Analysis of 2D Maps Based on Similarity in DFT-Calculated vs Experimental $^{13}$C–$^{15}$N Spin Couplings for a Representative Sample of Conformationally Rigid and Structurally Fixed Nitrogen-Containing Organic Compounds

Vladislav V. Stanishevskiy · Alla K. Shestakova · Vyacheslav A. Chertkov

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Abstract
In this work, we carried out an extended verification of the $^{13}$C–$^{15}$N spin–spin coupling constants as a new structural indicator of nitrogen-containing organic compounds. In this regard, we performed a quantum-chemical calculation (B3LYP with basis set 6-311++G(2df,2p)) for a representative sample of 193 spin–spin couplings for the currently known literature experimental data on them in the conformationally rigid and structurally fixed compounds. Comparison of theoretical couplings with experimental ones shows a statistically significant good to excellent agreement. A parallel analysis of the variability of the calculated values of $^{13}$C–$^{15}$N spin bonds with the variability of experimental data within groups of related compounds turned out to be practically useful. The approach developed can be used to quite reasonably determine the signs of spin–spin coupling constants $^{13}$C–$^{15}$N. It can also provide important additional information for assigning $^{13}$C peaks in cases where this cannot be done using standard NMR spectroscopy techniques.

1 Introduction

NMR spectroscopy, supported by modern quantum-chemical methods, has now become an indispensable tool for studying the structure and dynamics of organic compounds. The introduction of new pulsed, multidimensional NMR methods [1] and efficient methods of spectral analysis of complex multiplets [2, 3] make
available more accurate values of the NMR chemical shifts and indirect spin–spin coupling constants (SSCC). All this can make structure elucidation of new compounds more and more straightforward, accurate and reliable.

Further, a whole series of topical spectra-structural problems: characterizing the electronic and spatial structure of molecules arises on the basis of the parameters of the NMR spectra found in the experiment. Alternatively, vice versa, one can pose an inverse spectra-structural problem and predict what parameters of the NMR spectra can be expected for a given model configuration of a preassigned molecules [4, 5]. However, this approach has a number of disadvantages in comparison with modern methods for calculating the parameters of NMR spectra based on the quantum theory of molecular structure [6, 7].

However, in itself finding even the most accurate and reliable values of the NMR spectral parameters does not solve all the problems of structural chemistry for the compound under study. Nitrogen is an essential element involved in many interactions in living chemistry, the formation of hydrogen bonds, participation in the acid–base balance in vital systems. It plays a key role in the construction of a huge number of organic and natural compounds. Currently, structural studies of nitrogen-containing compounds require new approaches. In this respect, SSCC with $^{15}$N nuclei seem to be very promising.

The values of the couplings primarily depend on the structure of the molecule and depend relatively weakly on the effects of the medium and intermolecular interactions [8, 9], so they are widely used in conformational analysis [10, 11].

## 2 Methods

All quantum-chemical calculations in the present work were performed using the Gaussian 09 software package [12]. The structure of the studied objects was optimized in the isolated molecule approximation by the density functional method (DFT) with the hybrid density functional (B3LYP) with basis functions 6-311++G(2df,2p). The achievement of the global minimum was controlled by the presence of all real frequencies of the calculated oscillations in this geometric configuration. We have chosen DFT method, as it is more satisfactory according to such parameters as calculation time and self-consistency procedure (SCF) convergence. The specialized software package GaussView 5.0 was used for data preparation and visual control of the calculation progress.

The $^{14}$C$_{N}$ couplings were calculated also in the B3LYP approximation with the 6-311++G(2df,2p) basis set, the only DFT available in Gaussian 09 package [12]. All four constitutive terms: fermi-contact, spin-dipole, orbital-paramagnetic, and orbital-diamagnetic, were calculated altogether for the pre-optimized geometry of the molecule. In this technique, calculations were performed in the “mixed” mode [7], which allows to significantly reduce the level of computational resources [13]. A characteristic feature of this method is the calculation in two stages. At the first stage, the Fermi-contact term is calculated using a basis set containing an enlarged number of polarization components. According to our tests, the total size of the basis set increases by up to one and a half times compared to that which would
correspond to the above reference basis set 6-311++G(2df,2p). At the second stage, the remaining three terms are calculated with simplified basis sets. The tests show, that on this case, the estimates of all three terms, spin-dipole, orbital-paramagnetic, and orbital-diamagnetic practically change little compared to the calculations in the standard mode. Using “mixed” mode reduces the total calculation time by an average of about one and a half times. Our tests have shown that the estimates of all three terms—spin-dipole, orbital-paramagnetic and orbital-diamagnetic—change insignificantly compared to the standard mode (within 0.1–0.2 Hz). On the contrary, the term Fermi-contact term changes noticeably, which just obviously determines the higher resulting accuracy of this approach [13].

The use of the standard B3LYP functional instead of supposedly much more efficient NMR-oriented functionals, such as PBE0 or M06-2X [9], attracted us because the latter are not included in the widely used Gaussian 09 software package [12], which could significantly limit the scope of the results obtained.

3 Selection of Objects

Nitrogen is one of the most significant element involved in many interactions in living chemistry; it forms hydrogen bonds and can participate in acid–base equilibria. Nitrogen is part of a huge number of organic compounds and natural products. Nitrogen exists almost exclusively in the form of the 14N quadrupole isotope (~ 99.63%) with spin 1 and usually has a short spin–lattice relaxation time in NMR spectra. These intense and often strongly broadened signals of neighboring to the nitrogen atom groups in the 1H and 13C NMR spectra can almost completely mask weak 15N-satellites. This inevitably leads to a significant loss of accuracy in estimating the spin–spin coupling couplings associated with 15N, which could provide valuable information on the structure and dynamics of nitrogen-containing compounds [14]. The problem can be overcome using the 15N-labeled compounds [15, 16].

The average natural abundance of the spin ½ isotope 15N is only 0.364%. The specific magnetic properties of 15N nuclei with spin ½ and rather low relaxation rates of NMR signals make it highly informative and promising for spectroscopic NMR studies. This information may directly reflect the electronic structure of the heteroatom and its location relative neighboring protons and/or 13C nuclei. In practice, however, to measure the spin–spin interaction couplings involving 15N nuclei, the corresponding isotopically labeled compounds are required. This greatly limits the list of possible objects of study. With labeled compounds, the 13C– 15N coupling can be relatively easily measured from the corresponding doublet splitting from 13C NMR spectrum. It is this simplicity that determines the significance of these couplings for the practice of structural studies. Isotopic enrichment will also allow determination of the 15N–1H couplings. However, additional complications that inevitably arise in the course of elucidation of the multiplet structure of strongly nitrogen-coupled 1H NMR spectra can be a decisive factor limiting their (15N–1H couplings) wide use in research practice.

