-<sup>1</sup>H Correlation Spectroscopy (COSY), Heteronuclear single quantum coherence spectroscopy (HSQC), Heteronuclear Multiple Bond Correlation Spectroscopy (HMBC), Two Dimensional Nuclear Overhauser Effect Spectroscopy (2D-NOESY) NMR experiments.

## EXPERIMENTAL METHODS

### 2.1 Synthesis

All the substituted benzamides (1-19) were synthesized as shown in scheme 1. Substituted Benzoic acid was dissolved in THF solvent. After this 1, 1' -Carbonyldiimidazole reagent<sup>10</sup> was added to make the intermediate and kept for 10 to 15 minutes at RT. The evolved gas carbon dioxide during the reaction was removed by applying vacuum using rotavac. Bis(2-methoxyethyl) amine was added to the reaction mixture and kept for stirring for 10 to 15 minutes. Reaction was monitored by TLC and GC up to the completion. Reaction mixture was neutralized with 10% Sodium bicarbonate solution. The organic layer was separated out and THF was



Scheme 1: Synthesis of N,N-bis(2-methoxyethyl) substituted benzamides entries (1-19)

removed by vacuum to obtain the desired amide.

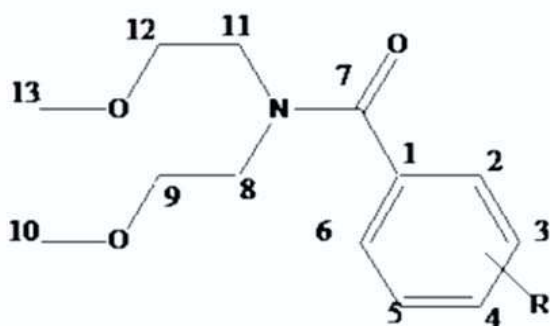
### 2.2 Materials and Physical measurements

The chemical shifts of <sup>1</sup>H and <sup>13</sup>C nuclei were referenced keeping spectrometer reference frequency at 0 ppm (SR=0). The synthetic Bis(2-methoxyethyl) substituted benzamide derivatives

1–19 were dissolved in CDCl<sub>3</sub> for NMR analysis. Spectra were scanned by taking 80 µl concentration of compounds in the 500 µl of solvent in 5 mm wilmad quartz NMR tube. All the NMR data were recorded on a Bruker Avance III 600 MHz spectrometer system (14 T; Ultra shield plus, Bruker Germany) at topspin 3.1 version and temperature range 288 to 293K using QNP cryoprobe. The <sup>1</sup>H NMR experiments were carried out by keeping relaxation delay 1 sec., spectral width 20ppm, and 90° pulse 5.25 µsec., pulse programme zg30, and fid resolution 0.366 Hz. For the <sup>13</sup>C NMR experiments the relaxation delay, spectral width and 90° pulse were kept 2s, 239 ppm, and 9.47 µsec. respectively. 2-dimensional experiments including COSY, HMBC were performed by acquiring 2048 data points for t<sub>2</sub> and 128 data points for t<sub>1</sub> while in HSQC t<sub>2</sub> and t<sub>1</sub> were adjusted at 1024 and 256 respectively. The long range coupling time for HMBC was 70 ms prior to Fourier transformation, zero filling of 2k and a sine squared bell window function were applied using topspin model 3.1. *Noesy* experiments were performed with 16 acquisitions for 256 increments in F1 and 1024 data points in F2. The spectral width in both dimensions was 10 ppm. Gradient based Phase sensitive noesys pulse program was used with mixing time 80 msec to 300 ms, 2s relaxation delay at temp 290° K.

## RESULTS AND DISCUSSION

Amides have been studied considerably, more effectively, by the use of Nuclear Magnetic Resonance Spectroscopy. It was realized that unambiguous <sup>1</sup>H and <sup>13</sup>C NMR assignment should be available in the literature for substituted benzamides, synthesized in laboratory. The structure of all the compounds and numbering used in proton and carbon nuclei assignment are shown in scheme 2. Resonance assignment of <sup>1</sup>H and <sup>13</sup>C is done based on the multiplicity pattern, δ and J, which is further confirmed by 2D NMR experiments like COSY, HSQC, HMBC and NOESY.



| Entry | R*     | Entry | R*                |
|-------|--------|-------|-------------------|
| 1     | 0      | 11    | 2,6-OMe           |
| 2     | 4-Cl   | 12    | 3,4-OMe           |
| 3     | 2-OMe  | 13    | 2,6-F             |
| 4     | 3-OMe  | 14    | 2,3-F             |
| 5     | 4-OMe  | 15    | 2,4-F             |
| 6     | 2-F    | 16    | 2,5-F             |
| 7     | 4-F    | 17    | 3,5-F             |
| 8     | 2,6-Cl | 18    | 2-NO <sub>2</sub> |
| 9     | 3,5-Cl | 19    | 4-NO <sub>2</sub> |
| 10    | 3,4-Cl |       |                   |

R\* = Substitution on Benzene Ring

Scheme 2. Structure of N,N-bis(2-methoxyethyl) Substituted Benzamides (1-19).

### Proton NMR

The full characterization of benzamides containing chemical shift (δ) of <sup>1</sup>H nucleus is shown in the Table 1 and coupling constant (J) of <sup>1</sup>H nucleus is given in Supplementary information. The <sup>1</sup>H NMR spectra of entries 1-19 showed clearly resolved two distinct regions, temperature independent aromatic region and temperature dependent aliphatic region with A<sub>2</sub>B<sub>2</sub>C<sub>2</sub>D<sub>2</sub> spin system for methylene protons. Entries 3/18 presented A<sub>2</sub>BB'CC'D<sub>2</sub> / A<sub>2</sub>B<sub>2</sub>CC'DD' systems for alkyl protons respectively. As far as the proton NMR spectrum of precursor Bis 2-methoxyethyl amine is concerned, this exhibited single peak for two methoxy groups at δ 3.36 ppm, while this signal further segregated into two for protons of both the methoxy groups after the formation of amide, resulting shifting of one signal towards the high field and other shifts at low field. In the similar manner, both the methylene protons attached to nitrogen and oxygen exhibited same δ value at 2.80 ppm and 3.50 ppm for protons of N-(CH<sub>2</sub>)<sub>2</sub> and (O-CH<sub>2</sub>)<sub>2</sub> groups respectively in amine, but these appeared as four well resolved signals, representing four separate methylene groups of aliphatic chain, in benzamides (Table 1, Fig. 2). This confers that protons of all four methylene groups of both the aliphatic chains attached to nitrogen and oxygen become magnetically different after formation of benzamides. In some cases this separation was observed at low temperature. This is well documented that internal rotation around single bond of amide (CO-N) is some what restricted due to partial double bond character of bond and this rotation is affected by various substitutions of amide nitrogen and carbon. The internal rotation around the bond normally occur via two transition states; anti TS<sub>1</sub> or syn TS<sub>2</sub> and causes rotamers formation in amides.<sup>11-23</sup>

