Journal of Molecular Structure 1002 (2011) 10–18

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

X-ray structures and computational studies of several cathinones

Jacek E. Nycz [a,*], Grzegorz Malecki [a], Marcin Zawiazalec [b], Tadeusz Pazdziorek [b]

[a] Institute of Chemistry, University of Silesia, ul. Szkolna 9, PL-40007 Katowice, Poland
[b] Department of Chemistry, Forensic Laboratory, The Regional Headquarters, Katowice, Poland

ARTICLE INFO

Article history:
Received 16 May 2011
Received in revised form 22 June 2011
Accepted 23 June 2011
Available online 6 July 2011

Keywords:
Cathinone
4-MEC
Methylone
Mephedrone
Buphedrone
X-ray

ABSTRACT

2-(Ethylamino)-1-(4-methylphenyl)propan-1-one (shortly named 4-MEC) (**1a**), 1-(1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one (shortly named methylone or 3,4-methylenedioxymethcathinone) (**1b**), 1-(3,4-dimethylphenyl)-2-(methylamino)propan-1-one (**1c**), 2-methylamino-1-(4-methylphenyl)propan-1-one (shortly named mephedrone; 4-MMC or 4-methylmethcathinone) (**1d**) and 2-(methylamino)-1-phenylbutan-1-one (shortly named buphedrone) (**1e**) and their aminium salts (**2a–e**), are examples of cathinones which were characterized by FTIR, UV–Vis, multinuclear NMR spectroscopy. By single crystal X-ray diffraction method structures of **2a**, **2b**, **2c** and **2d** were determined. NMR solution spectra showed readily diagnostic H-1 and C-13 signals from methyl, ethyl, *N*-methyl or *N*-ethyl groups. The diastereotopic methylene protons of **1a** appear as an ABX_3, and **1e** and **2e** appear as an $ABMX_3$ system. The geometries of the studied compounds were optimized in singlet states using the density functional theory (DFT) method with B3LYP functional. Electronic spectra were calculated by TDDFT method. In general, the predicted bond lengths and angles are in good agreement with the values based on the X-ray crystal structure data.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

The cathinones are a class of compounds containing α-aminopropiophenone moiety. They are derivatives of cathinone, a natural amphetamine-like alkaloid, which is the major pharmacologically active constituent extracted from fresh leaves and stems of *Catha edulis* Forsk, Celastraceae (Khat) [1]. This shrub is usually found in the southwestern part of the Arabian Penisula and East Africa, where it has been used for centuries for both spiritual and recreational purposes. Khat has been recorded in literature for the purpose of alleviating depression as early as 1237 by physician Nagub Ad Din [2,3].

There are a number of synthetic cathinones that are used recreationally. They are expected to act as a central nervous system stimulants by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake [4]. The first described synthesis of mephedrone as an example of cathinone was in 1929 [5]. Mitochondrial monoamine oxidases are flavin-containing enzymes (FAD or FMN) to catalyze the oxidative deamination of neurotransmitters and exogenous arylalkylamines [6]. The postulated metabolic pathways of cathinones are through the *N*-dealkylation and demethylenation, followed by the *O*-methylation and reduction of the keto moiety to alcohols, and the oxidation of the tolyl moiety to the corresponding alcohols or carboxylic acids [7,8].

Recently we presented two compounds, 1-pentyl-3-(4-methoxy-1-naphthoyl)indole (shortly named JWH-081) and 2-(2-methoxy-phenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone (shortly named JWH-250), as examples of cannabinoids. They were characterized by FTIR, UV–Vis, multinuclear NMR spectroscopy and single crystal X-ray diffraction method [9].

The current work focuses on further computational and X-ray studies to ascertain the atomic charges of selected cathinones, the energy of the frontier orbitals and the conformation of groups, which have not been determined by crystallographic studies yet. The identification of cathinones are of medical and forensic or doping interest.

2. Experimental

2.1. General

NMR spectra were obtained with Bruker Avance 400 operating at 400.13 MHz (^{1}H) and 100.5 MHz (^{13}C) at 21 °C; chemical shifts referenced to ext. TMS (^{1}H, ^{13}C); coupling constants are given in Hz. The ^{1}H and ^{13}C NMR calculations were performed with the ACD Labs NMR Predictor v.7 program considering the influence of different solvents ($CDCl_3$ or DMSO). FTIR spectra were recorded on a Perkin Elmer spectrophotometer in the spectral range 4000–450 cm^{-1} with the samples in the form of KBr pellets. Electronic spectra were measured on a spectrophotometer Lab. Alliance UV–Vis 8500 in the range 500–180 nm in CH_2Cl_2 solution. Chromatography was

* Corresponding author. Tel.: +48 323591206; fax: +48 322599978.
E-mail address: jnycz@us.edu.pl (J.E. Nycz).

