second-order rate constants for reaction from free solution, $V_{\max}/K_m$, there is essentially no effect of substituents on the rate.[24] The increase in binding with electron-withdrawing substituents that is required by this hypothesis implies that the binding step brings the substrate part way along the reaction coordinate toward the transition state with respect to the chemical reaction itself, as well as with respect to the entropy of approximation of reacting groups. The limiting case of this situation would be the utilization of the substrate binding energy to force the formation of a tetrahedral addition intermediate as a part of the binding step.[28]

[28] M. Caplow, *J. Amer. Chem. Soc.*, **91**, 3639 (1969).

The substituent effect on the overall equilibrium for acetanilide formation also provides an explanation for the fact that electron-withdrawing substituents decrease the rate of reaction of anilines with the acetyl-enzyme intermediates formed from acetyl-coenzyme A-arylamine acetyltransferase, but increase the rate of formation of this intermediate from substituted acetanilides; this reaction will be described in greater detail elsewhere.[5]

Acknowledgments. We are grateful to Barbara Riddle for advice and for a supply of enzyme and to Alan Fersht for communicating his results before publication.

Studies on the Carbon-13 Contact Shifts of a σ-Electron System. Conformational Dependence of Carbon-13 Contact Shifts in Six-Membered Rings[1]

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Abstract: Isotropic ^{13}C paramagnetic shifts for piperidine derivatives I–IV, quinuclidine (V), and 1-azaadamantane (VI) coordinated with paramagnetic nickel(II) acetylacetonate ($Ni(AA)_2$) have been observed in the completely proton-decoupled ^{13}C nmr spectra. These shifts with alternation in sign and attenuation in magnitude have been interpreted as due to Fermi contact shifts which are related to the electron spin densities on the carbon s atomic orbital. Different features of ^{13}C contact shifts were observed for N–H piperidines and *N*-methylpiperidines. For *N*-methylpiperidines, in which the lone-pair electrons are situated preferably at the axial position, α, β, and γ carbons experience alternate upfield and downfield ^{13}C contact shifts with rapid attenuation, while for N–H piperidines or 1-azaadamantane, in which lone-pair electrons have greater preference for the equatorial position, alternate ^{13}C contact shifts with slow attenuation were observed. For quinuclidine, however, an unexpected downfield ^{13}C contact shift (upfield shift for piperidine derivatives) was observed for the γ-carbon. These conformational dependencies of ^{13}C contact shifts have been discussed in terms of electron spin densities on the carbon atoms obtained by unrestricted Hartree–Fock SCF-MO calculations (INDO method). The experimental trends were reproduced by MO theoretical calculations for a cation radical in which an electron is abstracted from the neutral ligand molecule.

In this laboratory we have been interested in the nmr contact shifts for σ-electron systems and in their use in the elucidation of the mode of electron spin distribution through the σ skeleton and in the determination of molecular conformation. We have previously reported the proton contact shifts for piperidine,[3,4] quinuclidine,[3,4] aziridine,[5] ketoxime,[6] and aniline,[7] all of which have the oriented nitrogen lone-pair electrons serving as the σ binding site with the paramagnetic nickel(II) acetylacetonate ($Ni(AA)_2$). The proton contact shifts induced by the paramagnetic complexation have been shown to depend on the orientation of the lone-pair electrons and to be useful as a probe for studying molecular conformations.

Availability of the proton-decoupled ^{13}C nmr technique enables us to observe natural abundance ^{13}C nmr spectra of paramagnetic molecules in solution.[8] Recently we have reported[9,10] the ^{13}C nmr contact shift studies for aniline[9] and pyridine[10] complexed with

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[1] For preliminary research of this work, see I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *Chem. Commun.*, 1535 (1970).

[2] Japan Electron Optics Laboratory Co., Ltd., Akishima, Tokyo, Japan.

[3] T. Yonezawa, I. Morishima, and Y. Ohmori, *J. Amer. Chem. Soc.*, **92**, 1267 (1970).