This is confirmed by our analyses of the literature data: the 15N–1H couplings are much less common in the literature than the 13C–15N couplings; see as follows. The
The purpose of this work was to evaluate the possibilities of modern methods of quantum-chemical calculations for predicting the couplings of the $^{13}$C–$^{15}$N spin–spin couplings for a representative series of nitrogen-containing compounds. The result of this study should answer the question of how accurate this method can be for the practical evaluation of molecular structure recognition, conformational analysis, the study of tautomeric forms, charged moieties, etc.

The accuracy of the calculated data is significantly affected by systematic errors. These can be unaccounted for effects of the medium, inaccuracies in the optimization of the molecular geometry, say, the influence of unaccounted for conformational equilibria, tautomeric transformations, actual errors in the calculation method (a limited basis set used). We assume that at least a significant part of them may be associated with certain structural motifs. To check this, one can analyze a local series of compounds that have a common structural motif, and the compounds combined in it differ in the length and branching of carbon chains and/or the presence of various substituents. It can be expected that at least some of the systematic errors will be of a general nature for the entire local sample. In this case, the effective prediction accuracy of the desired property can be greatly improved. It can be noted that the use of this approach made it possible to obtain the accuracy of predicting the spin–spin coupling constants $^\text{H}J_{\text{HH}}$ in styrene in the range of 0.01–0.02 Hz [17].

This paper presents calculations of eight representative series of compounds, which, we hope, could allow us evaluate the effect of systematic errors more accurately. This study can be scaled up to other structural motifs with the emergence of reliable and, most importantly, diversely presented experimental data. Conclusions about the effect of systematic errors can only be drawn if there are a significant number of experimental points. Therefore, series with a small sample (2–3 objects) were not considered in this work.

When comparing experiment and calculation, one should also take into account the fact that experimental data may contain significant random errors, especially for NMR experiments made 30–40 years ago.

The calculation scheme used here includes two stages. At the first stage, using multidimensional optimization methods [6], the exact geometry of the molecule is found. Current research has been limited to conformationally rigid and structurally fixed nitrogen-containing compounds. We have made this restriction in order to focus on the method of calculating the spin–spin interaction constants. Accounting for conformational dynamics in terms of QMD [17, 18] is associated with the use of large computational resources and deserves independent study, for example, for aliphatic amines. In addition, the experimental data available in the literature [19, 20], in our opinion, require additional verification. The same applies to nitrogen-containing compounds involved in fast chemical exchange (prototropy, valence tautomerizm, etc.), for example, to pyrazole derivatives. In these cases, SSCC $^{13}$C–$^{15}$N involve exchange averaging, which worth studying separately.

Several nitriles and isocyanides containing exocyclic $sp$-hybridized nitrogen were included as objects in this work. Aromatic amines and nitro compounds contain nitrogen in the $sp^2$-hybridization state, but the electronic properties of the groups themselves are very different. Protonated anilines are compounds with $sp^3$-hybridization and considerable effective charge on the nitrogen atom. Among the cyclic
sites, we considered 3,4-hydroisoquinolines and indazoles, as well as a number of small molecules such as indole and pyridine derivatives. See Fig. 1.

The presented choice of objects covers a wide range of spatial and electronic structure factors of nitrogen-containing compounds and, as a consequence, a wide range of values of the $^3J_{\text{CN}}$ couplings and makes it possible to evaluate the correctness of the quantum-chemical method in calculating the $^3J_{\text{CN}}$ couplings of various types of nitrogen-containing moieties.

4 Discussion of Results

Crucial point of this work concerns assignment of signs of $^{13}\text{C}^{15}\text{N}$ coupling constants. It is well known, that the $^{15}\text{N}$ nucleus has a negative gyromagnetic ratio [4, 6]. Therefore, one could expect that overwhelming majority of the $^{13}\text{C}^{15}\text{N}$ constants studied in this work are negative (see as follows for more details). Our preliminary calculations shows that there should be at least few of them exactly positive ones. The modulus of coupling $^3J_{\text{CN}}$ can be determined experimentally as a doublet splitting from regular $^{13}\text{C}$ NMR spectrum. In contrast, experimental determination of the sign could require special NMR experiments, as for instance, triple selective experiment $^{13}\text{C}[^{1}\text{H}, ^{15}\text{N}]$, soft-COSY, COSY-45 or high resolution HMBC or HSQC [1, 21]. To date, evidence-based experiments of this class for $^{13}\text{C}^{15}\text{N}$ couplings have not been done, yet. Therefore, the question of what sign of presented here literature $^{13}\text{C}^{15}\text{N}$ constants remains relevant. Therefore, it is the matter of quantum-chemical calculations that should play a significant role in assigning their signs.

The use of calculated values makes it possible to determine the absolute value of the coupling without resorting to complicated and time-consuming NMR
experiments on a given compound. The determining factor remains the evaluation of the set of experimental and calculated data in the form of a two-parameter model, since this approach makes it possible to estimate the practical error in comparison of experimental couplings with theoretical ones. This approach looks good for cases then the coupling are big in modulo and theory gives reasonable approach to experiment. If, however, the coincidence between experimental and calculated values is not good enough, the sign of the coupling can be attributed erroneously. In this paper, we suggest criterion for making the decision based on confidence level of decision-making based on the methods of applied probability theory [22]. The decision can be based on a fairly representative sample of experimental and calculated data. Here, we test 2D map analysis based on the similarity between the calculated DFT and the experimental SSCC $^{13}$C$-^{15}$N as a critical approach for this feature.

4.1 Compounds with sp-Hybridized Nitrogen

Experimental and calculated values of the $^{1}J_{CN}$ and $^{2}J_{CN}$ couplings in the series of aliphatic 1–9 (Table 1) and aromatic nitriles 10–14 (Table 2) are presented in Tables 1 and 2.