0022-2860/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2011.06.030

carried out on Silica Gel 60 (0.15–0.3 mm) Machery Nagel. Melting points were determined on MPA100 OptiMelt melting point apparatus and uncorrected. Compounds **2a**, **2b**, **2c**, **2d** and **2e** were purchased from LGC Standards.

2.1.1. Synthesis of 1a, 1b, 1c, 1d and 1e

The water solution of **2a**, **2b**, **2c**, **2d** or **2e** was alkalified by K_2CO_3. Reagents were shaken for a few minutes. The mixture was poured into CH_2Cl_2. The organic phase was separated and dried by $MgSO_4$. After the solvent was evaporated, the residue was purified by chromatography.

2.1.2. Crystallization of 2a, 2b, 2c, 2d and 2e

The colorless crystals suitable for X-ray analysis were obtained by slowly solvents' evaporating at room temperature for **2a** and **2b**, and in −35 °C for **2c** and **2d**. Crystallization of **2e** is in progress.

2-(Ethylamino)-1-(4-methylphenyl)propan-1-one (**1a**) (yellowish liquid) ^{1}H NMR ($CDCl_3$) δ = 1.10 (t, J_{HH} = 7.1 Hz, 3H, CH_2CH_3), 1.29 (d, J_{HH} = 7.0 Hz, 3H, $CHCH_3$), 2.22 (m, 1H, NH), 2.41 (s, 3H, 4-CH_3Ar), 2.56 (ABX_3, J_{HHgem} = 12.8 Hz, J_{HH} = 7.1 Hz, 2H, CH_2CH_3), 4.29 (q, J_{HH} = 7.0 Hz, 1H, $CHCH_3$), 7.27 (d, J_{HH} = 8.2 Hz, 2H, aromatic), 7.86 (d, J_{HH} = 8.2 Hz, 2H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 15.44, 20.07, 21.63, 42.35, 57.51, 128.33, 129.42, 133.10, 144.21, 203.22.

N-Ethyl-1-(4-methylphenyl)-1-oxopropan-2-aminium chloridum (**2a**) (colorless solid) m.p. = 198–199 °C (methanol); ^{1}H NMR ($CDCl_3$) δ = 1.53 (t, J_{HH} = 7.3 Hz, 3H, CH_2CH_3), 1.81 (d, J_{HH} = 7.2 Hz, 3H, $CHCH_3$), 2.43 (s, 3H, 4-CH_3Ar), 3.06–3.27 (m, 2H, CH_2CH_3), 4.96–5.06 (m, 1H, $CHCH_3$), 7.31 (d, J_{HH} = 8.0 Hz, 2H, aromatic), 7.86 (d, J_{HH} = 8.2 Hz, 2H, aromatic), 9.02 (m, 1H, NH_2), 10.69 (m, 1H, NH_2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 11.79, 16.86, 21.80, 42.12, 57.83, 128.96, 129.89, 130.44, 146.05, 194.25; IR (KBr): 3438 (νNH), 2946 (νPhH), 2819, 2765 (νCH_3), 1651 (νC = O, scissor. NH_2), 1602 (νC=C), 1459 (νPhH), 1340, 1263 (νC-N), 768, 743 (wag. NH_2); UV–Vis (methanol; [nm]) (log ε): 259.0 (5.17), 211.0 (5.01); X-ray CCDC 823158.

1-(1,3-Benzodioxol-5-yl)-2-(methylamino)propan-1-one (**1b**) (yellowish liquid). ^{1}H NMR ($CDCl_3$) δ = 1.21 (d, J_{HH} = 7.0 Hz, 3H, $CHCH_3$), 2.27 (bs, 3H, NCH_3), 4.05 (q, J_{HH} = 7.0 Hz, 1H, $CHCH_3$), 5.97 (s, 2H, OCH_2), 6.79 (d, J_{HH} = 8.2 Hz, 1H, aromatic), 7.38 (s, 1H, aromatic), 7.51 (d, J_{HH} = 8.2 Hz, 1H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 19.79, 34.50, 59.15, 101.78, 107.90, 107.92, 124.32, 130.36, 148.22, 151.88, 201.24.

