THEORETICAL CALCULATION OF THE PEPTIDE NH-C$^\alpha$H VICINAL
COUPLING CONSTANT

V.N.Solkan and V.F.Bystrov[*]

Department of Chemistry, Moscow State University

[*]Shemyakin Institute for Chemistry of Natural Products
USSR Academy of Sciences, Moscow 117312

The dependence of the peptide NH-C$^\alpha$H coupling constant on the rotational state of the N-C$^\alpha$ bond (dihedral θ angle or torsion ϕ angle[1], see insert on Fig. 1) is of fundamental importance for conformational studies of naturally occuring and synthetic peptides. Earlier[2], such a dependence in the form of a Karplus-like curve[3] had been derived from experimental NMR data. Subsequently it appeared that choice of the model compounds for plotting this dependence has an important bearing on the numerical parameters of the $^3J_{NHCH}$ curve, especially for the $\theta \sim 0°$ ($\phi \sim 60°$) region. In particular, if one takes compounds with <u>trans</u>-amide bonds the NH-C$^\alpha$H coupling constant for $\theta = 0°$ turns out to be 8.0 - 9.4 Hz[4], whereas with <u>cis</u>-amide bonds the same angle corresponds to a value of 6.4 Hz[5] or even 5.6 - 6.0 Hz[6].

In order to provide a theoretical basis for the shape of the angular dependence of the $^3J_{NHCH}$ constant and to find an explanation for the discrepancy between the $^3J_{NHCH}$ (θ) curves empirically established for the different sets of compounds, we have made a theoretical caclulation of the vicinal NH-CH coupling in amides.

<u>Method of Calculation</u>. Calculation of the $^3J_{NHCH}$ coupling constant was based on the finite perturbation theory of nuclear spin coupling[7] with the use of unrestricted Hartree-Fock molecular orbital wavefunctions in the INDO approximation. The Fermi contact term served as the perturbation. The para-

meters for N-methylformamide (NMF) were those determined by X-ray analysis[8];
bond lengths (in Å) N-C 1.44, C'-N 1.36, C=O 1.22, C'-H 1.11, C-H 1.10 and
N-H 1.02; valence angles HC'O 122°, OC'N 125°, C'NC 117°, C'NH 117°, NCH 109°
and HCH 109°. For N-formylaminoacetaldehyde (NFA) O'=C'H-NH-$C^{\alpha}H_2$-C"HO", con-
sidered as model of the N-C^{α}-C(=O) fragment of the aminoacid residue, struc-
tural parameters were taken as for peptides[1,10]; bond lengths (in Å) C'=O
1.24, C'-H, C"-H 1.11, C'-N 1.32, N-C^{α} 1.47, N-H 1.02, C^{α}-H 1.09 and C^{α}-C"
1.52; valence angles HC'O 122°, O'C'N 122.9°, C'NC^{α} 123.4°, HNC^{α} 115.4°, NC^{α}H
124.1°, NC^{α}C" 111.8°, HC^{α}H 107.2° and C^{α}C"O" 124°. The cis- and trans-isomers
differed by a 180° rotation about the amide bond assumed to be planar. In
calculating the $^3J_{NHCH}$ dependence the ϕ and ψ angles were taken in 30° in-
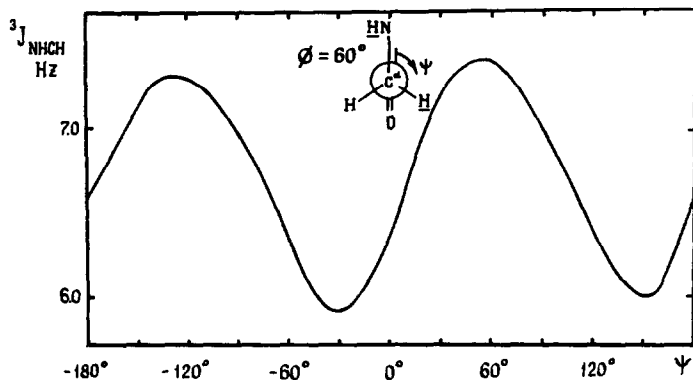tervals within the limits of -180° to 180°.
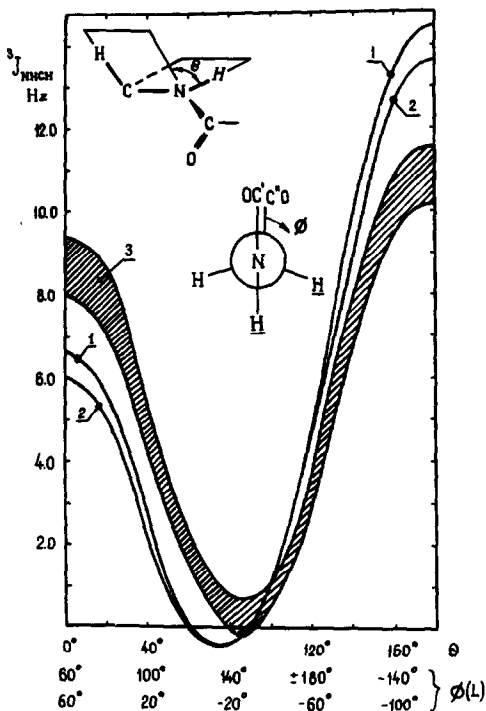
Fig. 1. Theoretical dependence of
the $^3J_{NHCH}$ coupling constant on the
rotational states about the N-C^{α}
bond for the trans-isomer (1) and
cis-isomer (2) of N-formylaminoace-
taldehyde at ψ=180°. (3)-Empirical
dependence for peptides[4].

