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ADDITIVITY OF ^{13}C - ^1H AND ^1H - ^1H SPIN-SPIN COUPLING CONSTANTS
IN SIX-MEMBERED AROMATIC NITROGEN-CONTAINING HETEROCYCLES

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541.67

We have analyzed proton-coupled ^{13}C NMR and PMR spectra of pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, and 1,2,4-triazine for one-molar solutions of the compounds in $\text{DMSO}-d_6$. Comparison of the values obtained for the ^{13}C - ^1H and ^1H - ^1H spin-spin coupling constants with the values calculated on the basis of the spin-spin coupling constants in pyridine and benzene has shown that it is possible to predict the constants using linear additive equations. Substantial nonlinear deviations (5-6 Hz) are observed for $^1J_{\text{CH}}$ when the carbon atom is located between two adjacent nitrogen atoms.

The investigation of the ^{13}C - ^1H and ^1H - ^1H spin-spin coupling constants in six-membered aromatic nitrogen-containing heterocycles is of great interest for the study of the structure of the compounds [1, 2] and electronic substitution effects [3-5]. Prediction of these values is especially important, since it substantially facilitates analysis of the NMR spectra.

In contrast to the chemical shifts for protons and ^{13}C nuclei, which on the whole are satisfactorily amenable to theoretical calculation [6, 7], the ^{13}C - ^1H spin-spin coupling constants calculated by modern quantum-mechanical methods (for example by the INDO method in the Fermi-contact nuclear interaction approximation [8]) agree poorly with their experimental values. In most cases, this forces us to use empirical rules based on additive computational equations to determine the constants. Previously, for the case of poly-substituted benzenes [9-11] and monosubstituted pyridines [12, 13], it has been established that there is an additive substituent effect on the ^{13}C - ^1H and ^1H - ^1H spin-spin coupling constants.

$${}^nJ_{\text{bz}}(\text{XYZ}) = {}^nJ_{\text{bz}}(\text{H}) + \sum_{i=\text{X,Y,Z}} ({}^nJ_{\text{bz}}(i) - {}^nJ_{\text{bz}}(\text{H})); \quad (1)$$

$${}^nJ_{\text{pyr}}(\text{X}) = {}^nJ_{\text{pyr}}(\text{H}) + A \times ({}^nJ_{\text{bz}}(\text{X}) - {}^nJ_{\text{bz}}(\text{H})), \quad (2)$$

where ${}^nJ_{\text{bz}}$ and ${}^nJ_{\text{pyr}}$ are the constants in benzene and the pyridine ring; X, Y, and Z are substituents; A is a set of constants depending on the type of constant and the position of the substituent on the ring (range of values, 0.7-1.4).

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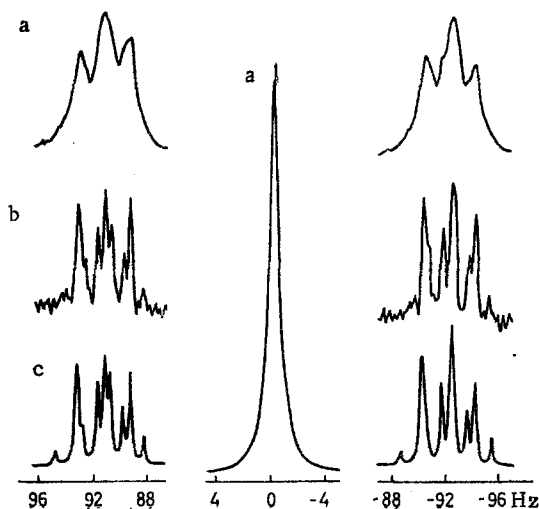


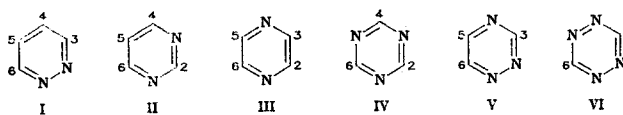
Fig. 1. PMR spectra of pyrazine (in the center, the principal signal; at the edges, the ^{13}C satellites): a) experimental spectrum; b) ^{13}C satellite spectrum after filtration; c) calculated spectrum; positive values of the scale are downfield.

TABLE I. Chemical Shifts for ^1H and ^{13}C , δ , and ^1H - ^1H Spin-Spin Coupling Constants for One-Molar Solutions of Compounds I-V in $\text{DMSO}-D_6$.