**Table 1A:** <sup>1</sup>H NMR Chemical shifts of N,N-bis (2-methoxyethyl) Substituted Benzamides for entries 1 to 19 in ppm. (for 2H to 6H Protons)

| Entry | R          | 2H      | 3H       | 4H       | 5H      | 6H      |
|-------|------------|---------|----------|----------|---------|---------|
| 1     | -          | 7.41 m  | 7.38 m   | 7.39 m   | 7.38 m  | 7.41 m  |
| 2     | -          | 7.40 d  | 7.39 d   | -        | 7.39    | 7.40    |
| 3     | 3.83 s     | -       | 6.91 dd  | 7.33dt   | 6.98 dt | 7.22 dd |
| 4     | 3.84 s     | 6.98 t  | -        | 6.93 ddd | 7.31 t  | 6.99 td |
| 5     | 3.85       | 7.42 d  | 6.92 d   | -        | 6.92 d  | 7.42 d  |
| 6     | -          |         | 7.06 ddd | 7.32 dt  | 7.15 dt | 7.34    |
| 7     | -          | 7.42 dd | 7.04 t   | -        | 7.04 t  | 7.42 dd |
| 8     | -          |         | 7.33 d   | 7.26 dd  | 7.33 d  | -       |
| 9     | -          | 7.34 d  | -        | 7.37 t   | -       | 7.34 d  |
| 10    | -          | 7.58 d  | -        | -        | 7.48 d  | 7.31 dd |
| 11    | 3.82       | -       | 6.58 d   | 7.28 t   | 6.58 d  | -       |
| 12    | 3.87, 3.88 | 7.06 d  | -        | -        | 6.84 d  | 7.03 dd |
| 13    | -          | -       | 6.93 dd  | 7.34 tt  | 6.93 dd | -       |
| 14    | -          | -       | -        | 7.18 dtd | 7.12 dt | 7.11m   |
| 15    | -          | -       | 6.83 dt  | -        | 6.90 dt | 7.33 dt |
| 16    | -          | -       | 7.05 m   | 7.06 m   | -       | 7.07 m  |
| 17    | -          | 7.00 m  | -        | 6.85 tt  | -       | 7.01 m  |
| 18    | -          | -       | 8.22 dd  | 7.57 dt  | 7.72 dt | 7.47 dd |
| 19    | -          | 7.58 d  | 8.21 d   | -        | 8.21 d  | 7.58 d  |

S: singlet, m: multiplet, t: triplet, td: triplet of doublet, d: doublet, dd: doublet of doublet, ddd: doublet of doublet of doublet, tt: triplet of triplet, dt: doublet of triplet, dtd: doublet of triplet of doublet.

**Table 1B:** <sup>1</sup>H NMR Chemical shifts of N,N-bis(2-methoxyethyl) Substituted Benzamides for entries 1 to 19 in ppm. (for 8H to 13H Protons)

| Entry | 8H      | 9H           | 10H     | 11H          | 12H          | 13H     |
|-------|---------|--------------|---------|--------------|--------------|---------|
| 1     | 3.54,bs | 3.44,bs      | 3.28,s  | 3.78,bs      | 3.67,bs      | 3.41,s  |
| 2     | 3.53,bs | 3.45,bs      | 3.31,s  | 3.76,bs      | 3.68,bs      | 3.40,s  |
| 3     | 3.40,bs | 3.39,3.35,bs | 3.23,s  | 3.74,3.82,bs | 3.68,t       | 3.41,s  |
| 4     | 3.55,bt | 3.46,bt      | 3.30,s  | 3.77,bt      | 3.69,bt      | 3.41,s  |
| 5^    | 3.59,bs | 3.47,bs      | 3.31,bs | 3.76,bs      | 3.68,bs      | 3.40,bs |
| 6     | 3.44,t  | 3.36,t       | 3.20,s  | 3.78,bs      | 3.64,t       | 3.35,s  |
| 7     | 3.49,bs | 3.41,bs      | 3.24,s  | 3.71,bs      | 3.63,bs      | 3.34,s  |
| 8     | 3.43,t  | 3.47,t       | 3.29,s  | 3.85,t       | 3.73,t       | 3.40,s  |
| 9     | 3.51,bt | 3.45,bt      | 3.30,s  | 3.74,bt      | 3.66,bt      | 3.39,s  |
| 10    | 3.52,s  | 3.45,s       | 3.30,s  | 3.74,s       | 3.66,s       | 3.39,s  |
| 11    | 3.39,t  | 3.38,t       | 3.25,s  | 3.80,t       | 3.70,t       | 3.42,s  |
| 12^   | 3.58,bs | 3.47,bs      | 3.29,bs | 3.71,bs      | 3.65,bs      | 3.36,bs |
| 13    | 3.47,t  | 3.40,t       | 3.24,s  | 3.78,t       | 3.67,t       | 3.38,s  |
| 14    | 3.46,t  | 3.40,t       | 3.23,s  | 3.77,bs      | 3.66,t       | 3.38,s  |
| 15    | 3.44,t  | 3.37,t       | 3.22,s  | 3.75,bs      | 3.62,t       | 3.36,s  |
| 16    | 3.49,t  | 3.42,t       | 3.27,s  | 3.78,bs      | 3.67,t       | 3.39,s  |
| 17    | 3.52bs  | 3.46,bs      | 3.31,s  | 3.75,bs      | 3.67,bs      | 3.39,s  |
| 18    | 3.41,bs | 3.42,bs      | 3.26,s  | 3.96,3.63,bs | 3.74,3.82,bs | 3.44,s  |
| 19    | 3.44,bt | 3.39,bt      | 3.24,s  | 3.73,bt      | 3.64,bt      | 3.35,s  |

bs=broad signal, bt=broad triplet, ^=broad merged six single peaks with joined base at 10°C t=triplet.