| №  | Compound                      | $^{1}J_{CN}$ | $^{2}J_{CN}$ | Solvent          | Refs.       |
|----|-------------------------------|-------------|-------------|------------------|-------------|
| 1  | CH$_3$C$^{15}$N               | −17.8       | 2.9         | CDCl$_3$         | Exptl, [23] |
|    |                               | −17.53      | 2.9         | C$_6$F$_6$       | Exptl, [24] |
|    |                               | −17.0       | n/a         | Acetone-D$_6$    | Exptl, [25] |
|    |                               | −17.5       | 3.0         | THF-D$_8$        | Exptl, [26] |
|    |                               | −17.8       | 3.34        | n/a              | Calcd$^a$  |
| 2  | $^{15}$NCCH$_2$COOH           | −17.56      | 2.85        | DMSO-D$_6$       | Exptl, [27] |
|    |                               | −17.93      | 3.28        |                  | Calcd$^a$  |
| 3  | $^{15}$NCCH$_2$COOEt          | −17.63      | 3.27        | CDCl$_3$         | Exptl, [27] |
|    |                               | −18.01      | 3.31        |                  | Calcd$^a$  |
| 4  | $^{15}$NCCH$_2$C$^{15}$N      | −17.9       | 1.89        | CDCl$_3$         | Exptl, [28] |
|    |                               | −17.3       | 3.0         | D$_2$O           | Exptl, [29] |
|    |                               | −16.22      | 3.55        |                  | Calcd$^a$  |
| 5  | $^{15}$NC(CH$_2$)$_2$C$^{15}$N| −16.4       | 3.0         | DMSO-D$_6$       | Exptl, [30] |
|    |                               | −16.91      | 3.39        |                  | Calcd$^a$  |
| 6  | PhCH$_2$C$^{15}$N             | −17.0       | 3.0         | CDCl$_3$         | Exptl, [31] |
|    |                               | −17.28      | 3.31        |                  | Calcd$^a$  |
| 7  | p-NO$_2$PhCH$_2$C$^{15}$N     | −17.1       | 3.0         | CDCl$_3$         | Exptl, [31] |
|    |                               | −17.07      | 3.32        |                  | Calcd$^a$  |
| 8  | Z-BrCH=CHC$^{15}$N            | −17.8       | 3.8         | CDCl$_3$         | Exptl, [28] |
|    |                               | −18.59      | 3.99        |                  | Calcd$^a$  |
| 9  | E-PhCH=CHC$^{15}$N            | −17.5       | 2.5         | C$_6$D$_6$       | Exptl, [32] |
|    |                               | −18.33      | 4.09        |                  | Calcd$^a$  |

$^a$This work
As can be seen from the values presented, the theoretical and calculated values of the couplings are in a narrow range of values for both aliphatic and aromatic derivatives. Thus, the direct coupling, according to the literature data, varies in the range $J_{\text{CN}} = -18.1$ to $-16.3$ Hz, and the coupling through two bonds $2J_{\text{CN}} = 1.89–3.8$ Hz.

Figure 2 shows the correlation between the experimental and calculated values of SSCC $J_{\text{CN}}$ and $2J_{\text{CN}}$ in the nitrile series 1–14.

A two-parameter linear regression model was used for statistical treatment of the experimental and calculated couplings:

$$J_{\text{exptl}} = \alpha J_{\text{calcd}} + \beta.$$  \hspace{1cm} (1)

For Eq. (1) in the nitrile series 1–14, the correlation coefficient is 0.99, with a slope coefficient insignificantly different from unity ($\alpha = 1.03 \pm 0.01$) and the free term differs slightly statistically from zero ($\beta = 0.28 \pm 0.17$), which can be

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**Table 2** Experimental and calculated values of $J_{\text{CN}}$ and $2J_{\text{CN}}$ couplings in the series of aromatic nitriles 10–14

| № | R | $J_{\text{CN}}$ | $2J_{\text{CN}}$ | Solvent | Refs. |
|---|---|---|---|---|---|
| 10 | H | -17.8 | n/a | n/a | exptl, [33] |
|   |   | -17.93 | 3.23 |   | calcd * |
| 11 | t-Bu- | -16.3 | 3.8 | $C_6D_6$ | exptl, [32] |
|   |   | -18.04 | 3.20 |   | calcd * |
| 12 | OMe | -18.1 | 2.7 | $C_6D_6$ | exptl, [34] |
|   |   | -17.98 | 3.22 |   | calcd * |
| 13 | Br | -16.3 | 3.8 | $C_6D_6$ | exptl, [32] |
|   |   | -17.90 | 3.25 |   | calcd * |
| 14 | NO$_2$ | -17.5 | n/a | $C_6D_6$ | exptl, [35] |
|   |   | -17.8 | 2.5-3.2 | DMSO-D$_6$ | exptl, [32] |

*a*This work

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As can be seen from the values presented, the theoretical and calculated values of the couplings are in a narrow range of values for both aliphatic and aromatic derivatives. Thus, the direct coupling, according to the literature data, varies in the range $J_{\text{CN}} = -18.1$ to $-16.3$ Hz, and the coupling through two bonds $2J_{\text{CN}} = 1.89–3.8$ Hz.

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For Eq. (1) in the nitrile series 1–14, the correlation coefficient is 0.99, with a slope coefficient insignificantly different from unity ($\alpha = 1.03 \pm 0.01$) and the free term differs slightly statistically from zero ($\beta = 0.28 \pm 0.17$), which can be
considered a satisfactory coincidence of quantum-chemical theory with the experiment for aliphatic and aromatic nitriles.

As can be seen from Fig. 2, the values of the $J_{CN}$ and $2J_{CN}$ couplings differ greatly, both by modulo and by sign. The high accuracy of the calculated values makes it possible to reliably determine the sign of the spin–spin coupling constant.

The calculated values of the two-bond coupling for nitriles 1–14 lie in the range of $2J_{CN} = 2.50–4.09$ Hz while the standard deviation of the experimental and calculated values of the couplings is 0.76 Hz which on intuitive basis allows us to assign of $J_{CN}$ as negative and $2J_{CN}$ as positive ones. All geminal $^{13}$C–$^{15}$N couplings from the second cluster have smaller modules. Still, comparison, for example of $2J_{CN}$ for compound 12 gives $(2 \times 2.7)/0.76 = 7.1$. This is significant for a confidence level above the 99.9% level. In this case, we take the modulus of the experimental value with the sign corresponding to the calculation and place it in this form in Table 2.

We showed that $J_{CN}$ in the whole nitrile series 1–14 has a negative sign, while $J_{CN}$ values are positive. A similar approach in determining the sign of the couplings is used for subsequent series of objects. In the event that the resulting estimate is significant at a level of less than 99%, we also put the estimate of this constant in the corresponding table, but we take the sign of the number in brackets.

It should be noted that all the above mentioned one-bond SSCC $^{13}$C–$^{15}$N are negative and relatively small in modulus compared, for example, with $^{13}$C–$^{13}$C couplings through triple bonds in acetylenes [4, 36]. This can be explained by the negative gyromagnetic ratio of $^{15}$N, which, moreover, is approximately 2.5 times smaller in modulus than that of carbon. Such narrow ranges of values of both $J_{CN}$ and $2J_{CN}$ couplings can be explained by the remoteness of the nitrile group from the main carcass of the molecule, or in other words, by the low degree of electronic coupling between the CN group and the groups that follow it. Thus, in aromatic substrates 10–14, value of the couplings of nitrogen and carbon through one and two bonds is almost unchanged in the transition from electron-donor to electron-acceptor substituent and is weakly dependent on the structural factors. All these lead to the visual fact that, apparently, there is no local correlation at all within both the clusters.