Compound	$\delta^1\text{H} \pm 0.001$ ppm (relative to TMS)					$\delta^{13}\text{C} \pm 0.02$ ppm (relative to TMS)				
	H ₍₂₎	H ₍₃₎	H ₍₄₎	H ₍₅₎	H ₍₆₎	C ₍₂₎	C ₍₃₎	C ₍₄₎	C ₍₅₎	C ₍₆₎
I	—	9,292	7,738	7,738	9,292	—	151,89	126,86	126,86	151,89
II	9,244	—	8,857	7,582	8,857	158,60	—	157,12	122,04	157,12
III	8,702	8,702	—	8,702	8,702	145,22	145,22	—	145,22	145,22
IV	9,396	—	9,396	—	9,396	166,07	—	166,07	—	166,07
V	—	9,832	—	8,906	9,515	—	157,89	—	149,98	151,10
Spin-spin coupling constant* ^1H - ^1H , Hz										
	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{2,6}$	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
I	—	—	—	—	5,10 (5,02)	1,85 (1,92)	1,46 (1,22)	8,29 (7,76)	1,85 (1,92)	5,10 (5,02)
II	—	0,34 (0,33)	1,52 (1,22)	0,34 (0,33)	—	—	—	4,96 (5,02)	2,52 (2,30)	4,96 (5,02)
III	2,73 (2,28)	—	1,70 (1,22)	-0,36 (-0,05)	—	-0,36 (-0,05)	1,70 (1,22)	—	—	2,73 (2,28)
IV	—	1,12 (0,79)	—	1,12 (0,79)	—	—	—	—	1,12 (0,79)	—
V	—	—	—	—	—	0,23 (0,41)	2,16 (1,50)	—	—	2,53 (2,39)

*The standard error in determining the constants is less than 0.04 Hz; within parentheses we give the values of the constants calculated using Eq. (3).

It seemed important to check the additive properties of the ^{13}C - ^1H and ^1H - ^1H spin-spin coupling constants for aromatic heterocycles containing more than one nitrogen atom on the ring. In this paper, we have investigated unsubstituted heterocycles (diazines: pyridazine I, pyrimidine II, pyrazine III; and triazines: 1,3,5-triazine IV, 1,2,4-triazine V; and also literature data are used for 1,2,4,5-tetrazine (VI) [5]).



The additive properties of the constants were tested using the linear equation which we proposed:

$${}^nJ_{\text{add}} = {}^nJ_{\text{bz}}(\text{H}) + \sum_{N_i} [{}^nJ_{i,\text{pyr}}(\text{H}) - {}^nJ_{\text{bz}}(\text{H})], \quad (3)$$

where summation is carried out relative to the number and position of the nitrogen atoms in the heterocycle. Data for the constants in pyridine [12] and benzene [14] are obtained in the literature with high accuracy.

Despite considerable information on the ${}^{13}\text{C}$ - ${}^1\text{H}$ and ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants in compounds I-VI [2, 5, 15], and also work on the study of the additivity of ${}^1\text{J}_{\text{CH}}$ [16], there was interest in obtaining these parameters for compounds under identical conditions, in order to eliminate the effect of solvent and concentration on the constants [3]. With this goal in mind, we have chosen one-molar concentrations for solutions of the compounds and the universal solvent DMSO- D_6 , used previously in the study of the constants in pyrazine derivatives [12, 13].

In Table 1 we give the parameters for the PMR spectra of compounds I-V, and also the chemical shifts for the ${}^{13}\text{C}$ nuclei. In the following, these parameters have been used for analysis of proton-coupled ${}^{13}\text{C}$ NMR spectra of the compounds. The values of the ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants in some cases are obtained by analysis of the ${}^{13}\text{C}$ satellites in the PMR spectra. Broadening of the signals in the PMR spectra due to coupling of protons with the quadrupole nuclei ${}^{14}\text{N}$ was compensated by artificial narrowing of the lines using filtration of the free induction decay by a Gaussian function, which allowed us to achieve resolution in the spectra on the order of 0.5 Hz. The most complicated case is represented in Fig. 1; the obtained values for the ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants in pyrazine are close to the constants for methylpyrazine [17] found from analysis of the principle lines of the PMR spectrum. In the rest of the cases, inaccurate values are given for the ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants in pyrazine in the literature [5].

In Table 1, we also present the values of ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants obtained using the additive equation (3). The greatest deviation between the experimental and calculated values for the constants was 0.66 Hz, the mean-square deviation was 0.33 Hz ($n = 15$). The result allows us to evaluate the applicability of additive calculations for predicting ${}^1\text{H}$ - ${}^1\text{H}$ spin-spin coupling constants in the investigated compounds.

