ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 3, pp. 354–361. © Pleiades Publishing, Ltd., 2019.
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Dynamic Structure of Organic Compounds in Solution According to NMR Data and Quantum Chemical Calculations: III.[1] Noradrenaline

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Received May 16, 2018; revised May 28, 2018; accepted June 19, 2018

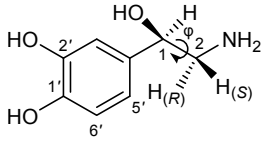
Abstract—Parameters of restricted internal rotation about the C–C bond of the O–C–C–N fragment in the neutral and protonated forms of noradrenaline in D_2O, CD_3OD, and DMSO-d_6 were estimated by quantum molecular dynamics and NMR methods. The one-dimensional internal rotation potentials were calculated in the MP2/aug-cc-pVTZ approximation. The multiplet structure of the ^1H NMR spectra of neutral and protonated noradrenaline in the given solvent series was resolved, and signals of diastereotopic methylene protons pro-*S* and pro-*R* were assigned. The conformational dependences of the proton coupling constants were calculated at the FPT-DFT 6-311++G(2*df*,2*p*) level of theory. The relative contributions of different rotamers were evaluated by solving a series of inverse vibrational problems in terms of the large-amplitude vibration model to achieve the best agreement between the calculated and experimental coupling constants. The neutral form of noradrenaline was shown to prefer conformation $\mathbf{g}^+$, while conformer $\mathbf{g}^-$ was found to be the minor one. Protonation of noradrenaline molecule essentially stabilizes conformer $\mathbf{g}^-$. In all cases, the contribution of conformer **t** with transoid orientation of the oxygen and nitrogen atoms did not exceed 1%. The obtained data can be useful for the construction of a quantitative model for noradrenaline binding to receptors at the molecular level.

Keywords: noradrenaline, protonation, conformation, rotamers, large-amplitude vibrations, spin–spin coupling constants.

DOI: 10.1134/S107042801903014X

Interest in noradrenaline is determined by its specific role in living systems where it acts as both hormone affecting almost all metabolic processes and neuromediator. The low volatility of noradrenaline and its poor solubility in most solvents create some difficulties in studying its physicochemical properties in the gas phase and in solution. Most publications were concerned with model compounds and were confined to theoretical calculations [2–4].

We set ourselves the task of characterizing the dynamic behavior of noradrenaline and its protonated form in solution at a quantitative level with the aid of quantum molecular dynamics and NMR spectroscopy [1, 5]. The noradrenaline molecule possesses a single chiral center, so that two mirror stereoisomers (enantiomers) are possible. Herein, both theoretical and experimental data were obtained for the natural *R* isomer of noradrenaline.



(*R*)-Noradrenaline

The conformational dynamics of noradrenaline is determined by exceptionally fast restricted internal rotation about the C^1–C^2 and C^1–$C^{4'}$ bonds. The main factor determining mutual arrangement of the functional groups is rotation about the C^1–C^2 bond, and both steric repulsion and electronic effects should be taken into account as well [4]. Intramolecular hydrogen bond between the aliphatic hydroxy proton and amino nitrogen atom in the neutral form is also important. Conformations of the aromatic hydroxy groups should also be considered.

The protonated form of noradrenaline in crystal is characterized by hydrogen bonding between a proton

[1] For communication II, see [1].

of the ammonium group and oxygen atom of the aliphatic hydroxy group [6]. Analogous strong hydrogen bonds are typical of protonated aliphatic 2-amino alcohols [7, 8] and their heterocyclic analogs [9]. The calculated hydrogen bond energy in the protonated forms of these compounds is considerably higher than in the corresponding free bases [7, 8], which may lead to a dramatic change of the molecular conformation on protonation [10]. It should be noted that this structural motif was utilized in the design of a number of pH-controlled molecular switches [11, 12].

The structure of the isolated noradrenaline molecule was optimized in terms of the second-order Møller–Plesset perturbation theory with aug-cc-pVTZ basis functions. Figure 1 shows the calculated potential energies of neutral noradrenaline molecule and its protonated form plotted against the OC^1C^2N dihedral angle (φ). The potential curve contains three minima. The global minimum corresponds to a dihedral angle φ of 57°, and somewhat higher energy (0.14 kcal/mol) was found for φ = –50°. These most stable conformers ($\mathbf{g}^+$ and $\mathbf{g}^-$) are characterized by *gauche* configuration with spatially close nitrogen and aliphatic OH oxygen atoms (Fig. 2).

