Precise Atomic Structures of L-DOPA, Dopamine, Noradrenaline, Adrenaline, Isoprenaline, 5-HTP, Serotonin and Histamine with Bond Lengths as Exact Sums of Adjacent Atomic Radii

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Abstract

The award of this year's Nobel Prize for researches on GPCRs brings to light the importance of the hormone and neurotransmitter molecules mentioned in the title, derived from amino acids. Presented here for the first time are their structures at the atomic level, based on the additivity of the covalent radii of adjacent atoms in bond lengths, which also holds for all the essential amino acids and many other biological molecules. The author hopes that the knowledge of the atomic structures of these compounds will bring deeper structural, chemical and geometric insights into their biochemistry leading to improved biomedical applications.

Keywords: hormone and neurotransmitter molecules, amino acids, atomic structures, additivity of atomic radii, structural biology, biomedicine, pharmacology

Introduction

'It's all about the structure' writes Buchen (2011) commenting on the outstanding researches on GPCRs by this year's chemistry Nobel laureates, Lefkowitz and Kobilka. Their many decades of work (Lefkowitz: http://www.lefkolab.org/Lefkowitz_Bio.html; Kobilka: http://med.stanford.edu/kobilkalab/) brought to limelight the molecular details of the capture (Rasmussen *et al*., a & b: 2011, Granier *et al*., 2008) by GPCRs of the hormone and neurotransmitter molecules such as those named in the title. These are the signaling molecules in yellow in the Figure shown by Buchen (2011). This sparked the present author's interest to investigate their structures down to the atomic detail. The author has shown in the past few years that the existing experimental data on the bond lengths in small as well as large molecules are exact sums of the appropriate radii of the adjacent atoms constituting the bond. This finding enabled the establishment of the precise atomic structures of many inorganic, organic and biological molecules. A detailed overview with pertinent literature can be found in (Heyrovska and Narayan, 2009). To mention a few, the known bond lengths in the molecular components of the life giving molecules, DNA and RNA (Heyrovska, a & b: 2008) as well as those in all the twenty essential amino acids (Heyrovska, 2008) that constitute proteins, were shown to be sums of the covalent atomic radii of the six main life sustaining elements: H (monovalent), O (divalent), N (trivalent), C (tetravalent), P (pentavalent) and S (hexavalent/divalent). The lengths of the hydrogen bonds between the pairs of nucleotides, Thymine & Adenine and Cytosine & Guanine in DNA and RNA and those in many other molecules were also explained by the additivity of atomic and ionic radii (Heyrovska, 2006).

Present work

The life saving hormone and neurotransmitter molecules, adrenaline, serotonin and histamine are biosynthesized (Lehninger, 1975, 2000) from the three essential amino acids, tyrosine, tryptophan and histidine, respectively. The conventional structures of these molecules can be seen in (Lehninger, 1975, 2000). The covalent radii of the atoms defined as (Pauling, 1960), $R_c = d(AA)/2$, where d(AA) is the bond length between any two atoms (A,A), which account for the bond lengths in all the amino acids (Heyrovska, 2008), are given here in Fig. 1. The atomic structures of the above mentioned three amino acids in the unionized state presented in (Heyrovska, 2008) can be seen in Figs 2a, 3a and 4a, respectively.