Plethora of papers witnessed that the barrier of rotation is governed by various factors like solvent polarity,<sup>24-30</sup> temp,<sup>20,31-33</sup> molecular phases,<sup>20,26</sup> substitution on carbonyl Carbon,<sup>20,34-39</sup> amide nitrogen and carbene of benzene ring attached to carbonyl.<sup>24,33</sup> Reports deduce that to attain the optimum possible stable ground state geometry, amides possess twist around the C<sub>ar</sub>-C(O),<sup>40</sup> C(O)-N<sup>41</sup> and N-CR<sup>40,41</sup> bonds. The steric repulsion between alkyl substitutes of amide nitrogen further destabilizes molecule and lead to frequent changes in alkyl chain geometry with respect to the benzene ring plane. In our case N, N-dialkyl benzamides are sterically crowded, having long alkyl chain and bulky substitutions on benzene ring, hence these molecules always try to adopt the twisted confirmation (Fig. 1a) by twisting C<sub>ar</sub>-CO and N-CR bond axis.<sup>42</sup> This is clearly visible by changing splitting pattern of proton signals of methylene groups with placement of substitution in benzene ring at low temperature.

In all benzamides, entries 1 to 19, proton signals of two methylene groups attached to nitrogen (N-(CH<sub>2</sub>)<sub>2</sub>) (H-8 and H-11,  $\delta$  range is 3.38-3.59 ppm and 3.63-3.96 ppm respectively) are more deshielded in comparison to the proton signals of their respective adjacent partners, two methylene groups attached to oxygen (O-CH<sub>2</sub>)<sub>2</sub> (H-9, and H-12,  $\delta$  range is 3.35-3.47 ppm and 3.62-3.82 ppm respectively) and appeared at low field always

(Table 1). This low field shifting of N-(CH<sub>2</sub>)<sub>2</sub> group may be attributed to the carbonyl group adjacent to Nitrogen.

### Cis-trans

Moreover within the two N-CH<sub>2</sub> groups, H-8 protons are always shielded by 0.13ppm to 0.42 ppm than the H-11 protons in all the entries (Scheme 2, Table 1). The available literature reveals that protons anti to carbonyl oxygen are always shielded in benzamides.<sup>34-38, 43,44</sup> The literature values of protons of different substituted group of benzamides are given in supplementary information. Our observation is congruent with the aforementioned findings of literature. H-8, trans to carbonyl group is shielded than H-11 [Cis to C(O)] for all the entries. The magnitude of shielding of H-8 protons is high for mono and di ortho substituted benzamides than other entries, which is 0.42 ppm (entries 8 & 11), 0.39 ppm (entries 18 & 3), 0.34ppm (entry 6) and 0.30 ppm (entries 13 to 16). (Table 1). The preponderance of the conformer in solution is further suggested by 2D NOESY experiment at 20°C in CDCl<sub>3</sub> solvent. Which established that H-8 and H-9 methylene protons remain away from carbonyl group and hence near to protons of benzene ring in space. The 3D spatial hydrogen interaction provided by 2D NOESY is shown in Fig. 1b, exhibiting correlation between H-8/H-9 and H-6/ H-3 protons respectively.

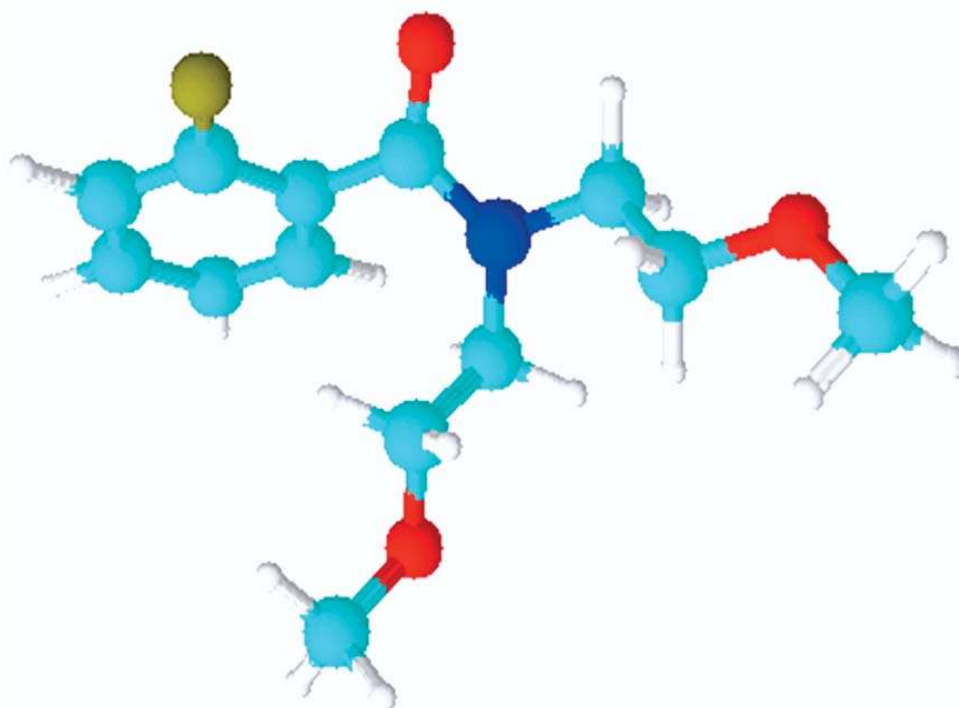


Fig. 1a: 3D Structure of 2-fluoro-N,N-bis (2-methoxyethyl)benzamide (entry-6) showing connectivity of protons in Space

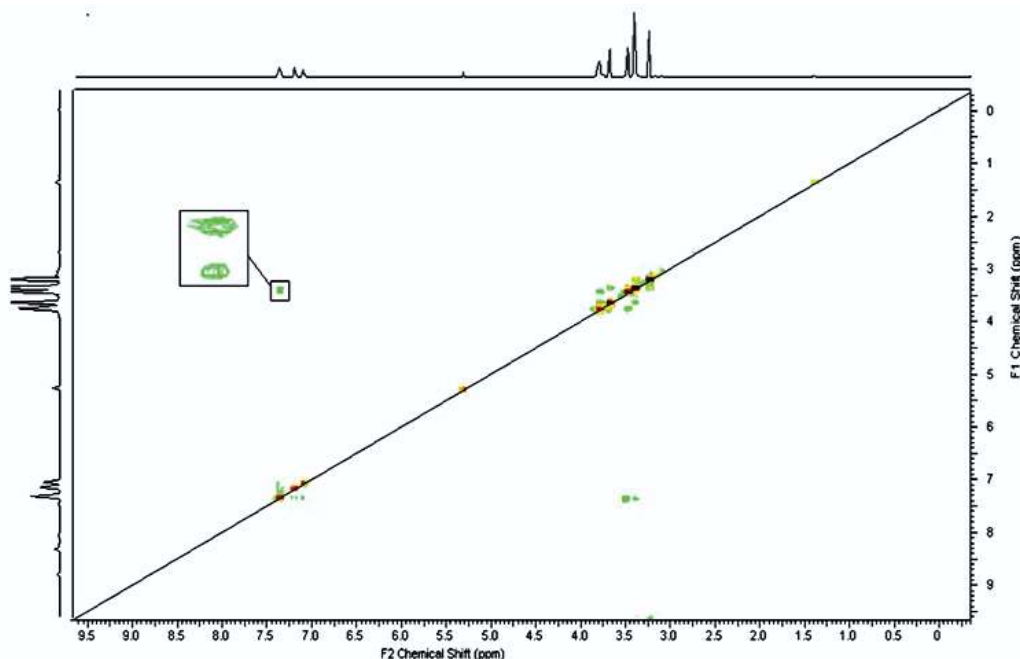


Fig. 1b:  $^1\text{H}$ - $^1\text{H}$ , 2D-NOESY Spectrum of Benzamide entry 6 Showing Connectivity of H8/H9 with H-6.