Results and Discussion. The calcu-
lated $^3J_{NHCH}$ constants have a positive
sign over almost the entire range of ϕ
values, which is a general rule for vici-
nal proton coupling. The small $^3J_{NHCH}$ va-
lues for θ angles in the 60° to 90° re-
gion (Fig. 1, curves 1 and 2) indicate
that in the NH-CH peptide fragment (by
analogy with the theoretical calculation
for the $^3J_{CHCH}$ coupling of the propene
=CH-CH_3 fragment[11]) the π-electron or-
bital of the amide nitrogen participates
in the transmission of the spin-spin
coupling.

The general shape of the theoretical
$^3J_{NHCH}$ angular dependence (Fig.1, curves 1
and 2) is that of a Karplus-like curve, con-
firming the basic assumption underlying the
empirical derivation of this dependence[3-6].

It is to be particularly noted that
the $^3J_{NHCH}$ values calculated for the en-

tire range of $\emptyset$ angles are smaller for the cis- than for the trans-isomers of both NMF and NEA (the curves for these compounds are quite similar). This is evidently the reason for the above mentioned discrepancy between the ste- reochemical $^3J_{NHCH}$ relation for peptides with trans-amide bonds[4] and for the set of compounds which contained also cis-amides[5,6]. Since the data used for plotting the latter[5,6] in the region of $\emptyset \sim 60°$ ($\theta \sim 0°$) were based main- ly on the cis-amides it was in just this region that the low $^3J_{NHCH}$ values (in comparison with the peptide $^3J_{NHCH}$ curve[4]) were most clearly manifested. The validity of the above is also supported by the fact that the observed $^3J_{NHCH}$ constant is lower for cis-NMF (4.45$\pm$0.05 Hz, pure liquid) than for trans-NMF (4.9 Hz[12]). Theoretical calculations taking account of the relative potential energies of the NH-CH$_3$ rotational states[13] give 4.7 and 5.1 Hz, respectively.