Moreover, the transition from aliphatic nitriles to aromatic nitriles changes the type of hybridization of the $sp^3$- and $sp^2$-carbon atom, respectively, involved in spin–spin interaction through two bonds with a nitrogen atom, which could affect the value of $2J_{CN}$. However, for both the experimental and calculated values of the $2J_{CN}$ couplings, a similar range of values is observed for both aliphatic and aromatic nitriles.

It should also be noted such a clear separation of clusters, one-bond couplings and geminal couplings (see Fig. 2) are accompanied by an alternation of signs: geminal couplings in all cases are positive and one-bond couplings are negative. This is in exact agreement with Dirac vector model of spin–spin coupling. However, the correct use of this approach requires additional verification that both spin–spin coupling data blocks are determined by the same dominant SSCC mechanism. Our calculations showed that all SSCC’s presented in Tables 1 and 2 are determined almost exclusively by the FC mechanism (from 65 to 75%). The SO term is the second most important, but in no case should its contribution exceed 25%. Since the stated
condition is fulfilled, one should expect negative values for one-bond $^{13}\text{C}^{15}\text{N}$ couplings and positive values for the corresponding geminal couplings.

The dependence of the values of the couplings is most pronounced when the nitrogen atom is in close proximity to the basic skeleton of the molecule. One striking example is the isocyanide group in which the nitrogen atom is in a state of $sp$-hybridization and bonded to two carbon atoms of different types. See Fig. 3.

Optimization of the geometry of the molecule confirmed the linear fragment of the isocyanide group in the isocyanide series 15–28. Figure 3 shows the couplings through one bond of a nitrogen atom to two different carbon atoms. The dotted line shows the $^1J_{\text{C}≡\text{N}}$ coupling with the end carbene carbon atom, and the solid line shows the $^1J_{\text{C}–\text{N}}$ coupling with the carbon atom of the main skeleton of the molecule [37].

The results of calculations of the $^1J_{\text{C}≡\text{N}}$ and $^1J_{\text{C}–\text{N}}$ couplings in the series of isonitriles are presented in Table 3.

The experimental value of the $^1J_{\text{C}≡\text{N}}$ coupling has a narrow range of values of $−8.88$ to $−5.2$ Hz and is almost independent of the structural features of the molecule skeleton. On the contrary, the value of the $^1J_{\text{C}–\text{N}}$ coupling essentially depends on the type of hybridization of the carbon atom. The values of the $^1J_{\text{C}–\text{N}}$ coupling vary within a very wide range of $−20.0$ to $−7.0$ Hz. As noted earlier, the $^2J_{\text{C}≡\text{N}}$ coupling in nitriles does not depend on the type of hybridization of the carbon atom; on the contrary, in the case of isocyanides, there is a clear dependence between the value of the coupling and the type of hybridization of the carbon atom involved in the spin–spin interaction.

Figure 4 demonstrates correlation dependence between the calculated and experimental values of couplings $^1J_{\text{C}≡\text{N}}$ and $^1J_{\text{C}–\text{N}}$ in the series of isocyanides, among which both isocyanides with $sp^2$-hybridized carbon atom of the main molecular framework and isocyanides with $sp^3$-hybridized carbon atom are presented.

The values of the experimental and calculated values of the coupling $^1J_{\text{C}≡\text{N}}$ are represented in Fig. 4 by the dotted area (filled triangles) and have a narrow scattering of values for the entire series of isonitriles 15–28.

Figure 4 (filled squares) shows the values of the $^1J_{\text{C}–\text{N}}$ coupling for isocyanides 15–21 in which the carbon atom bonded to nitrogen is in the $sp^3$-hybridization state. Here, we can recognize a total of three clusters, each combining constants with different nitrogen and/or carbon hybridizations. As can be seen from Fig. 4, the values of $^1J_{\text{C}–\text{N}}$ are larger than $^1J_{\text{C}≡\text{N}}$ and also lie within a narrow range, while the similar values of the couplings for the substrates containing $sp^2$-hybridized

![Fig. 3 Two types of the one-bond couplings ($^1J_{\text{C}≡\text{N}}$ and $^1J_{\text{C}–\text{N}}$) in isonitriles 15–28](image-url)
carbon atom (filled squares) significantly differ in value. Of particular note is the significant underestimation of the calculated values with the \( sp^2 \)-carbon atom at nitrogen.

It should be noted that all one-bond couplings of this type are negative. However, the relative values of the constants reveal an unexpected dependence. It could be expected that these constants with nitrogen would behave similarly to the related constants between carbon nuclei \(^{13}\text{C}–^{13}\text{C} \), for which there is an almost linear increase in the constant from the s-character of the bond between carbon atoms \([4]\). For all studied here SSCC through one bond with the participation of nitrogen, on the contrary, for the \( \text{C}≡\text{N} \) triple bond, the smallest values

Table 3 Experimental and calculated values of one-bond \(^1J_{\text{C=N}}\) and \(^1J_{\text{C–N}}\) couplings (Hz) in the series of isonitriles 15–28

| №  | Compound      | \( ^1J_{\text{exptl}} \) | \( ^1J_{\text{calcd}} \) | Refs. | \( ^1J_{\text{exptl}} \) | \( ^1J_{\text{calcd}} \) | Refs. |
|-----|---------------|---------------------------|---------------------------|-------|---------------------------|---------------------------|-------|
| 15  | \( \text{CH}_3\text{NC} \) | n/a                       | −10.7                     | [38]  | −7.55                      | −12.23                    |       |
| 16  | \( \text{EtNC} \)            | −7.4                       | n/a                       | [38]  | −6.76                      | −10.35                    |       |
| 17  | \( \text{PrNC} \)            | −7.99                      | n/a                       | [38]  | −6.96                      | −10.43                    |       |
| 18  | \( \text{i-PrNC} \)          | −7.4                       | n/a                       | [38]  | −5.96                      | −9.02                     |       |
| 19  | \( \text{t-BuNC} \)          | −6.7                       | n/a                       | [38]  | −5.20                      | −7.92                     |       |
| 20  | \( \text{Cyclo-C}_6\text{H}_{11} \text{NC} \) | −6.87                     | −8.13                     | [38]  | −6.40                      | −9.69                     |       |
| 21  | \( \text{H}_2\text{C}≡\text{CHCH}_2\text{NC} \) | −6.6                      | −9.82                     | [38]  | −6.56                      | −11.99                    |       |
| 22  | \( \text{H}_2\text{C}≡\text{CHNC} \) | −5.2                      | −16.4                     | [38]  | −7.59                      | −19.18                    |       |
| 23  | \( \text{(Z)}\text{-CH}_2\text{CH≡CHNC} \) | −7.01                     | −16.13                    | [38]  | −8.29                      | −18.88                    |       |
| 24  | \( \text{H}_2\text{C}≡\text{CHNC} \) | −7.0                      | −20.0                     | [38]  | −6.72                      | −23.59                    |       |
| 25  | \( \text{PhNC} \)            | −7.99                      | −18.5                     | [38]  | −7.52                      | −20.69                    |       |
| 26  | \( \text{p-CH}_3\text{-PhNC} \) | −7.3                      | −18.79                    | [38]  | −7.77                      | −21.09                    |       |
| 27  | \( \text{p-CH}_3\text{O-PhNC} \) | −7.57                     | −17.39                    | [38]  | −7.66                      | −21.35                    |       |
| 28  | \( 2,6-(\text{CH}_3)_2\text{PhNC} \) | −6.31                     | −17.25                    | [38]  | −7.88                      | −18.97                    |       |