It is important that strong intramolecular hydrogen bond involving the OH oxygen atom is formed in conformers $\mathbf{g}^+$ and $\mathbf{g}^-$ ($R_{H\cdots N}$ = 2.102 Å for the global minimum and $R_{H\cdots N}$ = 2.049 Å for the local minimum at φ = –50°). Although the H···N distance for the local minimum is shorter, a combination of all other electronic factors makes that conformer somewhat less favorable. Interestingly, the strongest hydrogen bond with $R_{H\cdots N}$ = 1.818 Å is observed in the saddle point at φ = –3°. However, this structure has a considerably higher energy than that corresponding to the global minimum because of strong steric repulsion intrinsic to the eclipsed conformation. No intramolecular hydrogen was found for the third potential energy minimum at φ = 181° (conformer **t**) due to remoteness of the hydroxy group from the amino group ($R_{O\cdots N}$ = 3.858 Å); therefore, the energy of **t** (2.94 kcal/mol) was significantly higher than that of the global minimum.

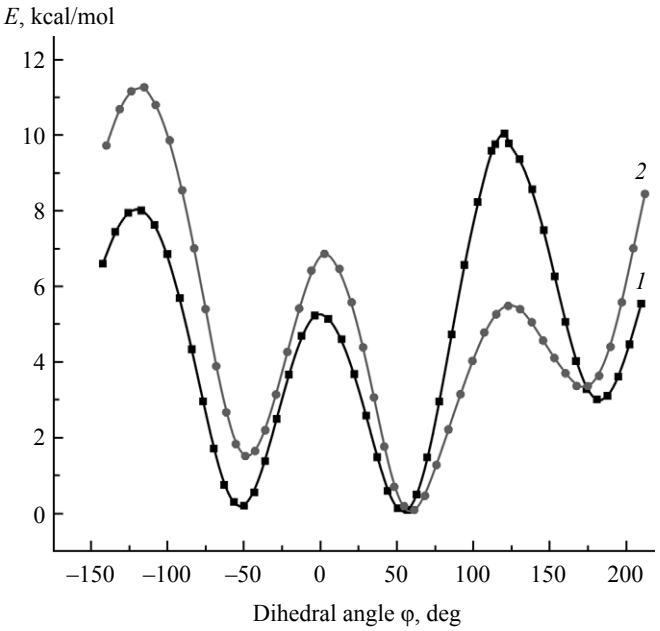


Fig. 1. Potential energy profiles of (*1*) noradrenaline and (*2*) its protonated form against the dihedral angle OC^1C^2N (φ).

A similar pattern is observed for the protonated form of noradrenaline. Its global minimum is located at a φ value of 61° (conformer $\mathbf{g}^+$; Fig. 3). However, the energy of the first local minimum (conformer $\mathbf{g}^-$, φ = –49°) is larger (1.32 kcal/mol) than the energy of the neutral species. Considerably higher second local minimum appears at φ = 175° (conformer **t**). As in the neutral molecule, there is a strong intramolecular hydrogen bond in conformers $\mathbf{g}^+$ and $\mathbf{g}^-$ of the protonated form, but this bond involves one of the three NH_3^+ protons rather than the OH proton. The hydrogen bond in $\mathbf{g}^+$ is much stronger than in $\mathbf{g}^-$ ($R_{H\cdots N}$ 1.865 and 2.026 Å, respectively). The strength of the intramolecular hydrogen bond in conformer $\mathbf{g}^+$ is the main factor responsible for the enhanced stability of protonated noradrenaline. Likewise, intramolecular hydrogen bonding in conformer **t** of the protonated form is impossible because of the long distance between the oxygen and nitrogen atoms ($R_{O\cdots N}$ = 3.636 Å).

