SCIENCE

Synthesis and structural analysis of novel para-aminobenzoic acid derivative

R. Minitha[1], G. Sreekala[2], J.B. Bhagyasree[3], J. Prabha[4], M. Jasmin[5]
[1]Government Polytechnic College, Ezhukone, Kollam
[2]Department of Chemistry, BJM Government College, Chavara, Kollam
[3,4,5]Government College, Attingal
E-mail address: minithabalan1@gmail.com

Abstract

Para-aminobenzoic acid derivative has been developed by one step reaction pathway by condensing with dimedone using solvothermal method. The enol form of diketone namely dimedone existed in the reaction medium and reacts with para-aminobenzoic acid. Single crystal X-ray diffraction technique is used to ascertain the molecular structure. The molecule crystallizes in the Orthorhombic, Pbca space group, with eight molecules per unit cell and with a= 13.8759(17), b= 13.1125(16), c=15.7472(14), α, β, ϒ= 90°. The intensity data were collected with CuKa radiation with λ = 0.71073 Å.

Keywords: Para-aminobenzoic acid, Dimedone, Condensation, Solvothermal, Molecular structure, Hydrogen bonding

1. Introduction

Para-aminobenzoic acid (PABA) is a well-known amino acid molecule in biochemistry, medicinal chemistry and with many industrial applications[1]. Although there are two recognized polymorphs of PABA, the system is not well-established[2].

PABA is synthesized and utilized as a substrate for the synthesis of folic acid in many bacterial species, yeasts and plants, i.e., playing a crucial role in this metabolic pathway. This compound belongs to the vitamins B group (vitamin B_x or B_{10})[3]. Its derivatives have potential applications as acetylcholinesterase inhibitors, ribosomal elongation, diuretics, cholinesterase inhibitors for the treatment of alzheimers disease and important substrate for the synthesis of various biological scaffolds[4-9]. The majority of biomolecules produced to date have required time-consuming and costly processes, therefore methods for single-step synthesis which maximize chemical reaction efficiency while obviating the need for lengthy separation and purification processes are of interest. Thus, over the past 10 years, there has been a lot of research focused on the development of small molecule-based pharmacophores that require straightforward synthesis and separation processes. Green chemistry standards also indicate that there has been a trend in recent years for the organic metamorphosis.

Para-aminobenzoic acid derivative of dimedone has been synthesized and characterized in this study. Physico-chemical method, such as elemental analysis was used to characterize the new compound. To determine the molecular structure, single crystal X-ray diffraction was studied.

2. Experimental

2.1 Materials

Para-aminobenzoic acid (Nice) and dimedone (Astron) for synthesis were obtained commercially and were used without further purification. Organic solvents were used as received.

2.2 Synthesis of PABA-DMN

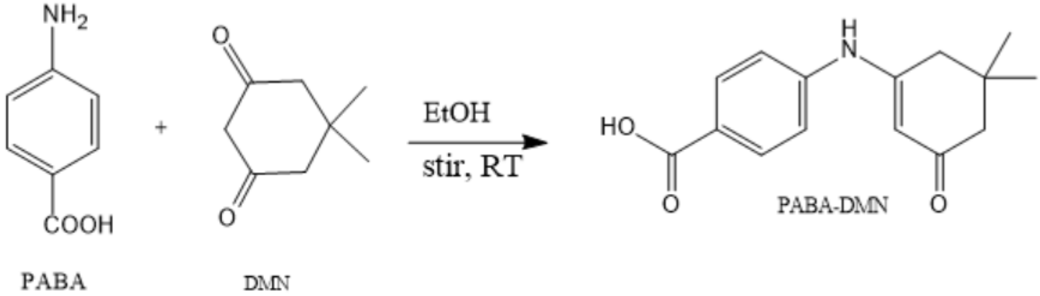
The following procedure was used to synthesize PABA-DMN: After dissolving 10 mmol (1.37 g) of para-aminobenzoic acid in 20 ml of ethanol, 10 mmol (1.40 g) of dimedone in 20 ml of ethanol was added to the initial solution, which was stirred for 15 minutes. The mixture was then refluxed for 1 hour. An orange solution was obtained. The solution was kept for 24 hr. The resulting orange precipitate was filtered through Whatman No.1 filter paper, washed with cold ethanol, and then dried in a desiccator. Following its recrystallization from acetic acid, pale orange crystals of PABA-DMN were produced for X-ray diffraction analysis.