[4] I. Morishima, K. Okada, M. Ohashi, and T. Yonezawa, *Chem. Commun.*, 33 (1971); *J. Amer. Chem. Soc.*, in press. The $Ni(AA)_2$-induced ^{13}C contact shifts give no information about the conformational equilibrium in piperidine itself. However, $Ni(AA)_2$ may not affect the lone-pair orientation, which is evidenced from the linear dependence of ^{13}C contact shift on the concentration of added $Ni(AA)_2$. If the conformational equilibrium is changed by the presence of $Ni(AA)_2$, the contact shift–concentration plots deviate from the linearity. This is also supported by the proton contact shift studies.[3]

[5] I. Morishima, K. Takeuchi, K. Fukuta, and T. Yonezawa, to be published.

[6] I. Morishima and T. Yonezawa, *J. Chem. Phys.*, **54**, 3238 (1971).

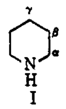
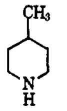
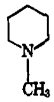
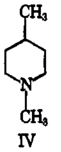
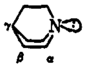
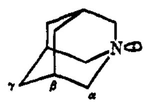
[7] T. Yonezawa, I. Morishima, Y. Akana, and K. Fukuta, *Bull. Chem. Soc. Jap.*, **43**, 379 (1970).

[8] D. Doddrell and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 4484, 5255, 6839 (1970).

[9] I. Morishima, T. Yonezawa, and K. Goto, *ibid.*, **92**, 6651 (1970).

[10] I. Morishima and T. Yonezawa, submitted for publication.

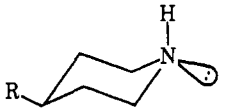
Table I. Proton and ^{13}C Contact Shifts for σ-Electron Systems

Molecules	Position	δ^{13}C[a]	^{13}C contact shift (rel values)	^{1}H contact shift[f] (rel values)
 I	α	145.8	+1.00[b]	−1.00
	β	165.8	−1.60	−0.47
	γ	167.5	+0.10	−0.11
 II	α	146.2	+1.00[b]	−1.00 (ax) −0.77 (eq)
	β	157.2	−1.60	+0.11 (ax) −0.67 (eq)
	γ	161.5	+0.10	−0.09 (ax)
	4-CH$_3$	170.2	−0.10	
 III	α	136.3	+1.00[c]	−1.00
	β	167.0	−0.35	+0.04
	γ	171.0	+0.20	−0.14
	NCH$_3$	146.0	+1.30	
 IV	α	136.1	+1.00[c]	−1.00 (ax) −0.38 (eq)
	β	157.8	−0.33	+0.09 (ax) −0.03 (eq)
	γ	161.9	+0.20	+0.04 (ax)
	4-CH$_3$	170.1	0	
	NCH$_3$	145.8	+1.50	
 V	α	145.0	+1.00[d]	−1.00
	β	166.0	−0.63	−0.12
	γ	171.8	−0.07	+0.11
 VI	α	134.0	+1.00[e]	−1.00
	β	160.0	−0.75	−0.77
	γ	156.5	+0.13	−0.30 (eq) −0.02 (ax)

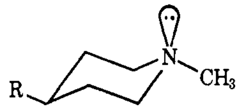
[a] In parts per million from CS$_2$. Measured in 50 v/v % CDCl$_3$ solution (I–IV) and in dilute CDCl$_3$ solutions (1 *M*) (V and VI). [b] The actual shift is 5 ppm per 0.05 mol of Ni(AA)$_2$ in the 50 v/v % CDCl$_3$ solution. [c] The actual shift is 4 ppm per 0.05 mol of Ni(AA)$_2$ in the 50 v/v % CDCl$_3$ solution. [d] For the actual shift, see Figure 3. [e] The actual shift is 4 ppm when 0.1 mol of Ni(AA)$_2$ is added to the 1 *M* solution of VI in CDCl$_3$. [f] Data taken from ref 4.

paramagnetic Ni(AA)$_2$ or Co(AA)$_2$ and shown that ^{13}C contact shifts can be used as an alternative powerful tool for elucidation of electron spin distribution of the ligand molecule and the geometric structure of the paramagnetic metal complexes.