Comparison of the potential energies at the stationary points provides an important but incomplete

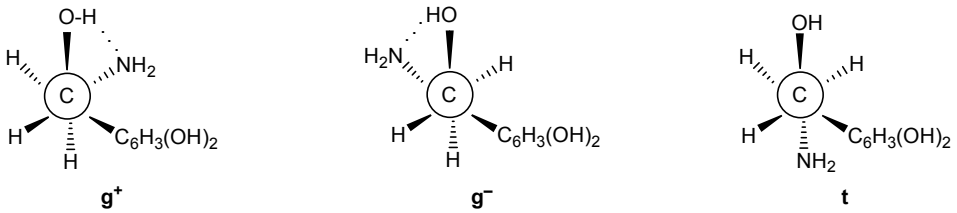


Fig. 2. Newman projections of the most stable conformers of noradrenaline along the C^1–C^2 bond.

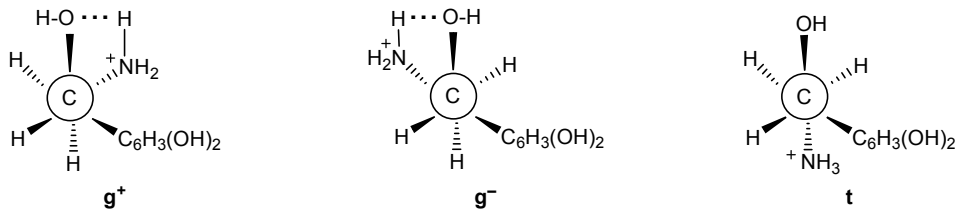


Fig. 3. Newman projections of the most stable conformers of protonated noradrenaline along the C^1–C^2 bond.

characterization of dynamic systems with restricted internal rotation and large-amplitude vibrations. While estimating the contributions of different conformations, factors determining the kinetic energy of the system should also be taken into account, in particular the potential energy curvature in the vicinity of the energy minimum, degree of participation of atoms in the vibrational movement (i.e., vibrational amplitude), and their weight [13]. This becomes especially important if heavy atoms and/or bulky fragments with a rigid structure are actively involved in vibrational motion. In the noradrenaline molecule, such a rigid structural fragment is the pyrocatechol moiety. In order to study the dynamic structure of noradrenaline and its protonated form we have determined the vibrational Hamiltonian [13] and calculated energy levels, vibrational wave functions, and distribution functions. The latter characterize the relative probability of a given state of a system and are necessary to estimate thermal motion-averaged coupling constants. Qualitative analysis of the distribution function makes it possible to identify peaks corresponding to the potential energy minima; the lower the energy minimum, the higher the distribution function peak. Peak integration gives quantitative estimate of the contribution of one or another form. By numerical integration of the distribution functions corresponding to the potentials shown in Fig. 1 we estimated the relative contributions of structures $\mathbf{g}^-$, $\mathbf{g}^+$, and **t** for both noradrenaline and its protonated form (Table 1). As follows from the given data, $\mathbf{g}^+$ is the major conformer of the two systems in the gas phase.

Conformational behavior of a system with internal rotation about one of its bonds is reflected primarily in those coupling constants for which the path of transmission of spin–spin coupling changes in the explicit form. Qualitative dependences of vicinal coupling constants on the dihedral angle including coupling transmission path are widely used in practice. Nevertheless, the geometry factor is not the only one responsible for variation of coupling constants. Here, an important role is played by the effects of substituents, multiple bonds, and structure of surrounding fragments [14]. Attempts to consider all these factors at a semiempirical level turned out to be quite cumbersome, and they did not ensure high accuracy in the prediction of coupling constants [15].

In this work we performed *ab initio* calculations of coupling constants at the FPT/DFT level [16]. Figure 4 shows the calculated dependences of vicinal coupling constants on the dihedral angle φ. The vicinal coupling constants between the 1-H proton and methylene protons 2-$H_{(S)}$ and 2-$H_{(R)}$ ($^3J_{1\text{-H,2-H}(S)}$ and $^3J_{1\text{-H,2-H}(R)}$) vary over a wide range, from 0.2 to 11.7 Hz. The coupling constants in the molecules under study are determined mainly by the geometry factor. The minimal values of $^3J_{1\text{-H,2-H}(S)}$ for noradrenaline are observed at φ ≈ –134° and 37°, and the maximum values, at φ ≈ –50° and 130°. A similar dependence was found for the pro-