### Chemical shift sequence of aliphatic chain

Now discussion is made on the  $\delta$  sequence pattern of methylene and methyl signals on the chemical shift scale, the sequence in which these are appeared at NMR Chemical shift scale. In general proton  $\delta$  of most of the benzamides (entries 1, 2, 4, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16, 17, and 19) methylene and methyl protons appeared in the order  $\text{NCH}_2$  (H-11),  $\text{OCH}_2$  (H-12),  $\text{NCH}_2$  (H-8),  $\text{OCH}_2$  (H-9),  $\text{OCH}_3$  (H-13) and  $\text{OCH}_3$  (H-10) starting from low field to high field. Under lined fonts are shown to differentiate one aliphatic chain from other in benzamides. The chemical shift sequence of protons is clearly demonstrated in the graph (Fig. 2), where  $\delta$  values of methylene and methyl protons are plotted against their respective entries. This clearly demonstrated the  $\delta$  trend, in which H-8, H-9 and H-10 of one alkyl chain are more shielded than H-11, H-12 and H-13 of another alkyl chain, when compared vis a vis with in molecule (Graph, Fig. 2). This distinctly shows that one alkyl arm, cis to the carbonyl oxygen is completely deshielded than the other arm, trans to carbonyl. Di ortho substituted chloro benzamide entry 8, follows slight variation in chemical shift sequence, which is H-11, H-12, H-9, H-8, H-13 and H-10 towards high field, where H-8 ( $\delta$  3.43 ppm) is slightly shielded than H-9 ( $\delta$  3.47 ppm) (Table 1). Entries 3, 11, 18 showed different patterns and exhibited complete true shielding of one arm (H-8, H-9, H-10) than other (H-11, H-12, H-13) irrespective of methyl and methylene groups. H-8 (3.40 ppm), H-9 (3.39 ppm),

H-10 (3.23ppm) protons of benzamide entry 3 are shielded than their respective H-11, ( $\delta$  3.77ppm) H-12, ( $\delta$  3.68 ppm) and H-13 ( $\delta$  3.41 ppm) protons. Similarly H-8 (3.39ppm), H-9 (3.38 ppm), H-10 (3.25ppm) of benzamide entry 11 are more shielded than their respective H-11, ( $\delta$  3.80ppm) H-12, ( $\delta$  3.70ppm) and H-13 (3.42 ppm) protons. Entry 18 follows  $\delta$  sequence pattern H-11, H-12, H-13, H-9, H-8, and H-10 towards high field, where H-8 ( $\delta$  3.41ppm) protons are slightly shielded than H-9 ( $\delta$  3.42 ppm) by 0.01 ppm. These all molecules are having bulky substitution at ortho position that is methoxy (entries 3, 11), chloro (entry 8) and nitro (entry 18) as mono and di substitution. Hence presence of the bulky substitution at ortho position brings variation in chemical shift sequence of methylene and methyl protons of aliphatic chain.

### Splitting of Proton Signals

The broadening and splitting of the proton signals of methylene group is dependent on the rotation around the  $\text{C}_{\text{ar}}-\text{C}(\text{O})$ ,  $\text{C}(\text{O})-\text{N}$ , and  $\text{N}-\text{C}_{\text{alkyl}}$  bonds and substitutions in amide benzamides. All the benzamides showed broadening/hump for the proton signals at room temperature therefore NMR spectra were recorded at low temperature ranging from  $20^\circ\text{C}$  to  $10^\circ\text{C}$  for all the compounds and resulted splitting and separation of signals for methylene protons of benzamides. Ortho substituted benzamides exhibited clear splitting/distorted triplet for methylene proton signals which is generated due to hindered rotation, while

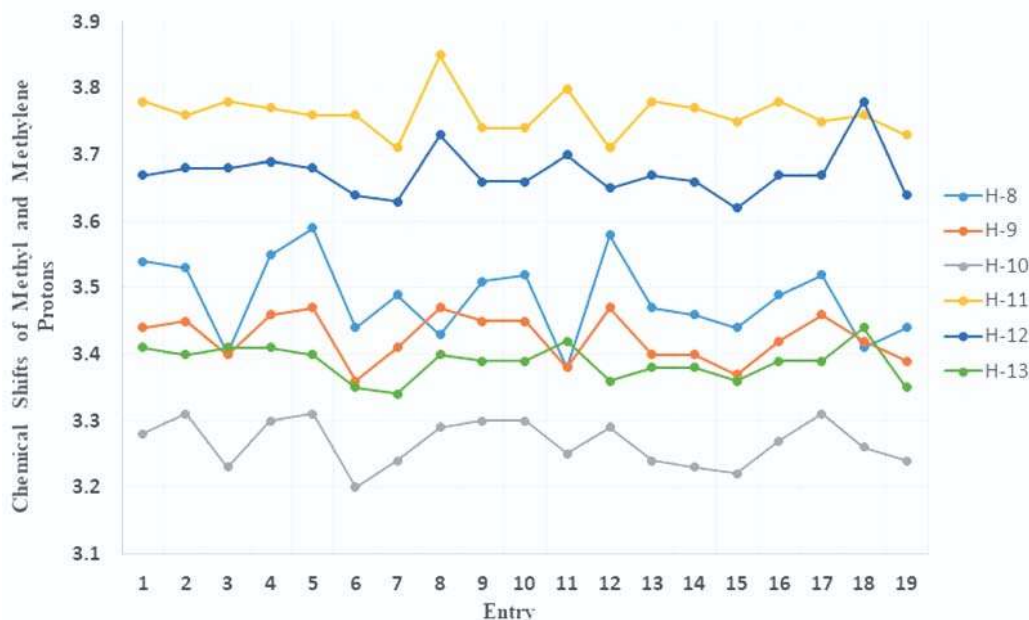


Fig. 2: Graph depicting the chemical shift trend in methyl and methylene protons in entries 1 to 19