Spectra recorded at 306 K, 1 M solutions in \( \text{CCl}_4/\text{CD}_3\text{CN}/\text{TMS} \) mixture with a volume ratio of 75:23:2

Fig. 4 Three-cluster 2D plot of calculated vs experimental values of \(^1J_{\text{CN}}\) couplings in isocyanides 15–28
are observed. We consider this fact unexpected and requires additional theoretical substantiation in the framework of the NJC/NBO approach [42].

For statistical treatment of experimental and calculated couplings in isocyanides, a two-parameter linear regression model according to Eq. (1) was used.

For Eq. (1) in the series of isocyanides 15–28, the correlation coefficient is 0.99, with the value of the slope coefficient being significantly different from unity (α = 1.23 ± 0.04) and free term (β = 1.44 ± 0.40), which allows us to judge about a systematic error in the quantum-chemical method used in the calculation of isocyanide couplings. The high value of the correlation coefficient indicates that the calculations take into account the redistribution of the electron density taking into account the transition of the carbon atom from \( sp^3 \)- to \( sp^2 \)-hybridization, and the calculated values of the couplings have the same dependence as the experimental values of the couplings. The root-mean-square deviation of the experimental and calculated values of the couplings is 1.22 Hz, which allows us to reliably determine the sign of the direct couplings. The couplings \( ^1JC-N \) and \( ^1JC≡N \) have negative values for the entire series of isocyanides 15–28.

Such significant differences between the \( ^1JC-N \) couplings in aromatic and aliphatic isonitriles can serve as a reliable support for structural studies of organic molecules.

### 4.2 Compounds with \( sp^2 \)-Hybridized Nitrogen

Table 4 shows the experimental and calculated values of the \( ^1JCN \) couplings in the series of aromatic nitro compounds 29–44. In spite of the different variation of the substituents in the benzene ring, the value of the \( ^1JCN \) coupling varies within a narrow range of values. Note that the introduction of electron-donor or electron-acceptor substituents has only a minor effect on the value of the coupling. 4-substituted compounds 35 and 44 contain in their composition opposite electron effects of the substituents, but the value of the coupling \( ^1JCN \) varies slightly.

In the optimization of the nitrobenzene 29 molecule, the nitro group is located in the plane of the benzene ring, which provides maximum overlap of the \( sp^2 \)-hybridized nitrogen with the pi-system of the molecule. The introduction of substituents in the ortho-position, as in compound 47, leads to the fact that the nitro group leaves the plane of the benzene ring, but it does not affect significantly the value of the coupling \( ^1JCN \).

As can be seen from the table, all calculated values of the \( ^1JCN \) couplings are in good agreement with experiment and allow us to reliably determine their sign. The standard deviation for this series of compounds is 1.01 Hz.

In the case of nitrobenzene (29), the authors [44] also measured long-range couplings, the values of which are shown in Table 5.

As can be seen from Table 5, the experimental and calculated values of the long-range couplings are in good agreement. Optimization of the nitrobenzene geometry and the subsequent calculation of the long-range constants show a correct interpretation of the electronic properties of the molecule, which is reflected in the accuracy of the calculation of the long-range couplings.
4.3 Unsaturated Nitrogen-Containing Heterocycles

Table 6 shows the values of the $^3J_{CN}$ $n=1–3$ [15N]3,4-dihydroisoquinoline and its derivatives. The $^3J_{CN}$ $n=1–3$ imino nitrogen atom couplings have a wide range of values, which makes it possible to judge the electronic structure of the nitrogen atom in such compounds. From the values of the couplings given in Table 6, it should be noted that the presence of a free pair of electrons on the nitrogen atom significantly affects the value of the $^1J_{CN}$ couplings. Thus, the coupling of the imine nitrogen atom and the $sp^2$-hybridized carbon atom C1 in [15N]3,4-dihydroisoquinoline (29) is $^1J_{C1N} = 2.9$ Hz.

When the unshared electron pair of nitrogen is bound during protonation or during N-oxide formation, the value of the $^1J_{C1N}$ couplings increases markedly and is in the range of $^1J_{C1N} = -15.6$ to $-21.5$ Hz for compounds 46–48.
According to our calculations, when pyridine is protonated, the coupling $^1J_{CN} = 0.45–0.70$ Hz depending on the solvent for free pyridine, and for protonated pyridine $^1J_{CN} = -12.1$ Hz (in trifluoroacetic acid) [46] (Table 7).

It is important to note that in the case of aromatic substrates, the value of the coupling is less than for 45.

The coupling of the imine nitrogen atom and the $sp^3$-hybridized carbon atom C-3 also increases in the transition from 45 $^1J_{C3N} = 3.4$ Hz to the compounds 46–48 $^1J_{C3N} = 5.9–7.8$ Hz, in which the unshared nitrogen pair is bound, but this increase in the coupling is not as significant as in the case of the imine carbon atom.

It is important to note that the values of the couplings through the two bonds $^2J_{C4N}$ and $^2J_{C9N}$ for compounds 46–48, as reported by the authors in [19] $^2J_{CN} < 1.0$ Hz,