Table 1. Conformational equilibrium parameters for the most stable conformers of noradrenaline and its protonated form (percent fractions of conformers $\mathbf{g}^-$, $\mathbf{g}^+$, and **t** are given)

Medium	Neutral form			Protonated form		
	$\mathbf{g}^-$	$\mathbf{g}^+$	**t**	$\mathbf{g}^-$	$\mathbf{g}^+$	**t**
Gas phase	28.0	71.6	0.4	10.3	89.2	0.5
DMSO-d_6	33.4	66.5	0.1	91.8	7.7	0.5
CD_3OD	36.0	63.5	0.5	95.1	4.3	0.6
D_2O	45.4	54.4	0.2	93.3	6.2	0.5

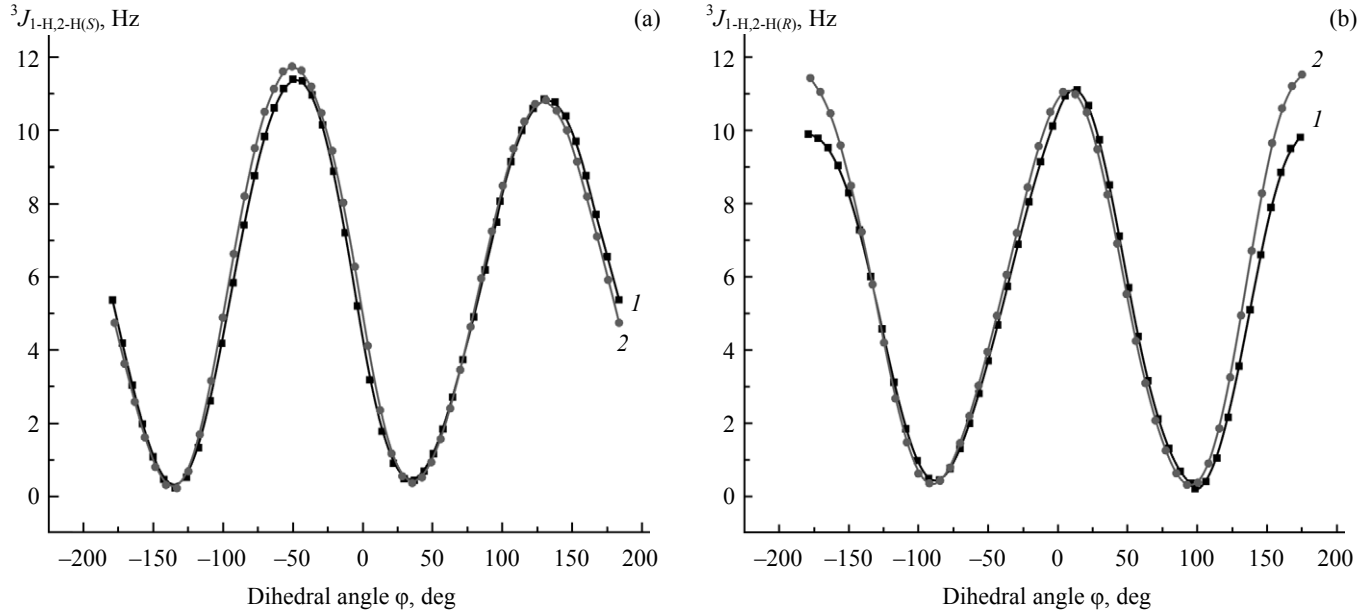


Fig. 4. Plots of the vicinal coupling constants (a) $^3J_{1\text{-H,2-H}(S)}$ and (b) $^3J_{1\text{-H,2-H}(R)}$ versus dihedral angle OC^1C^2N (φ) for (*1*) noradrenaline and (*2*) its protonated from.

tonated form of noradrenaline: the coupling constant $^3J_{1\text{-H,2-H}(S)}$ acquired minimum values at φ ≈ –133° and 35°, and maximum values, at φ ≈ –50° and 131°. It should be noted that the $^3J_{1\text{-H,2-H}(S)}$ values almost coincide at both minimum and both maximum points. The coupling constant $^3J_{1\text{-H,2-H}(R)}$ for noradrenaline had minimum values at φ ≈ –85° and 98° and maximum values at φ ≈ 13° and 174°. The smallest $^3J_{1\text{-H,2-H}(R)}$ values for protonated noradrenaline were observed at φ ≈ –92° and 92°, and the largest values, at φ ≈ 4° and 175°. Protonation of the nitrogen atom almost did not affect the coupling constants. Only the $^3J_{1\text{-H,2-H}(R)}$ value of protonated noradrenaline was higher by ~1.7 Hz at φ values ranging from ~150° to 180°.