for other para/meta substituted molecules, unsplit singlets were obtained even at 10°C for methylene protons. This shows that barrier of rotation for ortho substituted benzamides is higher than the para/meta substituted benzamides in the temperature range 15°C to 20°C, which leads to the more rotamers formation for para/meta substituted benzamides and resulted broad humps/singlets for methylene proton signals on NMR Scale. On the basis of available literature data (given as supplementary information) on free energies of activation of the amide bond rotation around (CO)-N bond for the amides/benzamides,<sup>20,34-48</sup> it can be concluded that at RT the barrier of rotation decreases with the increasing size of alkyl groups on nitrogen and carbonyl carbon of amide functionality<sup>20,49</sup> which leads to destabilization at ground state, intern facilitate the rotamers formation fast, and causes broadening of signals also. But on increasing the bulkiness at the ortho position of phenyl ring the barrier of rotation is increased around the amide bond and rotation becomes restricted which leads to the stabilization and facilitate the clear splitting. Therefore benzamides with di ortho, mono ortho, and no ortho substitution showed clear triplets (due to restricted rotation), incomplete splitting pattern (due to intermediate rotation), and unsplit signals (due to fast rotamer formation) for methylene proton signals respectively (Fig. 3). The electron with drawing/donating nature of substituents and their position on benzene ring influence the splitting of methylene proton signals

also. The <sup>1</sup>H spectra showing variation in NMR signals with temperature is given in supplementary information. After examining the proton spectra of all compounds meticulously it was concluded that Di ortho substituted benzamides entries 8, 11 and 13 presented very clear splitting pattern with little roofing, for protons of all four CH<sub>2</sub> groups. The proton spectra of mono ortho fluorine substituted benzamides entries 6, 14, 15 and 16 appeared as 1+3 pattern (one unsplit signal + 3 split signals) i.e. one CH<sub>2</sub> (H-11) as broad signal while other three CH<sub>2</sub> (H-8, H-9, H-12) appeared as distorted triplet as shown in the fig. 3. Molecule 3 with strong electron donating methoxy group at ortho position exhibited 3+1 (unsplit/ split signals) pattern. Splitting was observed only for H-12 (3.68 ppm), while both the geminal protons of H-9 (3.393, 3.353 ppm) and H-11 (3.74, 3.82 ppm) exhibited two separate δ with broad signals. Mono ortho nitro substituted benzamide 18 presented broad resonances for all the methylene protons and separation in resonances of geminal protons of H-11 and H-12 appeared at δ 3.968, 3.637 ppm and 3.74, 3.82 ppm respectively. Rest of the benzamides 1, 2, 4, 5, 7, 9, 10, 12, 17 and 19 showed unsplit broad singlets for all protons of methylene groups. Hence when rotamers formation fast and slow on NMR chemical shift scale the broadening and splitting of signals occur respectively. The three bond <sup>1</sup>H-<sup>1</sup>H coupling for methylene protons was found 5.5 Hz in distorted triplets of benzamides. Similar type coupling magnitude in X-CH<sub>2</sub>-CH<sub>2</sub>-Y type systems is reported.<sup>50</sup>

After overlapping the aromatic regions of para substituted benzamides 2 and 5 (given as supplementary information) it was concluded that

chlorine exerts more deshielding on ring protons H-3/5, than fluorine. (Table 1).

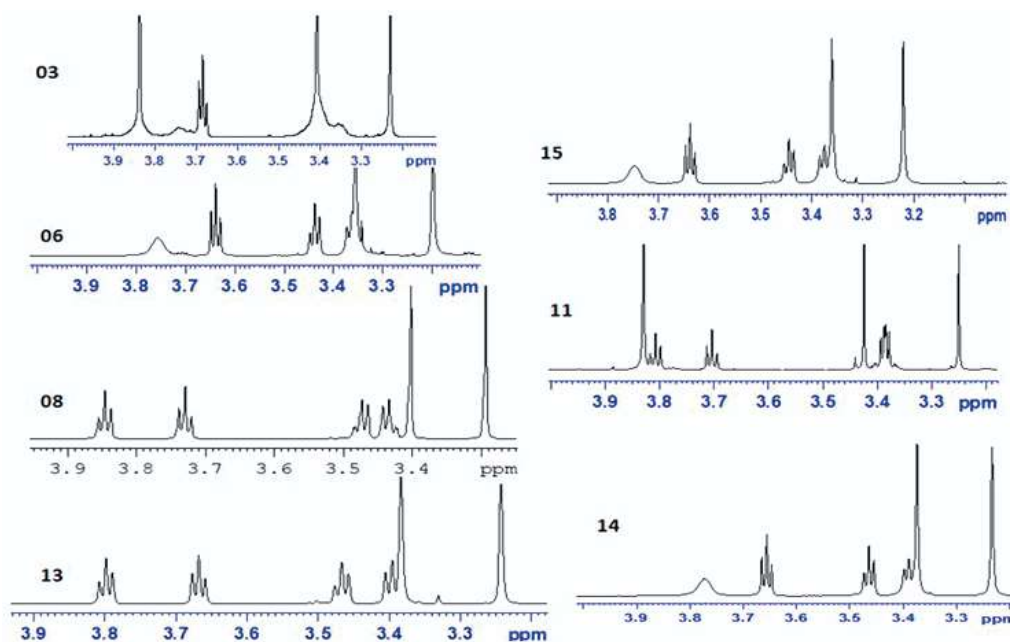


Fig. 3: Expanded  $^1\text{H}$  NMR Spectra of *N,N*-bis(2-methoxyethyl) substituted benzamides for entries 3,6,8,11,13,14,15, in  $\text{CDCl}_3$  showing splitting patterns of methylene protons in the chemical shift range 3 to 4 ppm.

#### 42D-COSY

The three bond proton connectivity for protons of  $\text{N-CH}_2$  and  $\text{O-CH}_2$  is confirmed by 2D- $^1\text{H}$ - $^1\text{H}$  COSY (Homonuclear Correlation Spectroscopy) NMR

experiment (Fig. 4), which deduced that adjacent proton signals are of the adjacent methylene groups and coupling with each other. Protons H-11/H-8 are coupling with H-12/H-9 protons respectively and showing correlation contours.

