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Molecular structure of noradrenaline according to gas-phase electron diffraction data and quantum chemical calculations

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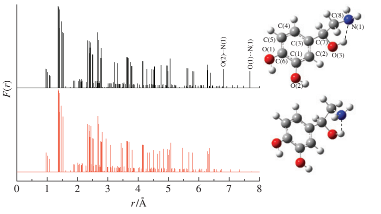
The structures of two main noradrenaline conformers were determined using gas-phase electron diffraction. These conformers are stabilized by intramolecular hydrogen bonds between the nitrogen atom of the amino group and hydrogen of hydroxyl group attached to an ethylamine carbon atom.



Noradrenaline (NA), also called norepinephrine, is an important compound attracting continual interest. Like other catecholamines such as adrenaline and dopamine, it plays an essential role in living organisms as hormone and neurotransmitter.[1,2]

Having some freedom degrees for internal rotation, NA can exist in various conformations with different arrangements of an ethylamine side chain and a catechol hydroxyl groups. The structure of NA was studied using *ab initio* and DFT calculations.[3] The possible NA conformers (in an amount of 108) have been revealed with density functional theory. A neutral unprotonated form of NA was not found in a crystal according to X-ray diffraction analysis; the zwitter-ion structure $^{-}O(OH)C_6H_4$–CH(OH)–CH_2–NH_3^+ can be formed by proton transfer from the *meta*-OH group to the NH_2 group.[4]

A vibrational spectroscopy study of NA[3] revealed two most stable conformers AG1a and GG1a (Figure 1). A combined IR and UV spectroscopic experiment identified only the AG1a conformer in a jet-cooled condition state.[5] The relative energies of NA conformers were estimated by DFT and *ab initio* methods. The most stable conformer AG1a was obtained by DFT/B3LYP/cc-pVTZ calculations. The df-MP2/cc-pVTZ and df-LMP2/aug-cc-pVTZ approach indicated the AG1a conformer, whereas MP2/aug-cc-pVTZ and MP2/cc-pVTZ calculations led to the GG1a conformer as a global minimum.

The aim of this work was to study the molecular structure of NA by a gas electron diffraction technique. The favorable NA conformer groups (GG and AG, Figure 2) were taken into consideration.[5] The letters G and A correspond to the *gauche* or *anti* configuration of the ethanolamine chain, *i.e.*, C^3–C^7–C^8–N^1 and O^3–C^7–C^8–N^1 atom positions, respectively. Last letters (a–d) describe the orientations of hydroxyl groups in the catechol moiety of NA.

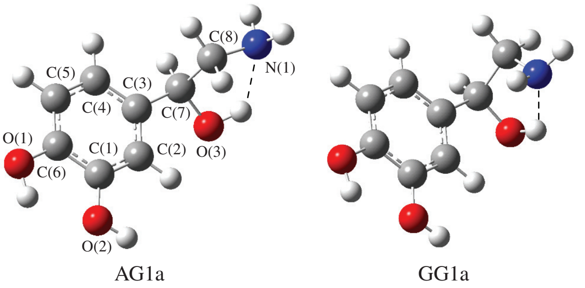


Figure 1 Molecular structure of the most abundant NA conformers. AG1a conformer has atom numbering as defined in this paper.

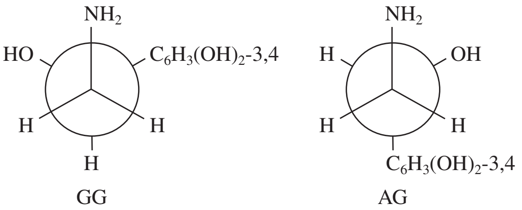


Figure 2 Newman projection of GG and AG conformers of NA around the C(7)–C(8) single bond.

The geometries of 20 most stable NA conformers (GG and AG) are optimized at B3LYP/cc-pVTZ, MP2/cc-pVTZ levels of theory using the Gaussian 03 program.[6] The harmonic vibrational frequency calculations were computed at B3LYP/cc-pVTZ and MP2/cc-pVTZ levels of theory, respectively. The CCSD/cc-pVTZ geometry optimization was performed for the most favorable conformers AG1a and GG1a.