We performed complete analysis of the ^{1}H NMR spectra of noradrenaline and its protonated form in D_2O, CD_3OD, and DMSO-d_6. The signals were assigned on the basis of the ^{1}H and ^{13}C NMR data, including signal multiplicity in proton-coupled spectra, and two-dimensional COSY, HSQC, and HMBC experiments for noradrenaline hydrochloride. The ^{1}H NMR spectrum of noradrenaline hydrochloride displayed well resolved multiplets of aromatic and aliphatic protons (Fig. 5).

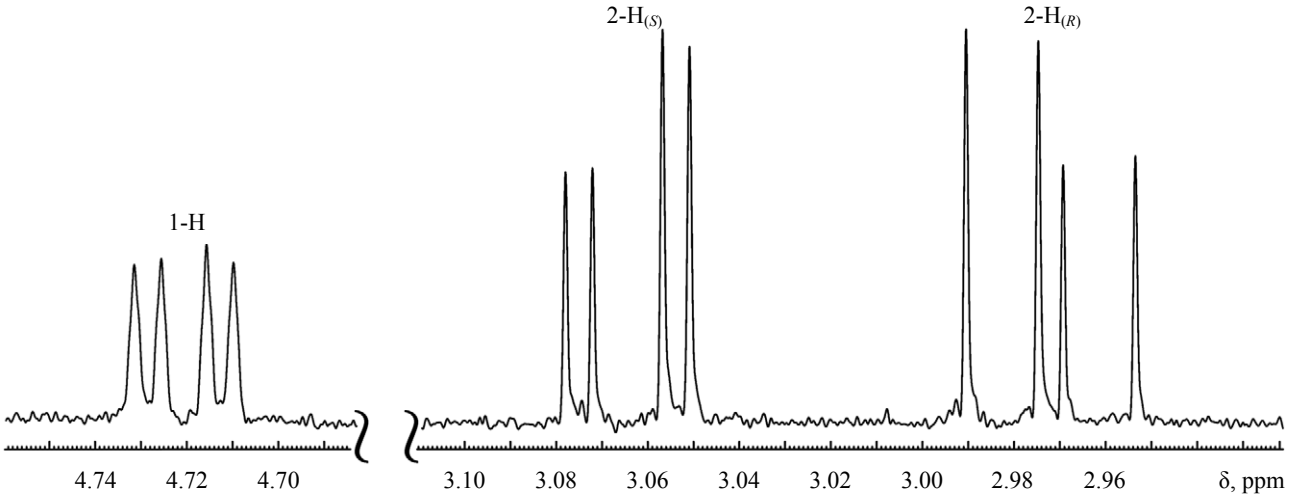


Fig. 5. Aliphatic proton region of the ^{1}H NMR spectrum of noradrenaline hydrochloride in CD_3OD at 303 K.

Table 2. Experimental and calculated $^{1}H–^{1}H$ coupling constants (Hz) of noradrenaline and its protonated form[a]

Coupling constant	DMSO-d_6		D_2O		CD_3OD	
	experimental	calculated	experimental	calculated	experimental	calculated
Neutral form						
$^{3}J_{1\text{-H,2-H}(R)}$	7.83(2)	8.00	7.55(2)	7.31	7.78(1)	7.86
$^{3}J_{1\text{-H,2-H}(S)}$	4.35(2)	4.47	5.60(2)	5.43	4.64(1)	4.70
$^{2}J_{2S,2R}$	–12.78(2)	–[b]	–13.08(2)	–[b]	–13.02(1)	–[b]
Protonated form						
$^{3}J_{1\text{-H,2-H}(R)}$	9.82(5)	9.81	8.81(2)	8.81	9.56(1)	9.57
$^{3}J_{1\text{-H,2-H}(S)}$	3.15(5)	3.39	4.04(2)	4.04	3.46(1)	3.47
$^{2}J_{2S,2R}$	–2.70(5)	–12.70	–13.08(2)	–13.08	–12.72(1)	–12.71

[a] In parentheses are given standard deviations for experimental coupling constants.
[b] Ill-conditioned estimate.