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**Table 6** Experimental and calculated values $^1J_{CN}$ couplings (Hz) in the series 3,4-dihydroisoquinolines 45–48

| № | X | $^1J_{C1N}$ | $^1J_{C3N}$ | $^2J_{C9N}$ | $^3J_{C1N}$ | $^3J_{C10N}$ | Refs. |
|---|---|---|---|---|---|---|---|
| 45 | N | -2.9 | 3.4 | 2.0 | n/a | n/a | exptl a, [45] |
| | | -4.05 | 7.21 | 2.08 | -2.06 | -2.87 | calcd c |
| 46 | NH$^+$ | -15.6 | -5.9 | n/a | -1.5 | -2.0 | exptl b, [45] |
| | | -17.20 | -5.53 | 0.710 | -3.04 | -4.91 | calcd c |
| 47 | N$^+$–O$^-$ | -21.5 | -7.8 | n/a | -3.4 | -2.4 | exptl a, [45] |
| | | -24.51 | -6.18 | 0.142 | -3.83 | -4.19 | calcd c |
| 48 | N$^+$–OH | -20.5 | -6.8 | n/a | -3.9 | -2.4 | exptl b, [45] |
| | | -19.74 | -6.30 | 0.57 | -3.69 | -4.81 | calcd c |

aSpectra recorded in CDCl$_3$ solution
bSpectra recorded in CDCl$_3$/CF$_3$COOH solution
cThis work

d---

**Table 7** Experimental and calculated values $^1J_{CN}$ couplings (Hz) in the pyridine derivatives

| № | Compound | $^1J_{CN}$ | $^2J_{CN}$ | $^3J_{CN}$ | Refs. |
|---|---|---|---|---|---|
| 49 | Pyridine | (+)0.45 | 2.4 | -3.6 | Exptl a, [46] |
| | | (+)0.7 | 2.6 | -3.8 | Exptl b, [46] |
| | | 1.74 | 2.68 | -4.00 | Calcd c |
| 50 | Pyridinium cation | -12.0 | (-)2.1 | -5.3 | Exptl a, [46] |
| | | -12.76 | -1.35 | -5.93 | Calcd c |
| 51 | Pyridine N-oxide | -15.24 | (+)1.32 | -5.13 | Exptl b, [47] |
| | | -14.60 | 0.79 | -4.99 | Calcd c |

aNeat
b30% (v/v) solution in methanol [46]
cThis work
d1.0 M CDCl$_3$
which correlates with the data of our calculations, so the calculated values of $^{2}J_{\text{C4N}}$ and $^{2}J_{\text{C9N}}$ are in the range 0.142–0.776 Hz. In 3,4-dihydroisoquinoline the same trend is observed, only the value of $^{2}J_{\text{C9N}} = 2.0$ Hz.

The couplings of nitrogen and carbon through three bonds in compounds 46–48 are more informative. According to the literature data [45], the values of the couplings for 46–48 are in the range $^{3}J_{\text{C8N}} = 1.5–3.9$ Hz, and $^{3}J_{\text{C10N}} = 2.0–2.4$ Hz.

In this case, the entire set of couplings comes out as one indivisible cluster, which characterizes a satisfactory correlation between theory and experiment. For Eq. (1) in the series of compounds under study (27 compounds), the correlation coefficient is 0.98, with the value of the slope coefficient ($\alpha = 1.05 \pm 0.04$) and the free term ($\beta = -0.05 \pm 0.32$). The combined data for 27 interactions make it possible to clearly demonstrate the high convergence of the calculated values for all measured combinations in a series of six-membered cycles (Fig. 5). The standard deviation in this series of compounds is 1.44 Hz.

Experimental values of the $^{a}J_{\text{CN}}$ couplings in the indazole series are extensively presented in the work [48]. The unsubstituted indazole has two types of nitrogen atoms of the N-1 pyrrole type and the N-2 pyridine type. The variation of the substituents and the selective introduction of the isotope tag, leads to a significant diversity of the spin–spin interaction transfer couplings and routes. Various indazoles studied in the work [48] are presented in the Table 8.

The experimental and calculated values of the $^{a}J_{\text{CN}}$ constants of the indazole series are shown in Table 9. The values of the constants depend substantially on the spin–spin coupling pathroute. The determination of the sign of the constants was made possible by the high degree of correlation between the experimental and calculated values of the constants.

Table 10 presents experimental and calculated values of $^{a}J_{\text{CN}}$ constants in $^{15}\text{N}$ indole. The experimental data were obtained in this work and are of great importance for the formation of a holistic picture about the structure and constants in the five-membered nitrogen-containing heterocyclic compounds. The high degree of correlation between the experimental data obtained and the quantum-chemical calculation together with the results for indazole derivatives is shown in Fig. 6.

Figure 6 shows the correlation between the experimental and calculated values of the $^{a}J_{\text{CN}}$ couplings in the indazole series 52–60 and indole 61 where $n = 1–4$. In this
Table 8  Location of substituents and isotopic labeling of the nitrogen atom in the indazole series

| Compound | N<sub>2</sub> | <sup>15</sup>N<sup>a</sup> | R<sup>1</sup> | R<sup>2</sup> |
|----------|-------------|----------------|-----------|-----------|
| 52       | N-1         | -              | -         | -         |
| 53       | N-2         | -              | -         | -         |
| 54       | N-2         | -              | NO<sub>2</sub> | -         |
| 55       | N-1         | CH<sub>3</sub> | -         | -         |
| 56       | N-2         | CH<sub>3</sub> | -         | -         |
| 57       | N-2         | CH<sub>3</sub> | NO<sub>2</sub> | -         |
| 58       | N-1         | -              | -         | CH<sub>3</sub> |
| 59       | N-2         | -              | -         | CH<sub>3</sub> |
| 60       | N-2         | -              | NO<sub>2</sub> | CH<sub>3</sub> |

<sup>a</sup> Position of isotopic label

Table 9  Experimental [48] and calculated values of the <sup>4</sup>J<sub>CN</sub> couplings (Hz) in the series of indazoles 52–60

| №  | 15N<sup>a</sup> | C-3  | C-4  | C-6  | C-7  | C-3a | C-7a | CH3– | Refs. |
|----|----------------|------|------|------|------|------|------|------|-------|
| 52 | N-1           | n/a  |      | -1.47| -2.02| -1.83| -5.8 | -13.56| –     | Exptl. [48] |
|    | −0.48         | −1.81| −2.04| −1.48| −7.77| −15.61| – | – | Calcd<sup>b</sup> |
| 53 | N-2           | n/a  | −1.10|      |      |      | 1.8  | 1.1  | –     | Exptl. [48] |
|    | 0.41          | −1.36| −0.98| 0.75 | 2.15 | 1.438| – | – | – |
| 54 | N-1           | n/a  | −1.65| −1.83| −1.10| −6.60| −15.03| −13.8| Exptl. [48] |
|    | −0.85         | −1.71| −1.99| −1.24| −7.39| −15.72| −15.46| – | Calcd<sup>b</sup> |
| 55 | N-2           | n/a  | (−)0.92| (−)0.55| n/a | 1.83 | (+)0.8| −5.5 | Exptl. [48] |
|    | 0.47          | −1.34| −1.01| 0.61 | 1.91 | 1.244| −8.23| – | Calcd<sup>b</sup> |
| 56 | N-1           | n/a  |      | −3.12| −7.33|(+)0.73| 1.83 | −6.4 | Exptl. [48] |
|    | 0.80          | −0.32| −3.69| −8.29| 2.08 | 3.142| −8.02| – | – |
| 57 | N-2           | −13.20| −3.30| (−)0.55| −4.22| −4.95| −1.28| −12.8| Exptl. [48] |
|    | −14.27        | −3.35| −0.65| −4.52| −6.09| −1.72| −14.18| – | Calcd<sup>b</sup> |
| 58 | N-2           | n/a  | −1.10| n/a  | n/a  | 1.83 | 1.28 | – | Exptl. [48] |
|    | 0.66          | −1.47| −0.47| 0.71 | 2.32 | 1.59 | – | – | – |
| 59 | N-2           | n/a  | −1.28| n/a  | n/a  | 1.83 | 1.28 | −5.9 | Exptl. [48] |
|    | 0.72          | −1.47| −0.91| 0.56 | 1.89 | 1.41 | −7.99| – | Calcd<sup>b</sup> |
| 60 | N-2           | −13.37| −3.48| n/a  | −4.03| −4.76|(−)0.73| −12.8| Exptl. [48] |
|    | −14.36        | −3.54| −0.43| −4.41| −6.05| −1.39| −13.51| – | Calcd<sup>b</sup> |