The additivity of atomic radii in bond lengths demonstrated for all the twenty essential amino acids (Heyrovska, 2008) is further confirmed here for the bond lengths from the crystallographic data for adrenaline (Andersen, a: 1975), noradrenaline (Andersen, b: 1975) and isoprenaline (Malone and Parvez, 1987), also known as epinephrine, norepinephrine and isoproterenol, respectively. The data are assembled in Table 1. The atom numberings in column 1 are as in (Malone and Parvez, 1987) and are shown in Fig. 2f. For the conventional and generic structures of these molecules, see (Lehninger, 1975, 2000; Andersen, a: & b: 1975; Malone and Parvez, 1987). The average lengths of the bonds between various atoms presented in column 5 have been compared with the corresponding radii sum in column 6. It can be seen from the differences (< 0.04 Å) in the last column between the average bond length and the radii sum that all the bond lengths are indeed sums of the radii of the adjacent atoms. The slight deviation of (+/-) 0.04 Å for the meta and para C-O bonds is perhaps indicative of the oxygen atoms engaged in hydrogen bonding (Lee, 2011). Thus, the precise atomic structures of these molecules have been established here for the first time as shown in Figs. 2-4. The C_α atom of the parent amino acid is marked in all the figures. Fig. 2a-f shows the structures of the sequence of the intermediate molecules (Lehninger, 1975, 2000; Goodall and Kirshner, 1957; Burkhard, 2001) in the biosynthesis of adrenaline from tyrosine. In Fig. 3a-c are presented the serotonin related molecules (Lehninger, 1975, 2000; Burkhard, 2001; Walther, 2003) synthesized from tryptophan. The last Fig. 4a,b brings the structures of the amino acid, histidine and its decarboxylated form, histamine (Lehninger, 1975). The 2D areas of the molecules, as shown for tyrosine in Fig. 2a enclosed by the frame in dotted lines, are given in the legends for Figs. 2-4.

It is hoped that these ultimate detailed structures of molecules at the atomic level will be of value for a better understanding of their capture and interaction with GPCRs, their function in biochemistry and biomedicine and drug design in pharmacology.

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COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

FIGURE LEGENDS

Figure 1. The covalent atomic radii, R_c, of carbon (C) (grey), nitrogen (N) (blue), oxygen (O) (orange), hydrogen (H) (green) and sulfur (yellow), which account for the bond lengths in all the twenty essential amino acids. Subscripts: s.b., g.b. and d.b. represent single, graphitic and double bond, respectively.

Figure 2. Atomic structures (2D) of the sequence of molecules synthesized from tyrosine with their areas in parenthesis. a) Tyrosine (area in dotted frame: 6.7 x 11 Å), b) L-DOPA (7.5 x 11 Å), c) dopamine (6.1 x 10.5 Å), d) noradrenaline (6.4 x 10.6 Å), e) adrenaline (6.4 x 12.1 Å), and f) isoprenaline (7.2 x 12.6 Å).

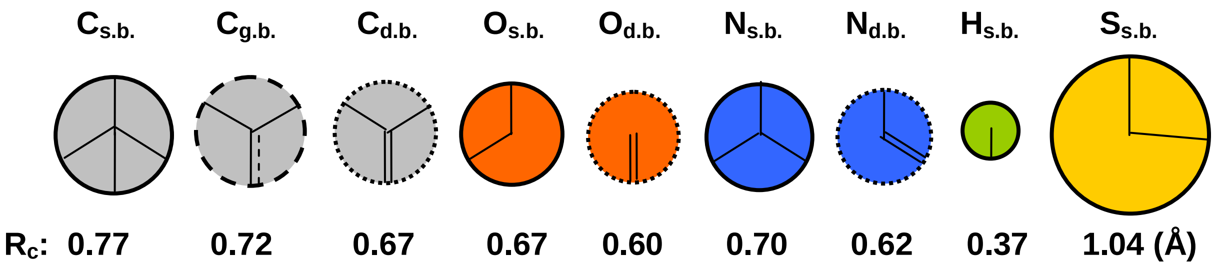
Figure 3. Atomic structures (2D) of the sequence of molecules synthesized from tryptophan with their areas in parenthesis. a) Tryptophan (7.8 x 11.2 Å), b) 5HTP (9.0 x 11.2 Å) and c) serotonin (7.9 x 10.7 Å).

Figure 4. Atomic structures (2D) of a) histidine (6.8 x 10.4 Å) and b) histamine (5.8 x 8.2 Å).