1-(1,3-Benzodioxol-5-yl)-*N*-methyl-1-oxopropan-2-aminium chloridum (**2b**) (colorless solid) m.p. = 225–226 °C (methanol); ^{1}H NMR ($CDCl_3$) δ = 1.80 (d, J_{HH} = 7.2 Hz, 3H, $CHCH_3$), 2.80 (bs, 3H, NCH_3), 4.76 (bs, 1H, $CHCH_3$), 6.11 (s, 2H, OCH_2), 6.92 (d, J_{HH} = 8.3 Hz, 1H, aromatic), 7.42 (s, 1H, aromatic), 7.53 (d, J_{HH} = 8.8 Hz, 1H, aromatic); ^{13}C{^{1}H} NMR (DMSO-*d6*) δ = 25.26, 40.13, 67.44, 111.99, 117.42, 118.04, 135.32, 136.97, 157.71, 162.18, 203.81; IR (KBr): 3435 (νNH), 2920 (νPhH), 2799, 2735 (νCH_3), 1679 (νC=O + scissor. NH_2), 1603 (νC=C), 1502, 1452 (νPhH), 1349, 1299 (νC-N), 1261, 1090 (νC-O), 767, 741 (wag. NH_2); UV–Vis (methanol; [nm]) (logε): 307.8 (4.97), 270.2 (4.88), 224.8 (5.19), 192.6 (5.41); X-ray CCDC 819333.

1-(3,4-Dimethylphenyl)-2-(methylamino)propan-1-one (**1c**) (yellowish liquid) ^{1}H NMR ($CDCl_3$) δ = 1.19 (d, J_{HH} = 7.1 Hz, 3H, CH_3CH), 1.93 (s, 1H, NH), 2.21 (s, 3H, 3-CH_3Ar), 2.22 (s, 3H, 4-CH_3Ar), 2.26 (s, 3H, NCH_3), 4.10 (q, J_{HH} = 7.0 Hz, 1H, CH_3CH), 7.12 (d, J_{HH} = 7.9 Hz, 1H, aromatic), 7.61 (dd, J_{HH} = 7.9 Hz, J_{HH} = 1.6 Hz, 1H, aromatic), 7.66 (s, 1H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 19.47, 19.58, 19.70, 34.40, 59.05, 125.65, 129.03, 129.65, 133.40, 136.82, 142.58, 202.85.

1-(3,4-Dimethylphenyl)-*N*-methyl-1-oxopropan-2-aminium chloridum (**2c**) (colorless solid) m.p. = 211–212 °C (methanol); ^{1}H NMR ($CDCl_3$) δ = 1.78 (d, J_{HH} = 7.2 Hz, 3H, CH_3CH), 2.30 (s, 3H, 3-CH_3Ar), 2.32 (s, 3H, 4-CH_3Ar), 2.84 (s, 3H, NCH_3), 4.95 (q, J_{HH} = 7.3 Hz, 1H, CH_3CH), 7.24 (d, J_{HH} = 8.2 Hz, 1H, aromatic), 7.67 (dd, J_{HH} = 7.9 Hz, J_{HH} = 1.4 Hz, 1H, aromatic), 7.72 (s, 1H, aromatic), 9.92 (bs, 1H, NH_2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 16.48, 19.77, 20.21, 31.64, 59.25, 126.54, 129.88, 130.32, 130.78, 137.71, 144.74, 194.43; IR (KBr): 3363 (νNH), 2907 (νPhH), 2806, 2735 (νCH_3), 1688 (νC=O), 1675 (scissor. NH_2), 1605, 1572 (νC=C), 1464 (νPhH), 1399, 1250 (νC-N), 763, 730 (wag. NH_2); UV–Vis (methanol; [nm]) (log ε): 262.0 (5.32), 210.0 (5.33); X-ray CCDC 822797.

2-Methylamino-1-(4-methylphenyl)propan-1-one (**1d**) (yellowish liquid) ^{1}H NMR ($CDCl_3$) δ = 1.23 (d, J_{HH} = 7.1 Hz, 3H, $CHCH_3$), 2.26 (bs, 1H, NH), 2.30 (s, 3H, 4-CH_3Ar), 2.34 (s, 3H, NCH_3), 4.14 (q, J_{HH} = 7.0 Hz, 1H, CH), 7.21 (d, J_{HH} = 8.1 Hz, 2H, aromatic), 7.80 (d, J_{HH} = 8.2 Hz, 2H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 19.64, 21.55, 34.47, 59.21, 128.25, 129.35, 133.01, 144.17, 202.68.