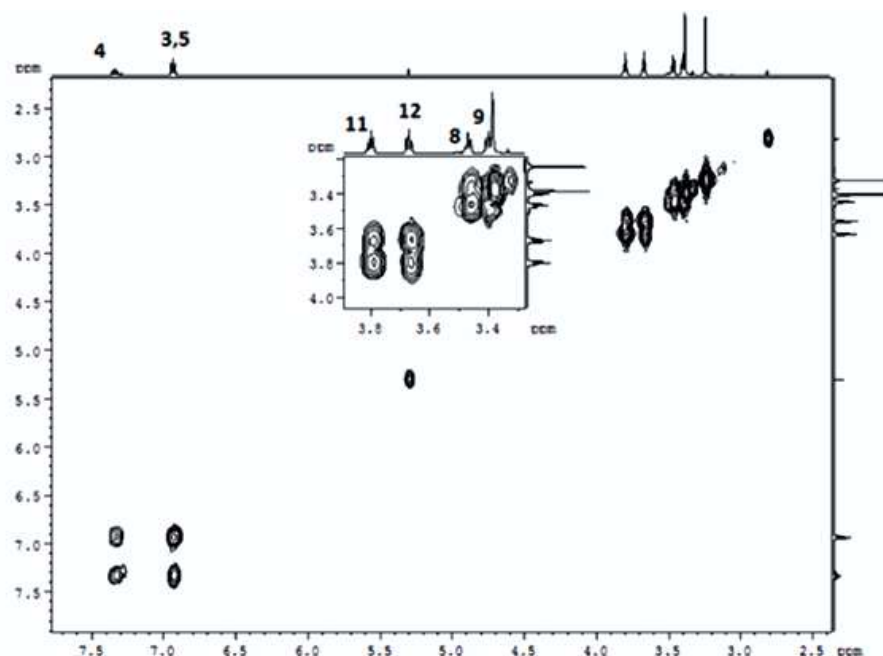


Fig. 4:  $^1\text{H}$ - $^1\text{H}$  COSY Spectrum of entry 13 showing three bond Connectivity for adjacent protons of methylene groups in  $\text{CDCl}_3$

### Carbon NMR

The full characterization of compounds containing chemical shift ( $\delta$ ) of  $^{13}\text{C}\{^1\text{H}\}$  nucleus is shown in the Table 2 and coupling constant ( $J$ ) is given in 2b table. The interpretation of  $^{13}\text{C}$  NMR signals of *N,N*-Bis-(2-methoxyethyl) substituted benzamide entries 1 to 19 was done with the aid of 2D heteronuclear correlation (HSQC) experiment, which allowed the unambiguous assignments of all protonated carbon resonances. For instance the carbon resonances of all the methoxy groups can easily be assigned in the range 55.34–55.90 ppm, as well as the aromatic and aliphatic carbon resonances at 103.95–130.86 ppm and 44.98–71.30 ppm respectively (Table 2). Chemical shift of carbonyl carbon of all the compounds shifted high field in comparison to carbonyl carbon of unsubstituted benzamide entry 1 (Table 2). This chemical shift varies from 0.05 to 10.13 ppm, in all benzamides, while this variation is 3 to 10 ppm in mono and di ortho substituted compounds. Further high range 5 to 10 ppm shift belongs to only halo substitution. The maximum 10 ppm and minimum 0.05 ppm shift was obtained for entries 13 (ortho di fluoro) and 4 (para-methoxy) respectively (Table 2). Hence it can be concluded that Carbonyl carbon is more shielded in weakly ring deactivating halo ortho substituted benzamides in comparison to the strong electron donating/ with drawing substituents, irrespective

to their position in benzene ring (o/p/m). Proton and carbon single bond correlation is elaborated with the help of HSQC (Heteronuclear single quantum correlation experiment) experiment. Aliphatic carbon resonances C-8 to C-13 ( $\delta$  range 44.98 ppm–71.30 ppm) presented correlations with H-8 to H-13 Proton resonances ( $\delta$  range 3.968 ppm–3.20 ppm). This helped in sequencing the resonances of protons and carbons on chemical shift scale. To understand the single bond correlation of proton with carbon, HSQC spectrum of benzamide 13 is shown in Figure 5 as example, which emphasizes the correlation of C-10,  $\delta$  58.84 ppm / C-13,  $\delta$  58.94 ppm with H-10,  $\delta$  3.24 ppm / H-13,  $\delta$  3.38 ppm respectively. Simultaneously this established the other correlations also like C-11,  $\delta$  45.97 ppm / C-12,  $\delta$  70.85 ppm with H-11  $\delta$  3.78 ppm / H-12,  $\delta$  3.67 ppm and C-8,  $\delta$  49.58 ppm / C-9,  $\delta$  70.58 ppm with H-8,  $\delta$  3.47 ppm / H-9,  $\delta$  3.40 ppm. Aromatic protons H-3/5  $\delta$  6.93 ppm, H-4,  $\delta$  7.34 ppm correlated with C-3/5,  $\delta$  111.70 ppm, and C-4,  $\delta$  130.86 ppm respectively. (Figure 5) The NMR spectra of various ortho, meta, para, diortho, and dimeta, placed methoxy in benzamides entries 3, 4, 5, 11, and 12 showed singlet in the  $\delta$  range 3.82–3.88 ppm and 55.34–55.90 ppm for proton and carbon resonances respectively. This assignment is done through single bond correlation of carbon and protons in HSQC NMR experiment.

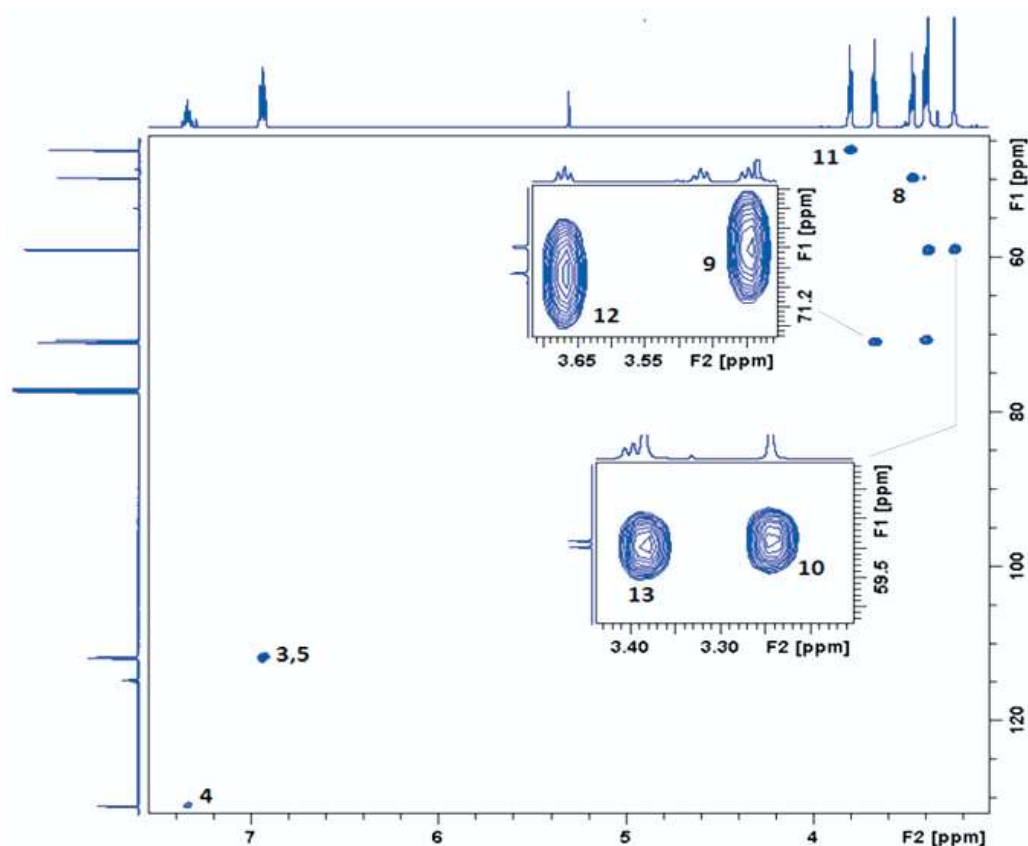
**Table 2:**  $^{13}\text{C}\{^1\text{H}\}$  NMR Chemical Shifts of *N,N*-bis(2-methoxyethyl) Substituted Benzamides for Entries 1 to 19 (1C to 7C).