Comparison of the theoretical curve with the experimental curve obtained for peptides[4] (Fig. 1, curve 3) shows that the former differentiates the maximum $^3J_{NHCH}$ values at $\theta = 0°$ ($\emptyset = 60°$) and $\theta = 180°$ ($\emptyset = -120°$) more dis- tinctly. For the over-all $^3J_{NHCH_2}$ constant of the glycyl residue the theo- retical curve is similar to the relation obtained experimentally[4], deviations occuring only for the minima at $\emptyset = \pm180°$ and $0°$.

The present state of theory of the coupling constant does not permit one to expect precise agreement between the theoretical calculations and experi- ment. However, it does allow a qualitative assessment of the effects the va-

rious structural parameters of the molecules can have on the NH-CH coupling.

The theoretical calculation has also revealed that the C^{α}-C(=O) torsion angle is an additional conformational factor affecting the $^3J_{NHCH}$ value (Fig. 2). At the same time the variation of the ψ angle alters the $^3J_{NHCH}$ constant much less (by not more than $\pm10\%$, i.e., by a maximum of $\pm$ 1 Hz) than does variation of the ϕ angle, so that this factor can by no means reduce the usefulness of the $^3J_{NHCH}$ (θ) curve in conformational studies of peptides. The angular effect must be taken into account when further refinment of the experimental ϕ-dependence of the $^3J_{NHCH}$ constant is attempted. The empirical $^3J_{NHCH}$ relation without account for the effect of the ψ angle or for possible deviation from planarity of the amide bond[14] should be presented in the form of permissible ranges as a function of ϕ (or θ) angle (Fig. 1, curve 3).

REFERENCES

1. IUPAC-IUB Commission on Biochemical Nomenclature, J.Mol.Biol. 52, 1 (1970).
2. V.F.Bystrov, S.L.Portnova, V.I.Tsetlin, V.T.Ivanov and Yu.A.Ovchinnikov, Tetrahedron 25, 493 (1969); V.F.Bystrov, S.L.Portnova, T.A.Balashova, V.I.Tsetlin, V.T.Ivanov, P.V.Kostetsky and Yu.A.Ovchinnikov, Tetrahedron Letters 5225 (1969).
3. M.Karplus, J.Chem.Phys. 30, 11 (1959); J.Am.Chem.Soc. 85, 2870 (1963).
4. V.F.Bystrov, V.T.Ivanov, S.L.Portnova, T.A.Balashova and Yu.A.Ovchinnikov, Tetrahedron, in press; V.F.Bystrov, S.L.Portnova, T.A.Balashova, S.A.Koz'- min, Yu.D.Gavrilov and V.A.Afanas'ev, Macromolecules, in press.
5. G.N.Ramachandran, R.Chandrasekaran and K.D.Kopple, Biopolymers 10, 2113 (1971).
6. C.M.Thong, D.Canet, P.Granger, M.Marraud and J.Néel, C.r.Acad.Sci., Ser. C 279, 580 (1969); J.Néel, Pure Appl. Chem. 31, 201 (1972); M.T.Cung, M.Marraud and J.Néel, Macromolecules, in press.
7. J.A.Pople, J.W.McIver, Jr. and N.S.Ostlund, J.Chem.Phys. 49, 2960 (1968).
8. Tables of Interatomic Distances and Configuration in Molecules and Ions, The Chemical Society, London, 1958.
9. G.N.Ramachandran and C.M.Venkatachatam, Biopolymers 6, 255 (1968).
10. E.M.Popov, G.M.Lipkind, S.F.Arkhipova and V.G.Dashevskii, Molek.Biol.(USSR) 2, 622 (1968).
11. G.E.Maciel, J.W.McIver, Jr., N.S.Ostlund and J.A.Pople, J.Am.Chem.Soc. 92, 4497 (1970).
12. J.G.Powles and J.H.Strange, Disc.Faraday Soc. 34, 30 (1962).
13. J.F.Yan, F.A.Monamy, R.Hoffmann and H.Scheraga, J.Phys.Chem.74, 420 (1970).
14. F.K.Winkler and J.D.Dunitz, J.Molec.Biol. 59, 169 (1971).