The free Gibbs energy differences of 20 low-lying GG and AG conformers were summarized in Table S1 (see Online Supplementary Materials). The MP2/cc-pVTZ data appoint GG1a to be the most stable form (by 1.06 kJ mol^{-1}, as compared with the AG1a conformer). However, according to the B3LYP/cc-pVTZ energy calculations, the GG1a conformer is less stable by about 2.5 kJ mol^{-1}. The CCSD/cc-pVTZ energy difference of 0.5 kJ mol^{-1} between AG1a and GG1a indicates AG1a as the most abundant conformer. The calculated relative energy differences in case of NA are most likely due to an inaccurate B3LYP estimation of hydrogen bonds occurring in these conformers and weak NH-π interaction. An unclear quantum chemical prediction regarding the global minimum of NA can result from a nearly the same ratio between GG1a and AG1a conformers.

To estimate mole fractions of NA conformers, the energy values from both B3LYP/cc-pVTZ and MP2/cc-pVTZ approaches were taken according to the Boltzmann distribution (see Table S1).

Table 1 Comparison of bond lengths (Å) in NA and related compounds determined from GED studies.

Bond	NA[a] (AG1a, GG1a)	Ethylamine[9]	Dimethylamine[10]	Vanillin[11]	NA X-ray[4]	Phenol[12]
C_{ring}–C	1.509(9), 1.529(9)				1.524	
C–C	1.538(9), 1.539(9)	1.531(6)	1.531(6)		1.511(3)	
$(C_{ring}–C_{ring})_{av}$	1.393(1)			1.397(4)	1.395	1.399(3)
C_{ring}–OH	1.364(1), 1.378(1)			1.361(9)	1.378	1.381(4)
C–N	1.466[b]	1.450(10)^{gauche} 1.470(10)^{trans}	1.465(2)		1.496	

[a] This work. [b] Fixed.

Based on the calculated mole fractions, we concluded that gaseous NA was a mixture of 20 conformers. A significant part of this mixture consisted of two conformation families, 49% AG1(a–d) and 27% GG1(a–d), whose structures differ in the configurations of pyrocatechol fragments (Figure S1). As concluded, the mole fractions of these conformations are sufficient (to 74% by B3LYP/ cc-PVTZ) to hold a majority in respect of other conformations.

Using MP2/cc-pVTZ and DFT/B3LYP/cc-pVTZ approaches we calculated the identical geometric parameters for all skeleton atoms in AG1(a–d) and GG1(a–d) conformers, respectively. The difference was revealed for OH group positions in pyrocatechol fragment (see Figure S1). Because of poor electron diffraction sensitivity to H atom positions, the structural analysis was performed for only AG1a and GG1a conformers. Although the gas phase electron diffraction (GED) analysis of neutral NA seems complicated, the presence of two different conformer families allowed us to carry out the structural analysis.[†]

Figure 3 shows the resulting radial distribution curves for an AG1a and GG1a conformer model (1 : 1 mixture). The final model can be characterized by single correlation coefficients of 0.8 and 0.7 in a least-squares correlation matrix (R_f = 7.0%). The test of single conformer models was also performed. The model of AG1a had R_f = 7.5%, whereas R_f for GG1a was 7.1%. The radial distribution curves of NA (see Figure 3) show a large number of terms with interatomic distances to 6 Å; the curves for GG1a and AG1a forms are almost indistinguishable in this field. The AG1a conformer has a characteristic peak in a region of 6.5–7.7 Å due to the terms O(2)···N(1) and O(1)···N(1), while the GG1a form has no terms with heavy atoms after 6.5 Å. Nevertheless, structural analysis demonstrated that the model of a GG1a and AG1a conformer mixture did not lead to a significant lowering of the *R*-factor value, as compared to the models of single conformers. This can be caused by either a predominant contribution of the GG1a conformer in gaseous NA or the MP2 assumption used in the GED model.