| Entry | 1C       | 2C       | 3C       | 4C       | 5C       | 6C       | 7C       |
|-------|----------|----------|----------|----------|----------|----------|----------|
| 1.    | 136.79   | 126.86   | 128.37   | 129.22   | 128.37   | 126.86   | 172.31   |
| 2.    | 135.17   | 128.59   | 128.57   | 135.25   | 128.57   | 128.59   | 171.29   |
| 3.    | 126.35   | 155.04   | 110.95   | 130.18   | 120.80   | 127.92   | 169.82   |
| 4.    | 137.93   | 112.23   | 159.43   | 115.23   | 129.53   | 119.03   | 172.05   |
| 5.    | 132.29   | 128.84   | 113.61   | 160.32   | 113.61   | 128.85   | 172.27   |
| 6.    | 124.90d  | 157.94d  | 115.76d  | 128.87d  | 124.42d  | 130.86d  | 167.21   |
| 7.    | 132.76d  | 129.24d  | 115.32d  | 163.02d  | 115.32d  | 129.24d  | 171.40   |
| 8.    | 135.27   | 131.88   | 128.14   | 130.35   | 128.19   | 131.88   | 165.55   |
| 9.    | 139.26   | 125.74   | 135.06   | 129.31   | 135.06   | 125.74   | 169.53   |
| 10.   | 136.50   | 129.43   | 132.63   | 133.49   | 130.43   | 126.59   | 169.94   |
| 11.   | 115.03   | 156.45   | 103.95   | 130.24   | 103.95   | 156.45   | 167.27   |
| 12.   | 128.91   | 110.86   | 148.61   | 149.81   | 110.45   | 120.03   | 172.09   |
| 13.   | 114.57t  | 158.79dd | 111.70dd | 130.86t  | 111.70dd | 158.79dd | 162.18   |
| 14.   | 127.08dd | 150.31dd | 146.37dd | 117.93dd | 124.78dd | 123.61dd | 165.92dd |
| 15.   | 121.22dd | 158.40dd | 104.17t  | 163.20dd | 111.80dd | 130.20dd | 166.46   |
| 16.   | 126.11dd | 158.49dd | 117.08dd | 117.39dd | 153.99dd | 115.72dd | 165.87   |
| 17.   | 139.69t  | 110.52dd | 162.70dd | 104.71t  | 162.70dd | 110.52dd | 169.64t  |
| 18.   | 133.05   | 145.16   | 124.66   | 129.64   | 134.20   | 128.95   | 168.28   |
| 19.   | 143.03   | 128.27   | 123.59   | 147.92   | 123.59   | 128.27   | 170.14   |

d=doublet, dd=doublet of doublet, t=triplet, Other Carbon signals, where it is not mentioned, appeared as single peak.

**Table 3** Continued  $^{13}\text{C}\{^1\text{H}\}$  NMR Chemical Shifts of *N,N*-bis(2-methoxyethyl) for Entries 1 to 19. (8C to 13C)

| Entry | 8C    | 9C    | 10C   | 11C   | 12C   | 13C   | OCH3  |
|-------|-------|-------|-------|-------|-------|-------|-------|
| 1.    | 49.68 | 70.63 | 58.90 | 45.41 | 70.97 | 58.90 | -     |
| 2.    | 49.81 | 70.31 | 58.90 | 45.37 | 70.90 | 58.90 | -     |
| 3.    | 49.13 | 71.05 | 58.76 | 45.60 | 70.97 | 58.94 | 55.52 |
| 4.    | 49.68 | 70.63 | 58.91 | 45.37 | 70.93 | 58.92 | 55.34 |
| 5.    | 49.89 | 70.64 | 58.94 | 45.53 | 70.90 | 58.96 | 55.34 |
| 6.    | 49.32 | 70.52 | 58.75 | 45.47 | 70.81 | 58.90 | -     |
| 7.    | 49.77 | 70.22 | 58.84 | 45.29 | 70.80 | 58.86 | -     |
| 8.    | 49.32 | 70.75 | 58.92 | 45.92 | 70.69 | 58.89 | -     |
| 9.    | 49.90 | 69.87 | 58.93 | 45.32 | 70.82 | 59.07 | -     |
| 10.   | 49.85 | 69.90 | 58.94 | 45.22 | 70.81 | 58.94 | -     |
| 11.   | 49.13 | 71.07 | 58.77 | 45.97 | 71.30 | 58.89 | 55.79 |
| 12.   | 49.91 | 70.66 | 58.88 | 45.42 | 70.94 | 58.88 | 55.90 |
| 13.   | 49.58 | 70.58 | 58.84 | 45.97 | 70.85 | 58.94 | -     |
| 14.   | 49.46 | 70.29 | 58.80 | 45.48 | 70.77 | 58.92 | -     |
| 15.   | 49.56 | 70.28 | 58.88 | 45.45 | 70.80 | 58.83 | -     |
| 16.   | 49.44 | 70.26 | 58.84 | 45.46 | 70.81 | 58.96 | -     |
| 17.   | 49.70 | 69.89 | 58.94 | 45.20 | 70.77 | 58.95 | -     |
| 18.   | 49.56 | 69.92 | 58.87 | 45.26 | 70.48 | 58.98 | -     |
| 19.   | 49.70 | 69.62 | 58.86 | 44.98 | 70.69 | 58.89 | -     |