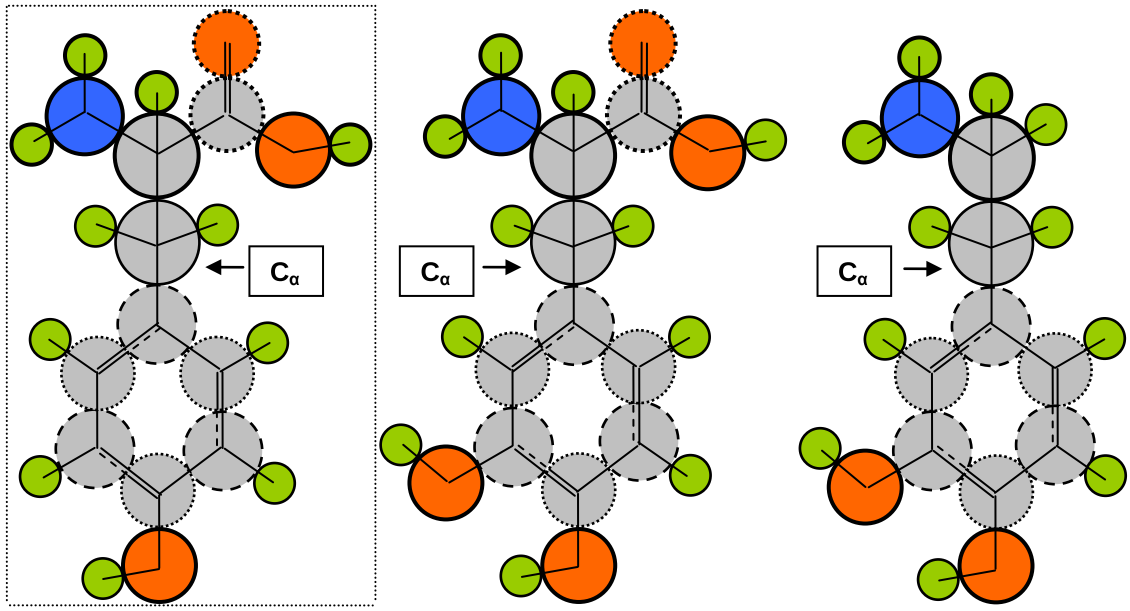
Table 1. Experimental bond lengths, d(AB) comapred with covalent radii sum, $R_c(sum) = R_c(A)+R_c(B)$ for adrenaline[10a], noradrenaline[10b] and isoprenaline[11]. R_c = 0.72 (C1,3,5); 0.67 (C2,4,6); 0.77 (C7-11); 0.67 (O); 0.70 (N), (in Å).

A-B	d(AB) Adren.	d(AB) Norad.	d(AB) Isopre.	$d(AB)_{av}$	$R_c(sum)$	$d(AB)_{av}$-$R_c(sum)$
C1-C2	1.40	1.39	1.38	1.39	1.39	0.00
C2-C3	1.40	1.40	1.39	1.40	1.39	-0.01
C3-C4	1.41	1.41	1.37	1.39	1.39	0.00
C4-C5	1.39	1.38	1.40	1.39	1.39	0.00
C5-C6	1.38	1.40	1.38	1.39	1.39	0.00
C6-C1	1.39	1.39	1.40	1.39	1.39	0.00
C1-C7	1.51	1.52	1.52	1.52	1.49	-0.03
C7-C8	1.51	1.51	1.52	1.51	1.54	0.03
C9-C10			1.52	1.52	1.54	0.02
C9-C11			1.53	1.53	1.54	0.01
C8-N	1.49	1.50	1.48	1.49	1.47	-0.02
N-C9	1.48		1.48	1.48	1.47	-0.01
C3-O	1.35	1.34	1.38	1.35	1.39	0.04
C4-O	1.38	1.38	1.38	1.38	1.34	-0.04
C7-O	1.43	1.42	1.46	1.44	1.44	0.00

RH_Figure 1.