Of greatest interest in this work was investigation of the additive properties of the ${}^{13}\text{C}$ - ${}^1\text{H}$ spin-spin coupling constants as some of the most informative parameters of the NMR spectra for aromatic compounds [12]. The values of the constants obtained in this work for compounds I-V are given in Table 2. In order to determine the constants, we analyzed the proton coupled ${}^{13}\text{C}$ NMR spectra; a typical example is given in Fig. 2. Comparison of the ${}^{13}\text{C}$ - ${}^1\text{H}$ spin-spin coupling constants with their values using the additive equation (3) (Table 2) allowed us in individual cases to refine the signs and magnitudes of constants determined previously [2, 15]. The greatest deviation between experimental values for the constants and calculated values is found for ${}^1\text{J}_{\text{CH}}$ when the carbon atom is located between adjacent nitrogen atoms (for example, $\text{C}(2)$ is pyrimidine). The range of deviations for the investigated compounds is 4.9-5.7 Hz. The characteristic features of nonlinear effects in these cases have been noted earlier for the chemical shifts of the ${}^{13}\text{C}$ nuclei in compounds II, IV, and VI [6]. Although a detailed explanation of the nonlinear effects within the framework of available theoretical calculations of the ${}^{13}\text{C}$ - ${}^1\text{H}$ spin-spin coupling constants is quite difficult, using pairwise corrections for the ${}^{13}\text{C}$ - ${}^1\text{H}$ spin-spin coupling constants of triazine and tetrazine (IV-VI) improves somewhat the results of the additive calculations (Table 2).

$${}^nJ_{\text{add}} = {}^nJ_{\text{add}} + 0.5 \times \sum_{N_i N_j} \Delta^n J_{ij}, \quad (4)$$

where ${}^nJ_{\text{add}}$ is from Eq. (3), $\Delta^n J = ({}^nJ_{\text{exp}} - {}^nJ_{\text{add}})$ diazine are the pairwise corrections from comparison of experimental values of the constants and those calculated using Eq. (3) in diazines (Table 2); the summation is carried out over all possible pairs of nitrogen atoms in the heterocycle.

Generalizing the results obtained for the ${}^{13}\text{C}$ - ${}^1\text{H}$ spin-spin coupling constants in compounds I-VI, let us describe qualitatively the additive properties of the constants. We observe a mean-square deviation of the experimental values and those calculated using the linear equation (3) for ${}^1\text{J}_{\text{CH}} = 0.94$ Hz ($n = 7$; we do not consider the constants for cases when the carbon atom is located between two adjacent nitrogen atoms in the ring); for ${}^2\text{J}_{\text{CH}} = 0.75$ Hz ($n = 8$); for ${}^3\text{J}_{\text{CH}} = 0.63$ Hz ($n = 9$); and for ${}^4\text{J}_{\text{CH}} = 0.31$ Hz ($n = 6$). When using pairwise corrections for compounds IV-VI, we observe mean-square deviation of the experimental values

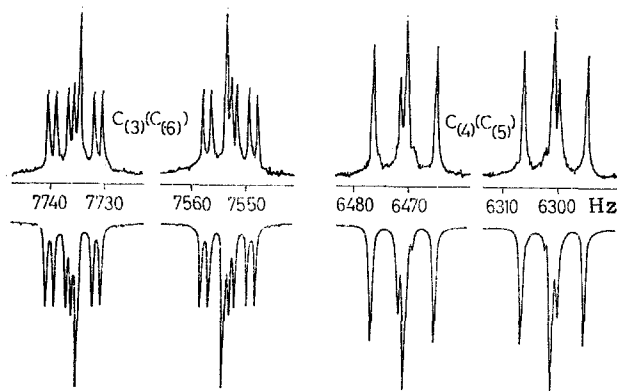


Fig. 2. Experimental and calculated proton-coupled ^{13}C NMR spectra for pyridazine, δ scale.

TABLE 2. Values of the ^{13}C - ^1H Spin-Spin Coupling Constants (Hz) for Compounds I-VI