Experimental spectra were recorded in DMSO-D<sub>6</sub>

<sup>a</sup>Position of isotopic label

<sup>b</sup>This work
case also, the entire set of couplings comes out as one cluster, which characterizes a good correlation between theory and experiment.

Two-parameter linear regression model of Eq. (1) was used for statistical treatment of experimental and calculated couplings.

For Eq. (1) in the series of compounds under study (53 compounds), the correlation coefficient is 0.99, with the value of the slope coefficient \( \alpha = 1.10 \pm 0.02 \) and the free term \( \beta = -0.8 \pm 0.10 \). The combined data for 53 combinations make it possible to clearly demonstrate the high convergence of the calculated values for all measured combinations in a series of five-membered nitrogen-containing heterocycles. The standard deviation for series of compounds is 0.59 Hz, which makes it possible to reliably determine the sign of connections that exceed this value. Moreover, conjugations at the 3rd and 4th bonds fit well into the overall picture, which reliably describes the structural parameters in indazoles according to the calculated values.

### 4.4 Aromatic Amines and Ammonium Ions

Aromatic amines 62–74 are characterized by the nitrogen in the \( sp^2 \)-hybridization state, in which the unshared electron pair of the nitrogen atom of the amino group overlaps with the aromatic pi-system. When the amino group is protonated, the nitrogen enters the \( sp^3 \)-hybridization state and an effective charge arises on the nitrogen.

An important aspect is to study the behavior of the direct \( ^1J_{CN} \) coupling in the series of substituted amines 62–74 and anilinium ions 75–85, since protonation

**Table 10** Experimental and calculated values \(^{1}J_{CN}\) couplings (Hz) in the indole

| Compound | \( ^{1}J_{C2N} \) | \( ^{2}J_{C3N} \) | \( ^{3}J_{C4N} \) | \( ^{1}J_{C5N} \) | \( ^{2}J_{C6N} \) | \( ^{3}J_{C7N} \) | \( ^{1}J_{C8N} \) | \( ^{2}J_{C9N} \) | Refs. |
|----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------|
| [61]     | -13.08         | -2.55          | -1.19          | (+)0.14        | -2.02          | -1.63          | -15.37         | -4.80          | exp [49] |
|          | -14.27         | -3.65          | -1.40          | 0.18           | -2.12          | -1.63          | -16.41         | -5.91          | calc \( a \) |

\( a \) This work

**Fig. 6** Correlation plot of calculated vs experimental values of \(^{1}J_{CN}\) couplings in the indazole series 52–60 and indole 61
leads to a change in the type of nitrogen atom hybridization and, consequently, in the value of the coupling.

Thus, experimental and calculated values of $^{1}J_{\text{CN}}$ couplings are presented in Table 11. As can be seen from the above values in the case of anilines, the location of substituents in the benzene ring of the molecule has a significant influence on the value of the coupling.

It is well known that the electronic properties of the substituent, differently affect the value of the coupling. For example, for 4-nitroaniline containing electron-accepting substituent, the value of coupling $^{1}J_{\text{CN}} = -14.7 \text{ Hz}$ while the donor CH$_3$O-substituent in 4-methoxyaniline changes the value of coupling $^{1}J_{\text{CN}} = -11.0 \text{ Hz}$. Since the substituents are at a distance relative to the amino group, these changes in the value of the couplings are mainly due to electronic effects in the molecule. Due to the fact that $^{1}J_{\text{CN}}$ in anilines changes even when the substituent is introduced into the deleted para-position, the values of the couplings change over a wide range, which can be used in structural studies.

Table 12 presents experimental and calculated values of $^{2}J_{\text{CN}}$ constants in aniline and diphenylamine. As can be seen from Table 12, the experimental and calculated values of the long-range couplings are in good agreement.

Calculated values of $^{2}J_{\text{CN}}$ couplings in anilines 62–74 and 86, are also in good agreement with the literature data. According to our calculations, there is only considerable systematic error in the estimation of the $^{1}J_{\text{CN}}$ couplings, however, the influence of electronic effects finds a clear trend in the calculated values. The RMS deviation for series of compounds is 0.86 Hz.

Table 11 Experimental [50] and calculated (this work) values of $^{1}J_{\text{CN}}$ couplings in substituted anilines a 62–74 and anilinium cations 75–85

| Number | Substituent | $^{1}J_{\text{CN}}$ Calc | $^{1}J_{\text{CN}}$ Exp | Number | Substituent | $^{1}J_{\text{CN}}$ Calc | $^{1}J_{\text{CN}}$ Exp |
|--------|-------------|--------------------------|------------------------|--------|-------------|--------------------------|------------------------|
| 62     | 2,4,6-(Br)$_3$ | -17.6 | -18.47 | 75     | 2,4,6-(Br)$_3$ | -13.5 | -12.23 |
| 63     | 2,4-(NO$_2$)$_2$ | -16.9 | -19.27 | 76     | 2-NO$_2$, 4-Cl | -11.0 | -8.29 |
| 64     | 4-NO$_2$ | -14.7 | -13.51 | 77     | 2-Br | -11.0 | -8.13 |
| 65     | 3-Cl | -13.2 | -10.77 | 78     | 2-Cl | -10.9 | -7.69 |
| 66     | 3-Br | -13.2 | -10.81 | 79     | 2-NO$_2$ | -10.4 | -7.63 |
| 67     | 3-CF$_3$ | -12.5 | -11.40 | 80     | 4-NO$_2$ | -9.2 | -4.50 |
| 68     | 3-OCH$_3$ | -12.5 | -10.03 | 81     | 4-Br | -9.2 | -4.60 |
| 69     | 4-Cl | -12.5 | -10.76 | 82     | 4-Cl | -9.1 | -4.69 |
| 70     | 4-Br | -12.5 | -10.76 | 83     | 4-F | -8.6 | -4.95 |
| 71     | H | -12.1 | -10.18 | 84     | H | -8.6 | -6.77 |
| 72     | 3-CH$_3$ | -11.8 | -10.12 | 85     | 3-Br | -7.9 | -4.03 |
| 73     | 4-CH$_3$ | -11.8 | -10.02 |  |  |
| 74     | 4-OCH$_3$ | -11.0 | -9.59 |  |  |

*1.0 M solution in DMSO-D$_6$

*2.0 M solution in HFSO$_3$
As can be seen from Table 11, the values of the $^1J_{CN}$ couplings in the protonated form of anilines 75–85 are in the range $-13.5$ to $-7.9$ Hz and differ markedly from the analogous values for non-protonated anilines. It should be noted that there is a marked decrease in the value of the couplings modulo. When aniline is protonated, nitrogen transitions to the $sp^3$-hybridization state and the planar conformation of the hydrogen atoms is broken. Although the range of values of the $^1J_{CN}$ couplings remains approximately the same with the corresponding range of values for anilines, the nature of the effect on the direct coupling changes.