1-(4-Methylphenyl)-*N*-methyl-1-oxopropan-2-aminium chloridum (**2d**) (colorless solid) m.p. = 230–231 °C (methanol); ^{1}H NMR ($CDCl_3$) δ = 1.79 (d, J_{HH} = 7.1 Hz, 3H, $CHCH_3$), 2.43 (s, 3H, CH_3), 2.85 (bs, 3H, NCH_3), 4.94 (bs, 1H, $CHCH_3$), 7.30 (d, J_{HH} = 8.0 Hz, 2H, aromatic), 7.84 (d, J_{HH} = 8.1 Hz, 2H, aromatic), 9.32 (m, 1H, NH_2), 10.51 (m, 1H, NH_2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 16.49, 21.78, 31.72, 59.33, 129.00, 129.90, 130.58, 146.05, 194.25; IR (KBr): 3356 (νNH), 2964, 2910 (νPhH), 2803, 2741, 2722 (νCH_3), 1687 (νC=O), 1606 (scissor. NH_2), 1572 (νC=C), 1456 (νPhH), 1358, 1248 (νC-N), 756, 734 (wag. NH_2); UV–Vis (methanol; [nm]) (logε): 259.0 (5.20), 211.0 (5.02); X-ray CCDC 822035.

2-(Methylamino)-1-phenylbutan-1-one (**1e**) (yellowish liquid) ^{1}H NMR ($CDCl_3$) δ = 0.84 (dt, J_{HH} = 7.4 Hz, J_{HH} = 1.3 Hz, 3H, CH_2CH_3), 1.49 ($ABMX_3$, dqd, J_{HH} = 14.1 Hz, J_{HH} = 7.4 Hz, J_{HH} = 5.2 Hz, 1H, CH_2CH_3), 1.73 ($ABMX_3$, dqd, J_{HH} = 14.1 Hz, J_{HH} = 7.4 Hz, J_{HH} = 5.2 Hz, 1H, CH_2CH_3), 2.07 (bs, 1H, NH), 2.29 (s, 3H, $NHCH_3$), 4.01 (dd, J_{HH} = 6.5 Hz, J_{HH} = 5.3 Hz, 1H, $CHCH_2$), 7.40 (bt, J_{HH} = 7.5 Hz, 2H, aromatic), 7.49 (tt, J_{HH} = 7.4 Hz, J_{HH} = 1.3 Hz, 1H, aromatic), 7.89 (dd, J_{HH} = 8.3 Hz, J_{HH} = 1.2 Hz, 2H, aromatic); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 9.76, 26.39, 34.79, 65.07, 127.92, 128.52, 133.01, 136.19, 203.02.

N-Methyl-1-oxo-1-phenylbutan-2-aminium chloridum (**2e**) (colorless solid) m.p. = 190–191 °C (methanol); ^{1}H NMR ($CDCl_3$) δ = 1.02 (t, J_{HH} = 7.6 Hz, 3H, CH_2CH_3), 2.18 (dqd, J_{HH} = 15.0 Hz, J_{HH} = 7.5 Hz, J_{HH} = 5.1 Hz, 1H, CH_2CH_3), 2.39 ($ABMX_3$, dqd, J_{HH} = 15.0 Hz, J_{HH} = 7.5 Hz, J_{HH} = 5.1 Hz, 1H, CH_2CH_3), 2.85 (s, 3H, NH_2CH_3), 5.04 (t, J_{HH} = 5.2 Hz, 1H, $CHCH_2$), 7.52 (t, J_{HH} = 7.7 Hz, 2H, aromatic), 7.65 (t, J_{HH} = 7.4 Hz, 1H, aromatic), 7.98 (d, J_{HH} = 7.3 Hz, 2H, aromatic), 9.91 (m, 2H, NH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ = 8.98, 23.71, 32.21, 63.98, 128.77, 129.19, 134.14, 134.70, 194.60.

2.2. DFT calculations

The calculations were carried out by using Gaussian09 [10] program. The DFT/B3LYP [11,12] method was used for the geometry optimization and electronic structure determination. The geometry optimizations were made for gas phase molecules. The calculations were performed using the polarization functions for all atoms: 6-31G** – carbon, nitrogen, oxygen and hydrogen. The contribution of a group to a molecular orbital was calculated using Mulliken population analysis. GaussSum 2.2 [13] was used to calculate group contributions (aromatic, *N*-aliphatic, $CH_3CHC(=O)$ fragments) to the molecular orbitals and to prepare the density of states (DOS). The DOS spectra were created by convoluting the molecular orbital information with Gaussian curves of unit height and Full Width at Half Maximum (FWHM) of 0.3 eV. The electrostatic potential (ESP) surfaces were plotted by using gOpenMol v2.31 program. The electronic spectra were calculated by the time-dependent density functional (TDDFT) [14] method based on the optimized geometries in the singlet states.

Download English Version:

https://daneshyari.com/en/article/1410283

Download Persian Version:

https://daneshyari.com/article/1410283

Daneshyari.com