The aliphatic part of the spectrum was analyzed in terms of the *ABX* spin system. At this stage we succeeded in distinguishing ab_+ and ab_- subspectra in the methylene proton region. Analysis of the relative line intensities in the subspectra unambiguously indicated that the coupling constants $^{3}J_{1\text{-H,2-H}(S)}$ and $^{3}J_{1\text{-H,2-H}(R)}$ have the same sign. On the basis of numerous available experimental data (see, e.g., [17, 18]) the geminal coupling constant for the diastereotopic methylene protons was assigned a negative sign. The final coupling constant values (Table 2) were obtained by treatment of the data for 12 line frequencies of the experimental spectrum and transitions in the calculated spectrum using LAOCOON PC program [19, 20].

It has recently been shown [7, 8] that many β-amino alcohols tend to change their conformation upon variation of the acidity of the medium. Primary and secondary aliphatic amines are strong bases; the pK_a values of the corresponding conjugate acids range from 6 to 9 [21]. Taking this into account, we analyzed the NMR spectra of noradrenaline upon variation of pH using NMR titration technique. The titrant was a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This base was selected on the basis of the following considerations. First, it is much more basic (pK_a of conjugate acid 12.84±0.20 [21]) than noradrenaline (pK_a 8.30±0.13 [22]); second, its NMR signals do not overlap those of noradrenaline in all the examined solvents at any basicity. We believe that the choice of DBU was also successful since it displays no nucleophilic properties [23] and therefore does not affect the substrate behavior, thus allowing long-term NMR experiments to be performed. For each titration point, the ^{1}H NMR spectra were recorded, and the multiplet structure of aliphatic proton signals was iterated, each time using the data for 12 spectral components. The mean-square deviations of line frequencies in the experimental and calculated spectra were in the range from 0.01 to 0.05 Hz. As a result, we obtained fairly smooth titration curves for chemical shifts of the three aliphatic protons and two vicinal and one geminal coupling constants. Table 2 contains the experimental and calculated parameters of the ^{1}H NMR spectra of noradrenaline as free base and protonated form.

Signal of the aliphatic protons of neutral noradrenaline are observed in a stronger field relative to those of the protonated form (on the average by 0.3 ppm), which is typical of amino alcohols [10, 12]. The methylene protons of noradrenaline base give strongly coupled multiplet signals. The $2\text{-H}_{(S)}$ signal is located upfield from the $2\text{-H}_{(R)}$ signal. The geminal coupling constant $^{2}J_{2S,2R}$ changes only slightly upon variation of the solvent and acidity. The vicinal coupling constant $^{3}J_{1\text{-H,2-H}(S)}$ is always smaller than $^{3}J_{1\text{-H,2-H}(R)}$; as the acidity increases, the former constant further decreases (the difference reaches 1.46 Hz for noradrenaline in D_2O), while the latter simultaneously increases by 1.26 to 2.00 Hz.

An important aspect of conformational analysis is consideration of the effects of the medium. Our quan-

tum chemical calculations were performed for the gas phase. In many cases, the results of such calculations provide good estimates for nonpolar molecules and nonpolar solvents [24]. Noradrenaline and especially its protonated form are polar molecular entities, and solvent effects should necessarily be included while simulating their NMR parameters. The available published data [25, 26] suggest that solvents almost do not affect coupling constants in rigid systems.

In the final stage of our study we made an attempt to solve the reverse spectral–structural problem, i.e., to find such potential energy surface parameters that would ensure best description of the experimental coupling constants. For this purpose, multidimensional optimization was used [1]. The Hamiltonian was modified with various sets of trigonometric functions ($\cos\varphi$, $\cos 2\varphi$, etc.). In all cases, the inclusion of only one first term ($\cos\varphi$) allowed us to eliminate almost completely the difference between the experimental and calculated coupling constants for both noradrenaline and its protonated form (Table 1).