2.3 X-ray crystallography

Utilizing graphite monochromated MoKα (λ=0.71073Å) radiation with a Bruker axs kappa apex2 CCD diffractometer, crystallographic data were obtained. Apex2/SAINT for cell refinement, SAINT/XPREP for data reduction, and Apex2 for data collecting were utilized[10]. Structure solution and refinement was carried out by SIR92 and SHELXL-2014[11-12]. Using a riding model, all non-hydrogen atoms were refined and geometrically fixed. Molecular graphics employed were ORTEP3 and Mercury 3.3.

3. Results and discussion

A new organic molecule, PABA-DMN was synthesized by reacting para-aminobenzoic acid and dimedone (Scheme 1) in ethanol. The reaction was carried out at room temperature and yield was around 90%. The new molecule formed as an orange coloured solid was highly stable, non-hygroscopic and melts at 270°C. The expected Schiff base is not formed via condensation reaction while a new molecule is formed. The diketone, dimedone in ethanol existed as enol form and the enol form reacted with amino group of para-aminobenzoic acid.



Scheme 1: Formation of PABA-DMN

Figure 1. Synthesis of PABA-DMN

Figure 2. Recrystallized form of PABA-DMN

3.1 Analytical data

The analytical data and physical characteristics of PABA-DMN molecule (Table 1) indicates that the molecular formula as, $C_{15}H_{18}NO_3$. The compound is insoluble in non-polar solvents but is soluble in most of the polar solvents like DMF, acetic acid, chloroform, etc.

Table 1. Analytical data of PABA-DMN

Molecular formula	Colour	Yield (%)	M.p. (^oC)	Elemental analysis (%) found (calculated)		
				C	H	N
$C_{15}H_{18}NO_3$	Orange	90	270	69.44 (69.23)	6.91 (6.92)	5.52 (5.38)

3.2 Spectral analysis

UV-Vis spectrum of PABA-DMN is recorded in DMSO. It gives high energy absorption at 217 nm is due to π→π* transition of C=O and C=N. The absorption band at 255 nm is assigned to n→π* transition of C=N. The main stretching frequencies of the FT-IR spectrum of the PABA-DMN are tabulated in Table 2. The FT-IR spectrum of HCAAP shows strong bands at 1680 and 1639 cm^{-1}. The band at 1680 cm^{-1} is assigned to υ(C=O) of the carboxylic group in para-amino benzoic acid. The C=O present at dimedone moiety gives stretching vibrations at 1639cm^{-1}. Weak absorption at 1559 cm^{-1} is due to C=C vibrations of dimedone. A broad absorption band at 3429 cm^{-1}, indicating hydrogen bond due to carboxylic OH and NH present in PABA-DMN. A narrow band at 3064 cm^{-1}, indicating aromatic rings. A narrow band at 2905 cm^{-1}, showing aliphatic compounds. ^{1}H-NMR spectrum of the compound was carried out in d_6 – DMSO at room temperature using TMS as an internal standard. PABA-DMN shows peaks between 6.963 - 7.965 ppm which are attributable to the aromatic protons, peaks at 11.585 ppm and 14 ppm which are attributable to the acidic OH proton and NH proton respectively. The free methyl protons were observed at 2.5 ppm. Methylene protons give peak at 3.4 ppm.

Table 2. Selected infrared spectral assignments of PABA-DMN

Selected infrared bands	**Assignments**
3429	Hydrogen bonded υ(O-H) and υ(N-H)
3064	Aromatic υ(C-H)
2905	Aliphatic υ(C-H)
1680	Carboxylic υ(C=O)
1639	Dimedone υ(C=O)
1559	Dimedone C=C

3.3 The molecular structure

Single crystals were grown from acetic acid solutions and were analyzed by X-ray diffraction. A translucent orange block-like crystals of molecular formula $C_{15}H_{18}NO_3$ and approximate dimensions 0.400 x 0.300 x 0.200 mm was used for the X-ray crystallographic analysis. The X-ray intensity data were measured ($\lambda = 0.71073$ Å). The total exposure time was 3 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 22218 reflections to a maximum θ angle of 28.656^{o} (0.75 Å resolution). The final cell constants and volume below are based upon the refinement of the XYZ-centroids of 3646 reflections above 20 $\sigma(I)$ with $2.975° < \theta < 28.656°$. Crystal structure of PABA is reported earlier is used for the structural comparison of new compound synthesized from dimedone[13].