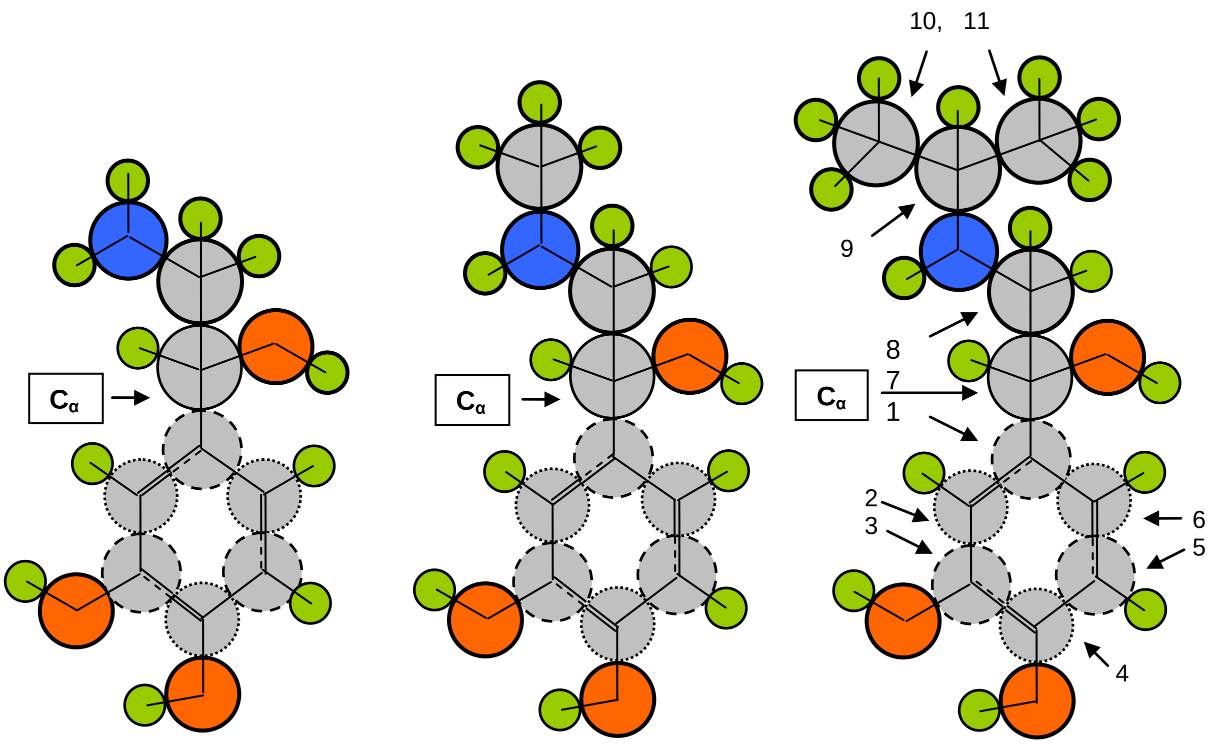
RH_Figure 2 a-f.



a) Tyrosine
$RCHNH_2COOH$
$R = C_{\alpha}H_2ph(OH)$

b) L-Dihydroxy Phenyl Alanine = (L-DOPA)
$RCHNH_2COOH$
$R = C_{\alpha}H_2ph(OH)_2$