For the series of studied anilines, the significant influence of electron effect of substituent in benzene ring is clearly seen while for anilinium ions the values of direct coupling depend less on the electronic properties of substituents, for example for compounds 80 and 81 where in the 4th position substituents with opposite electron effect are located, the value of coupling remains the same. The effect can be realized due to a change in the length of the CN triple bond due to the effects of conjugation of the aromatic ring with the CN bond.

The substituent at the ortho-position with respect to the protonated ammonium group has a significant influence. It should be noted that the nature of the properties of the substituent plays a minor role; the location of two bulk substituents in the ortho-positions of the benzene ring has a much greater influence on the value of the coupling. Thus, the steric loading of the ortho-positions leads to a noticeable increase in the value of the $^1$JCN bond. Apparently, this is also related to some specific orbital interactions.

As in the case of anilines, the calculated values of the $^1J_{CN}$ couplings give an overestimate and a systematic error is observed. However, it should be noted that the calculated values still feel a dynamic change in the nature of the effect on the direct coupling. For the same compounds 80 and 81, the calculated values differ by 4.5 Hz from the experimental values, but they differ relative to each other by only 0.1 Hz, as in the case of the experimental values. The RMS deviation for series of compounds is 0.91 Hz.

Such a serious systematic error in the calculations may be caused by a number of factors. In the case of incomplete protonation of the amino group under experimental conditions, the $^1J_{CN}$ coupling will be the average of the contributions of the two forms of free aniline and aniline ion. In the case of protonated compounds and the effect of steric effect, the choice of solvent, both for spectrum registration and for quantum-chemical calculations, plays an important role. Calculations in the isolated molecule approximation give very accurate estimates of the couplings for objects weakly interacting with the solvent. It should be noted that the experiment for this

| Compound | $^1J_{CN}$ | $^2J_{CN}$ | $^3J_{CN}$ | $^4J_{CN}$ | Refs |
|----------|----------|----------|----------|----------|-----|
| Aniline  | −11.47   | −2.67    | −1.29    | (−)0.27  | Exptl [51] |
|          | −10.18   | −3.33    | −1.23    | −0.47    | Calcd$^a$ |
| Diphenylamine (86) | −15.3 | −2.3 | −1.5 | n/a | Exptl [52] |
|          | −17.75   | −2.66    | −1.87    | −0.04    | Calcd$^a$ |

$^a$This work
series of compounds was carried out quite a long time ago and, apparently, requires additional verification.

### 4.5 All Studied Compounds Together

The correlation between the experimental and calculated values of the entire set of studied in this work spin–spin coupling constants is shown in Fig. 7.

A two-parameter linear regression model was used for statistical processing of experimental and calculated couplings.

For Eq. (1) in a series of the studied compounds (193 couplings), the correlation coefficient is equal to 0.98 with the value of the slope coefficient insignificantly differing from unity ($\alpha = 1.01 \pm 0.01$) and almost zero free term ($\beta = 0.08 \pm 0.16$). The totality of the data on 193 couplings allows to demonstrate a high convergence of the calculated values and the possibility of using the obtained data for predicting the values of the couplings. The root-mean-square deviation for the entire data sample is 1.5 Hz, which allows us to reliably determine the sign of the couplings exceeding this value. As can be seen from Fig. 6, some sets of values have overestimated calculated results, which can be explained by systematic errors of the calculated method.

The use of such dependencies makes it possible to estimate the value of the couplings and to plan NMR experiments in advance, where preliminary knowledge of the value of the couplings is necessary. It should be noted that the standard deviation for the entire set of studied data on the $^{13}$C–$^{15}$N constants, as expected, has a value that exceeds this parameter for all eight local samples studied (see above). The best agreement between the calculated and experimental values is observed for a number of five-membered nitrogen-containing heterocycles. It is the compounds of this class (namely substituted indoles, pyrroles, indazoles, oxa- and thiazoles, etc.) that seem to us the most important from the point of view of predicting their structure by NMR. In these five-membered cycles, which are very important for pharmaceutics, the set of “standard” spectral parameters (with the participation of $^1$H and $^{13}$C nuclei) is very limited, which causes growing interest in the search for new approaches to elucidation of their structure, including those based on the use of spin–spin constants interactions involving $^{15}$N nuclei.

![Fig. 7 Overall correlation between calculated and experimental values of $^3$J$_{CN}$ couplings in all studied compounds](image)
5 Conclusion

Analysis of 2D maps based on similarity in DFT-calculated vs experimental $^{13}\text{C}^{\text{15}}\text{N}$ spin couplings for a representative sample of conformationally rigid and structurally fixed nitrogen-containing compound support, that quantum-chemical calculation of the SSCC values together with the analysis of their experimental values can be a powerful tool for solving structural problems. The DFT-calculated $^{13}\text{C}^{\text{15}}\text{N}$ spin couplings are in good agreement with the experiment at a statistically high to excellent confidence level. This approach can provide important structure information for assigning $^{13}\text{C}$ peaks of new nitrogen-containing organic compounds as well as for setting up unknown signs of spin–spin couplings $^{13}\text{C}^{\text{15}}\text{N}$.

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Author Contributions VVS—performed analysis of the literature, optimization of geometry and quantum-chemical evaluation of spin–spin coupling constants $^{13}\text{C}^{\text{15}}\text{N}$ for the selected compounds, prepared figures, compiled tables based on the data obtained, and also actively participated in the discussion of the results and made an oral report on this topic at the Spinus-2022 conference; AKS performed all NMR experiments and analyzed results for compound 61, participated in the discussion of the text of the manuscript, compiled Table 10, and edited the figures; VAC took an active part in the planning, writing, editing and discussion of the results, participated in statistical treatment of the result. All the authors have read and agreed to the final version of the manuscript.

Declarations

Conflict of Interest The authors declare no conflict of interest.

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