Comparison of the conformer populations in different media showed that increase of the polarity of the medium in the series gas phase < DMSO-d_6 < CD_3OD < D_2O was accompanied by smooth increase of the contribution of conformer $\mathbf{g}^-$ of neutral noradrenaline. Protonation of noradrenaline leads to substantial stabilization of conformer $\mathbf{g}^-$ in the examined solvents, presumably due to very high polarity of that conformer. The dipole moment of $\mathbf{g}^-$ is 14.6 D, which is considerably higher than the dipole moment of $\mathbf{g}^+$ (9.5 D). In all cases, the contribution of structure **t** with transoid orientation of the oxygen and nitrogen atoms did not exceed 1%. These data could form the basis for the construction of a quantitative model of noradrenaline binding to receptors at the molecular level.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 303 K on a Bruker AV-600 spectrometer (600 MHz for ^{1}H) from solutions in D_2O, CD_3OD, and DMSO-d_6. Tetradeuterotrimethylsilylpropionic acid sodium salt (TSP-d_4, δ –0.0015 ppm) was used as standard for aqueous solutions. The complete signal assignment for (*R*)-(–)-noradrenaline hydrochloride (Aldrich), including diastereotopic 2-$H_{(R)}$ and 2-$H_{(S)}$ proton signals, was made for its solution in DMSO-d_6 using the data of proton-coupled ^{13}C NMR spectra and two-dimensional COSY, HSQC, and HMBC experiments (for details, see [27]).

For NMR titration, initial solutions of noradrenaline hydrochloride in the corresponding deuterated solvent with a concentration of 0.05–0.07 M were prepared (initial volume 0.68 mL). The titrant was a 1 M solution of DBU in the same solvent, which was added in 2–10 μL portions to the substrate solution directly in an NMR ampule, and the mixture was thoroughly stirred by shaking. The ampule was kept for 5–7 min in the NMR probe for temperature equilibration, and ^{1}H NMR spectrum was recorded. After 10–15 successive additions of the titrant, the volume of the solution changed by no more than 10% of the initial volume.

Quantum chemical calculations were performed using Gaussian 09 software package [28]. The potential energy surfaces were constructed by scanning the molecular energy with respect to the dihedral angle $C^{4'}C^1C^2N$ with optimization of all other geometric parameters in the relaxed scan mode [24]. The scanning was conducted in both forward and backward directions with a step of 7.5°. Points corresponding to lower energies were finally selected.

The coupling constants were calculated at the FPT/DFT B3LYP/6–311++G(2*df*,2*p*) level of theory in the mixed mode with account taken of Fermi contact, spin–dipole, paramagnetic spin–orbit, and diamagnetic spin–orbit contributions [16]. This calculation mode includes two stages. In the first stage, the Fermi contact term was calculated using a basis set with a large number of polarization components. This term contributes most to the coupling constant value, and those space regions which directly comprise nuclei involved in the spin–spin coupling are especially important for its calculation. Augmentation of basis set with additional polarization functions enhances the accuracy of determination of electron density in the nuclei zone. The calculation of the remaining three terms does not require so high quantum chemical approximation level, so that they were calculated in the second stage using less cumbersome basis sets. We thus succeeded in shortening the overall computational time by a factor of 2–3 without appreciable loss in accuracy. The conformational dependences of coupling constant were used in the form of 11-term analytical approximations including a free term and coefficients at $\cos(n\varphi)$ and $\sin(n\varphi)$ where n = 1–5. In all cases, these harmonic expansions allowed determination of coupling constants with an accuracy of no less than 0.02 Hz.

The energy levels and internal rotation wave functions were determined by numerical solution of

Schrödinger equations by the Ritz variational method [13]. One-dimensional vibrational problems were solved using a basis set consisting of 360 trigonometric functions; the Hamiltonian eigenvalues were calculated with an accuracy of no less than 10^{-8} kcal× mol^{-1} using Revibr 6.23 procedure [29]. The kinetic energy Hamiltonian was built up by supplementarily calculating mass-weighted reaction path coordinates for each local conformation characterizing internal rotation with respect to the dihedral angle φ (see above; total of 48 points) according to [30].

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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