**Fig. 5:** 2D  $^1\text{H}$ - $^{13}\text{C}\{^1\text{H}\}$ , HSQC NMR spectrum of entry 13 in  $\text{CDCl}_3$  showing single bond connectivity of Carbons and Protons

### Heteronuclear Multiple Bond Correlation (HMBC)

To confirm the assignments made by the use of HSQC experiment and to assign the signals corresponding to quaternary carbons, HMBC (Heteronuclear Multiple Bond Correlation) NMR spectra of benzamides were recorded (Fig. 6). This experiment established the connectivity of carbon with neighboring protons via two/three bond. In the HMBC spectra, of all benzamides H-8 protons were long range coupled to carbon signals at  $\delta$  69.62–71.07 ppm, 44.98–45.97 ppm and 162.18–172.31 ppm (Fig. 6, Scheme 2). The first resonances were assigned as C-9, second as C-11 and third were attributed to C-7 resonance. In the similar manner H-11,  $\delta$  3.63–3.82 ppm exhibited long range connectivity with C-12,  $\delta$  70.48–71.30 ppm C-8,  $\delta$  49.13–49.91 ppm and C-7. Methyl carbons of alkyl chains C-10,  $\delta$  58.75–58.94 ppm, C-13,  $\delta$  58.83–59.07 ppm, were long range coupled to the H-9,  $\delta$  3.36–3.47 ppm and H-12,  $\delta$  3.62–3.82 ppm respectively, and these in turn coupled to the respective carbons C-8 and C-11. C-1 (114.57–143.03 ppm) was assigned through the long range couplings with H-5  $\delta$  6.57–

8.21 ppm and H-3  $\delta$  6.57–8.76 ppm in benzamides where both positions C-5 and C-3 are not occupied by substitution on benzene ring. Here to demonstrate the two and three bonds important connectivity between carbon and protons, HMBC spectrum of entry 13 is shown as example in the figure 6. The overlapped signals of two Quaternary carbons C-2 and C-6 of entry 13 were assigned separately, at  $\delta$  159.46 ppm and 157.06 ppm, respectively with the help of 2D HMBC, experiment and shown their long range coupling with H-4,3 and H-4,5 of ring protons respectively. In all mono and di substituted methoxy benzamides entries 3, 4, 5, 11 and 12 the methoxy protons at  $\delta$  3.83, 3.84, 3.85, 3.82 and 3.87/3.88 ppm respectively were long range coupled to their respective quaternary  $^{13}\text{C}$  signals at  $\delta$  155.04(C-2), 159.43(C-3), 160.31(C-4), 156.45(C-2/6) and 149.81(C-3)/148.61(C-5) ppm, respectively (Scheme 2). Beside that carbon resonances showed splitting due to the coupling with fluorine in benzamides 6, 7, and 13–17. Fluorine coupling with carbon was observed in the range 244–251 Hz, 12–26 Hz, 4–13 Hz and 2–6 Hz for one, two, three and four bond respectively.

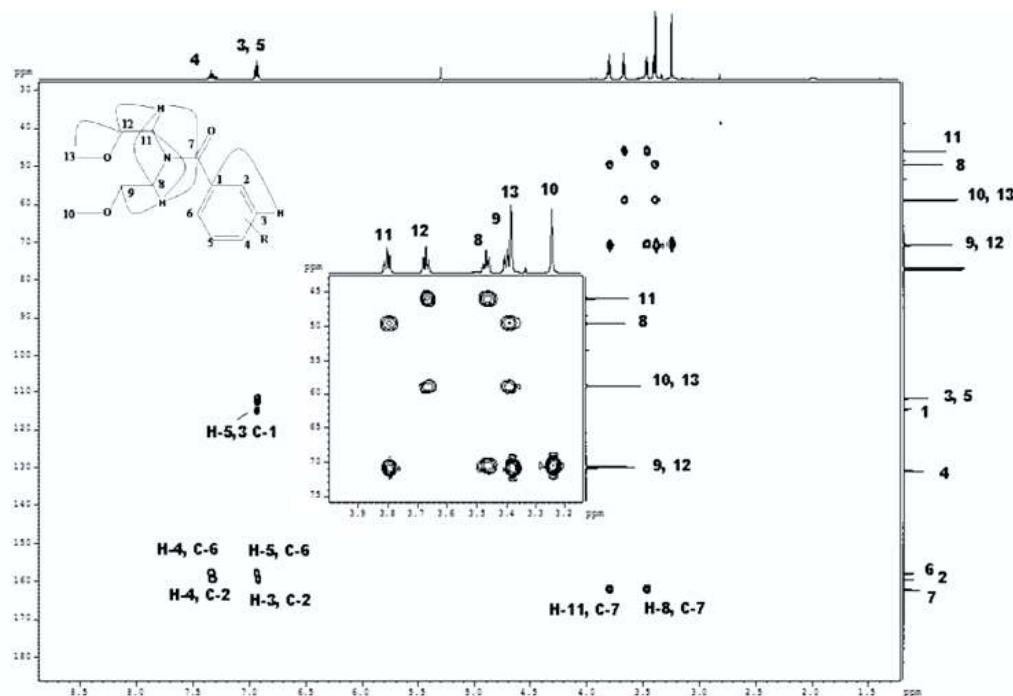


Fig. 6: 2D  $^1\text{H}$ - $^{13}\text{C}\{^1\text{H}\}$ , HMBC NMR Spectrum of Entry 13 in  $\text{CDCl}_3$ , showing long connectivity of Carbon with Proton

### CONCLUSION

In summary, here we report the complete  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of benzamide derivatives. The results obtained from the present investigation revealed

that the *N,N* Dialkyl substituted benzamides are sterically crowded and floppy at room temperature, possess low barrier of rotation, cause formation of multiple rotamers. This rotation further creates broadening in the methylene proton signals. Low

temperature lowers the tumbling especially in ortho substituted benzamides and exhibited clear splitting for alkyl chain methylene proton signals. The Splitting and Sequencing of chemical shift of methylene/methyl protons at NMR Scale is affected by Substitution in benzene ring. Molecules adopted twisted geometry because of bulky alkyl chain and bulky substitution in benzene ring.

### Supplementary Information (SI)

Coupling constant values of Proton and Carbon NMR, literature values of  $^1\text{H}$  NMR chemical shifts of cis-trans alkyl groups, Activation energy literature values of rotamers and over lapped  $^1\text{H}$  spectra of aromatic region and  $^1\text{H}$  NMR showing variable temperature analysis for this article can be accessed from supplementary information.

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