Com- pound	n_{JCH}	J_{exp}^*	J_{add}^\dagger	Com- pound	n_{JCH}	J_{exp}^*	J_{add}^\dagger
I	$^1J_{3,3}$	182.55 (0.04)	183.38	III	$^1J_{2,2}$	183.50 (0.03)	183.38
	$^2J_{3,4}$	2.78 (0.04)	3.04		$^2J_{2,3}$	10.50 (0.03)	10.41
	$^3J_{3,5}$	5.90 (0.04)	5.76		$^3J_{2,6}$	9.64 (0.03)	10.00
	$^4J_{3,6}$	-1.53 (0.04)	-1.19		$^4J_{2,5}$	-1.40 (0.03)	-1.19
	$^1J_{4,4}$	169.88 (0.05)	168.77	IV	$^1J_{2,2}$	208.19 (0.02)	202.51 (207.35)
	$^2J_{4,3}$	6.58 (0.05)	7.96		$^3J_{2,4}$	7.87 (0.02)	8.95 (8.00)
	$^2J_{4,5}$	0.11 (0.05)	0.59	V	$^1J_{3,3}$	207.85 (0.04)	202.97 (207.68)
	$^3J_{4,6}$	5.22 (0.05)	5.17		$^3J_{3,5}$	9.17 (0.04)	9.23 (9.06)
II	$^1J_{2,2}$	202.95 (0.03)	197.53		$^4J_{3,6}$	-1.24 (0.04)	-0.76 (-1.24)
	$^3J_{2,4}$	10.36 (0.03)	10.31	$^1J_{5,5}$	190.29 (0.04)	188.36 (189.30)	
	$^4J_{2,5}$	-0.37 (0.03)	-0.44	$^2J_{5,6}$	8.88 (0.04)	10.02 (8.64)	
	$^1J_{4,4}$	182.63 (0.04)	182.92	$^3J_{5,3}$	7.40 (0.04)	8.64 (7.54)	
	$^2J_{4,5}$	2.71 (0.04)	2.80	$^1J_{6,6}$	189.29 (0.05)	188.89 (188.39)	
	$^3J_{4,2}$	8.93 (0.04)	9.72	$^2J_{6,5}$	9.52 (0.05)	10.26 (9.39)	
	$^3J_{4,6}$	5.27 (0.04)	5.48	$^4J_{6,3}$	-1.91 (0.05)	-1.51 (-1.90)	
	$^1J_{5,5}$	169.44 (0.03)	169.23	VI	$^1J_{3,3}$	214 [5]	208.41 (212.62)
	$^2J_{5,4}$	7.50 (0.03)	8.20		$^4J_{3,6}$	—	-1.08 (-1.95)
	$^4J_{5,2}$	-1.78 (0.03)	-1.94				

*The experimental values for the constants: in parentheses, the standard error; in square brackets, citations to the literature.

†Values of the constants, calculated using Eq. (3); in parentheses, using pairwise corrections, Eq. (4).

of the constants and those calculated using Eq. (4) for all $^1J_{\text{CH}} = 0.94$ Hz ($n = 5$), and for the rest, $J_{\text{CH}} = 0.15$ Hz ($n = 7$).

Thus, as a result of the investigations carried out, we have shown the applicability of the additive equations (3) and (4) for predicting values of the ^{13}C - ^1H and ^1H - ^1H spin-spin coupling constants in compounds I-VI, which, together with the results of preceding papers [Eqs. (1) and (2)] may be used to determine constants in complex aromatic nitrogen-containing heterocycles.

EXPERIMENTAL

The ^{13}C NMR and PMR spectra were recorded on a Bruker WP-200 SY spectrometer operating in the pulse regime (operating PMR frequency, 200.13 MHz; and ^{13}C NMR frequency, 50.33 MHz), for one-molar solutions of compounds I-V in DMSO- D_6 containing 3-5% (with respect to volume) TMS. Stabilization was accomplished using the NMR signal from the deuterium of the solvent. The temperature was $23 \pm 2^\circ$.

Conditions for Recording the Spectra. PMR spectra: ampul of diameter 5 mm; width of complete spectrum, 2 kHz; width of aromatic region, 400-600 Hz (number of accumulations >100; in the case of pyrazine, 2500). ^{13}C NMR spectra: ampul 10 mm; width of complete spectrum,

10 kHz (number of scans, 100; regime of complete proton spin decoupling); width of aromatic region, 1-2 kHz (number of accumulations more than 2000; delay between pulses, 10 sec). We used 32K computer memory capacity for accumulation of the free induction decay signal, and 16K for spectra after Fourier transformation.

The width of the line (at half height) in the PMR spectra for protons not having nitrogen atoms in the neighborhood (through two bonds) is equal to 0.3-0.4 Hz; for protons having one and two nitrogen atoms in the neighborhood, it was 0.9 and 1.4 Hz, respectively. For proton coupled ^{13}C NMR spectra, the values are 0.3-0.5 Hz. A Lorentz-Gauss transformation is used to narrow the PMR spectral lines [18].

All the spectra are calculated using the interaction program PANIC on the Aspect-2000 minicomputer. The ^{13}C NMR spectra were analyzed on the basis of the calculated parameters of the PMR spectra. In individual cases, for determination of the constants we used the ^{13}C satellites of the PMR spectra, taking into account the isotopic shifts of protons caused by substitution of the ^{12}C nucleus by ^{13}C . The initial parameters of the spectra were taken from [2, 5, 15]; the observed errors for the calculated parameters (taking into account the digital resolution of the spectra) are presented in Tables 1 and 2.

In this work, we used preparation II from the Fluka Company (Switzerland). Most of the rest of the compounds were obtained by familiar methods: I [19], III [20], IV [21], V [22]. The values of their physical constants correspond to those given in the literature.

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