c) Dopamine
RCH_2NH_2
$R = C_{\alpha}H_2ph(OH)_2$

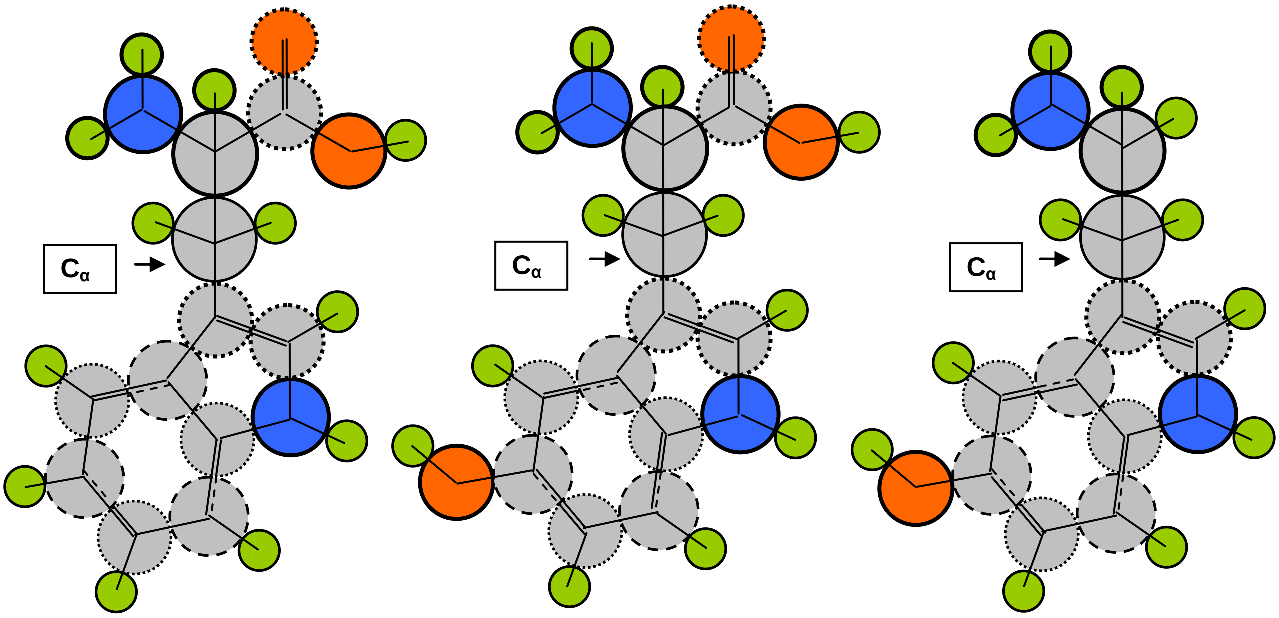


d) Noradrenaline
$R'CH_2NH_2$
$R' = C_{\alpha}H(OH)ph(OH)_2$

e) Epinephrine (Adrenaline)
$R'CH_2NHCH_3$
$R' = C_{\alpha}H(OH)ph(OH)_2$

f) Isoprenaline
$R'CH_2NHCH(CH_3)_2$
$R' = C_{\alpha}H(OH)ph(OH)_2$

RH_Figure 3 a-c.

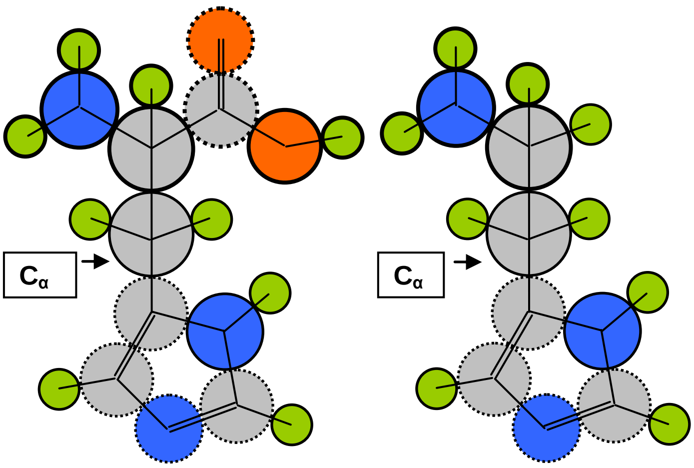


a) Tryptophan
$RCHNH_2COOH$
$R = C_αH_2CCHNHph$

b) 5 Hydroxy L-Tryptophan (= 5-HTP)
$RCHNH_2COOH$
$R = C_αH_2CCHNHph(OH)$

c) Serotonin
RCH_2NH2
$R = C_αH_2CCHNHph(OH)$

RH_Figure 4 a,b.



a) Histidine
$RCHNH_2COOH$
$R = C_αH_2(CNHCHNCH)$

b) Histamine
RCH_2NH_2
$R = C_αH_2(CNHCHNCH)$