PABA-DMN belongs to Orthorhombic system with Pbca space group. An ORTEP view of the PABA-DMN, with the atom numbering scheme is shown in Figure 3. The structure refinement parameters and crystal data are presented in Table 3. There are eight molecules per unit cell. Important bond lengths and bond angles are tabulated in Tables 4 and 5. The molecules are associated through intermolecular hydrogen bonding and molecular topology is given in Figure 4. Hydrogen bonding is a non-covalent interaction which play an important role in cell packing and supramolecular association in the synthesized compound. The stability of the compound in solid state also influenced by hydrogen bonding.

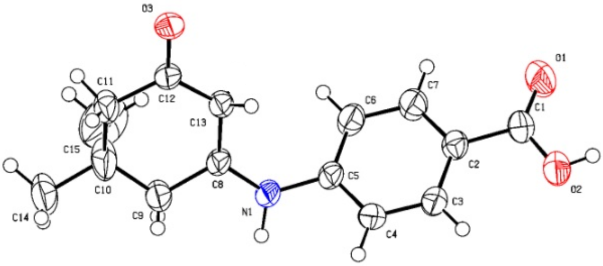


Figure 3. ORTEP of PABA-DMN

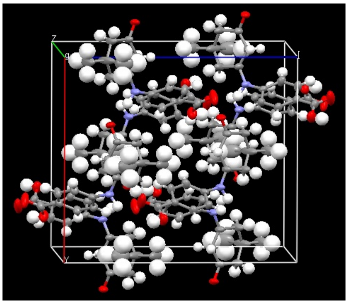


Figure 4. Packing and hydrogen bonding in PABA-DMN

Table 3. Crystal data and structure refinement for PABA-DMN

Empirical formula	$C_{15}H_{18}NO_3$
Formula weight	260.3
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 13.8759(17) A
	b = 13.1125(16) A
	c = 15.7472(14) A
	alpha = 90 deg.
	beta = 90 deg.
	gamma = 90 deg.
Volume	2865.2(6) A^3
Z	8
Calculated density	1.207 Mg/m^3
Absorption coefficient	0.084 mm^-1
F(000)	1112
Crystal size	0.400 x 0.300 x 0.200 mm
Theta range for data collection	2.975 to 28.656 deg.
Limiting indices	-18<=h<=18, -17<=k<=17, -21<=l<=12
Reflections collected / unique	22218 / 3646 [R(int) = 0.0472]
Completeness to theta = 25.242	99.40%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.983 and 0.967
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3646 / 0 / 179
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1=0.0875, wR2 = 0.2592
R indices (all data)	R1 = 0.1314, wR2 = 0.3092
Extinction coefficient	n/a
Largest diff. peak and hole	1.322 and -0.652 e.A^-3

Table 4. Bond lengths [Å] for PABA-DMN

C(1)-O(1)	1.198(4)	C(8)-C(13)	1.365(3)
C(1)-O(2)	1.307(4)	C(8)-C(9)	1.493(4)
C(1)-C(2)	1.477(4)	C(9)-C(10)	1.424(5)
C(2)-C(7)	1.375(4)	C(10)-C(11)	1.443(5)
C(2)-C(3)	1.378(4)	C(10)-C(14)	1.487(5)
C(3)-C(4)	1.385(4)	C(10)-C(15)	1.695(10)
C(4)-C(5)	1.374(4)	C(11)-C(12)	1.488(4)
C(5)-C(6)	1.372(4)	C(12)-O(3)	1.251(3)
C(5)-N(1)	1.416(4)	C(12)-C(13)	1.396(3)
C(6)-C(7)	1.380(4)	N(1)-H(1N)	0.97(4)
C(8)-N(1)	1.333(3)	O(2)-H(2)	0.82

Table 5. Bond angles [°] for PABA-DMN

O(1)-C(1)-O(2)	122.5(3)	C(10)-C(9)-C(8)	116.1(3)
O(1)-C(1)-C(2)	123.9(3)	C(9)-C(10)-C(11)	117.4(4)
O(2)-C(1)-C(2)	113.6(3)	C(9)-C(10)-C(14)	116.0(4)
C(7)-C(2)-C(3)	119.3(3)	C(11)-C(10)-C(14)	115.1(3)
C(7)-C(2)-C(1)	118.4(3)	C(9)-C(10)-C(15)	100.6(5)
C(3)-C(2)-C(1)	122.3(3)	C(11)-C(10)-C(15)	100.2(4)
C(4)-C(3)-C(2)	120.6(3)	C(14)-C(10)-C(15)	103.7(5)
C(5)-C(4)-C(3)	119.4(3)	C(10)-C(11)-C(12)	116.8(3)
C(6)-C(5)-C(4)	120.4(3)	O(3)-C(12)-C(13)	122.2(2)
C(6)-C(5)-N(1)	121.8(3)	O(3)-C(12)-C(11)	117.7(2)
C(4)-C(5)-N(1)	117.7(3)	C(13)-C(12)-C(11)	120.1(2)
C(5)-C(6)-C(7)	119.9(3)	C(8)-C(13)-C(12)	120.7(3)
C(2)-C(7)-C(6)	120.4(3)	C(8)-N(1)-C(5)	127.1(2)
N(1)-C(8)-C(13)	124.6(3)	C(8)-N(1)-H(1N)	118(2)
N(1)-C(8)-C(9)	114.3(2)	C(5)-N(1)-H(1N)	115(2)
C(13)-C(8)-C(9)	121.0(2)	C(1)-O(2)-H(2)	109.5