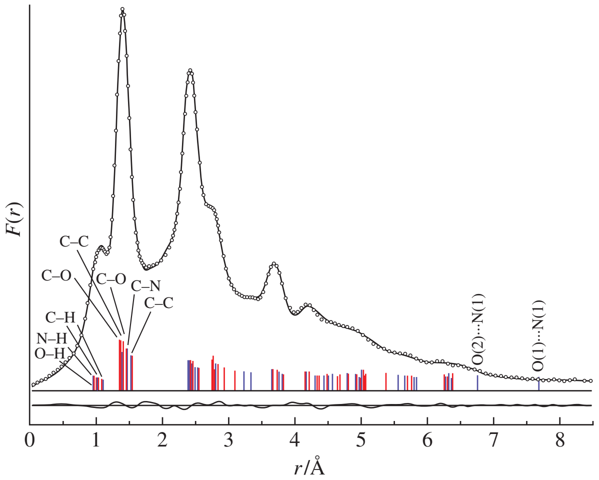


Figure 3 Experimental (open circles) and theoretical (solid line) radial distribution curves *F*(*r*) with difference curve for the mixture of AG1a and GG1a conformers. The distribution of distances is indicated by blue (AG1a conformer) and red (GG1a conformer) terms.

Intramolecular hydrogen bonds in NA occur in the catechol moiety (O–H···O, 2.05 Å), in the ethanolamine chain (N···HO, 2.05 Å) and between them (C–H···O). The N···OH hydrogen bond located in the OCCN side chain leads to a significant constriction of the side chain and stabilization of both AG1a and GG1a conformers as the most abundant forms. Its length determined from GED data (2.05 Å) is lower than the sum of the van der Waals radii of nitrogen and hydrogen atoms (2.6 Å).

The structural parameters of NA obtained from GED data are consistent with the results of MP2 and CCSD calculations: a difference between the experimental and calculated values does not exceed 0.01 Å for the bond distances or 3.6° for the bond angles (Table S3). The refined torsion angles (see Table S3) deviate by about 7° and 13° from the theoretical ones and they can be considered as effective values obtained after averaging conformations. These deviations do not principally change the conformation of two studied forms, AG1a and GG1a. Being responsible for conformation variety of NA structure, the ethanolamine part of NA is the most flexible one in a molecule. Table 1 contains single bonds in NA compared to some amine and catechol compounds. The cathechol fragment of NA is nearly planar both in crystal and gas phases. The zwitter-ion structure obtained by X-ray analysis shows different bond lengths [C(8)–N(1), C(1)–O(2)] compared to neutral form from gas electron diffraction one.

Thus, we carried out the first GED structural study of NA. The main conformations of NA molecule are stabilized by intramolecular hydrogen bonds. Some differences in bond lengths for gas and crystal phases occur due to either a neutral or a zwitter-ion form.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.07.018.

[†] Commercial NA (purity 99%) from Aldrich was used without additional purification. The analysis of NA performed on a QTarp AB Sciex 3200 hybrid tandem mass spectrometer with two ionization sources [Turbo Spray (ESI) and Heated Nebulizer (APCI)] allowed us to ensure the existence of a pure substance under experimental conditions. The electron diffraction patterns were obtained on an EG-100M device with an accelerating voltage of 60 kV at 446 K in the Gas Electron Diffraction Laboratory at M. V. Lomonosov Moscow State University. The experimental and theoretical molecular components of the intensity of scattering sM(s) and the difference curve are shown in Figure S2.

The UNEX program[7] was applied to process GED data using a least-squares method. The structural parameters of the AG1a conformer were refined in the groups with corresponding parameters of the GG1a conformer (Table S3). The vibration amplitudes and harmonic vibrational corrections to the internuclear distances ($r_{h1} - r_a$) were calculated from MP2/cc-pVTZ force constants using the SHRINK program.[8] The mean amplitudes were grouped in respect of different radial distribution peaks. The molecular model included 63 independent parameters.

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