4. Conclusions

Through one-step, economical, facile synthesis, we have synthesized a new compound from para-aminobenzoic acid and dimedone. Condensation of para-aminobenzoic acid and dimedone in a molar ratio of 1:1 in ethanol solvent resulted in the formation of a new β-enaminone. This compound is non-hygroscopic, insoluble in common organic solvents and soluble in acetic acid, dimethylformamide and dimethylsulphoxide respectively. Analytical data confirm the formation of a new compound which is further confirmed from single crystal X-ray diffraction study. compound crystallized in orthorhombic system with Pbca space group. Para-aminobenzoic acid is a pharmacophore hence its new derivative must be a new candidate against pathogenic microorganisms and finds applications in biomedical field.

Acknowledgments

The authors are grateful to, Department of Chemistry, BJM Govt. College for providing lab facility and SAIF Cochin for single crystal X-ray diffraction data.

Conflict of Interest

Declare that there are no conflicts of interest or financial interests between the authors.

References

1. S.I. Akberova; (2002); New Biological Properties of p-Aminobenzoic Acid; Biol. Bull.; 29; 390–393.
2. S. Gracin; A.C. Rasmuson; (2004); Polymorphism and Crystallization of p-Aminobenzoic Acid; Cryst. Growth Des.; 4(5); 1013–1023.
3. C.W. Tabor; M.V. Freeman; J. Baily; P.E. Smith; (1951); Studies on the metabolism of para-aminobenzoic acid; J. Pharmacol. Exp. Ther.; 102; 98-102.
4. J. Correa-Basurto; I.V. Alcántara; L.M. Espinoza-Fonseca; J.G. Trujillo-Ferrara; (2005); p–Aminobenzoic acid derivatives as acetylcholinesterase inhibitors; Eur. J. Med. Chem.; 40(7); 732–735.
5. T. Katoh; H. Suga; (2020); Ribosomal Elongation of Aminobenzoic Acid Derivatives; J. Am. Chem. Soc.; 142(39); 16518–16522.
6. P.W. Feit; (1971); Aminobenzoic acid diuretics. 2. 4-Substituted-3-amino-5-sulfamoylbenzoic acid derivatives; J. Med. Chem.; 14(5); 432–439.
7. S.K. Shrivastava; S.K. Sinha; P. Srivastava; P.N. Tripathi; P. Sharma; M.K. Tripathi;

A. Tripathi; P.K. Choubey; D.K. Waiker; L.M. Aggarwal; M. Dixit; S.C. Kheruka; S. Gambhir; S. Shankar; R.K. Srivastava; (2019); Design and development of novel p-aminobenzoic acid derivatives as potential cholinesterase inhibitors for the treatment of Alzheimer's disease; Bioorg. Chem.; 82; 211–223.

8. Z.U. Nisa; A. Tashfeen; (2020); para-Aminobenzoic Acid-A Substrate of Immense Significance; Mini-Rev. Org. Chem.; 17(6); 686–700.
9. A. Kluczyk; T. Popek; T. Kiyota; P. de Macedo; P. Stefanowicz; C. Lazar; Y. Konishi; (2002); Drug Evolution: p-Aminobenzoic Acid as a Building Block; Curr. Med. Chem.; 9(21); 1871–1892.
10. Bruker; (2004); APEX2, XPREP and SAINT-Plus. Bruker AXS Inc., Madison, Wisconsin, USA.
11. G.M. Sheldrick; (1997); SHELXS-97 Program for the Solution of Crystal Structures; University of Gottingen; Gottingen; Germany.
12. L.J. Farrugia; (2012); J. Appl. Cryst.; 45; 849–854.
13. T.F. Lai; R.E. Marsh; (1967); The crystal structure of p-aminobenzoic acid; Acta Cryst.; 22; 885–89.