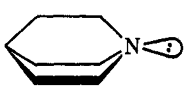
In the present article we report the ^{13}C contact shifts in the σ-electron system of a six-membered ring. We will show the utility of ^{13}C contact shifts in conformational studies and in the elucidation of the mode of electron spin distribution through the σ skeleton. The paramagnetic systems examined here are the complexes of Ni(AA)$_2$ with piperidine (I), 4-methylpiperidine (II), *N*-methylpiperidine (III), 1,4-dimethylpiperidine (IV), quinuclidine (V), and 1-azaadamantane



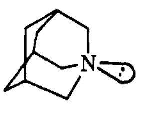
I, R=H
II, R=CH$_3$



III, R=H
IV, R=CH$_3$



V



VI

(VI). V and VI have oriented lone-pair electrons in a rigid σ skeleton and are suitable for the present study.

It has been shown that the isotropic ^{13}C paramagnetic shifts in the Ni(AA)$_2$ complexes are caused mainly by the contact interaction which is related to the electron spin density on the carbon, as is the case also for the proton resonances.[9,10] The ^{13}C contact shift is given by the equation[11]

$$\frac{\Delta H}{H} = -a_C\frac{\gamma_e}{\gamma_C}\frac{g\beta S(S+1)}{3KT}$$

where the ^{13}C hyperfine coupling constant a_C is given by

$$a_C = \frac{4\pi}{3}g\beta\gamma_C\hbar\langle S_z\rangle^{-1}\,|\varphi(r_{C_s})|^2\rho_{C_s}$$

and ρ_{C_s} is the unpaired electron density on the carbon s atomic orbital and the other symbols have their usual meaning.[11,12] In this work we calculated electron spin densities on the various carbon atoms in the above ligand molecules by using the unrestricted Hartree-Fock SCF-MO model for all valence electrons (INDO method).[12] The observed trends of the ^{13}C contact shifts were reproduced by the model calculations for the cation radical in which an electron is eliminated from the highest occupied lone-pair orbital in the neutral ligand molecule.

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(11) H. M. McConnell and D. B. Chesnut, *J. Chem. Phys.*, **29**, 107 (1958).

(12) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *ibid.*, **47**, 2026 (1967); *J. Amer. Chem. Soc.*, **90**, 4201 (1968). Similar observations have been obtained for pyridine derivatives.[9,11]

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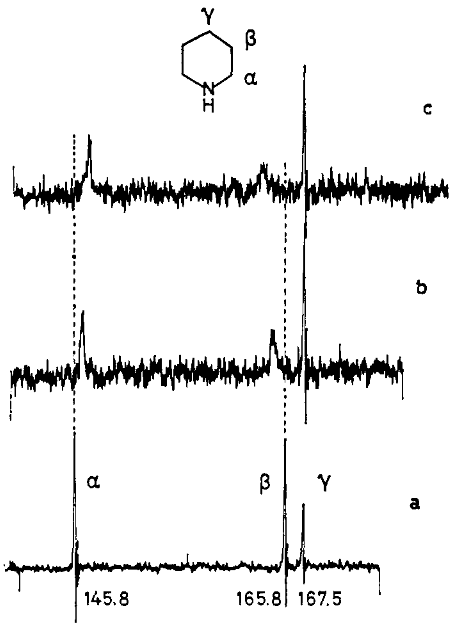

Figure 1. Completely proton-decoupled ^{13}C nmr spectra at 25.1 MHz for piperidine: (a) in the 50 v/v% $CDCl_3$ solution; (b) in the presence of 0.02 *M* $Ni(AA)_2$ in this solution; (c) in the presence of 0.03 *M* $Ni(AA)_2$ in this solution.

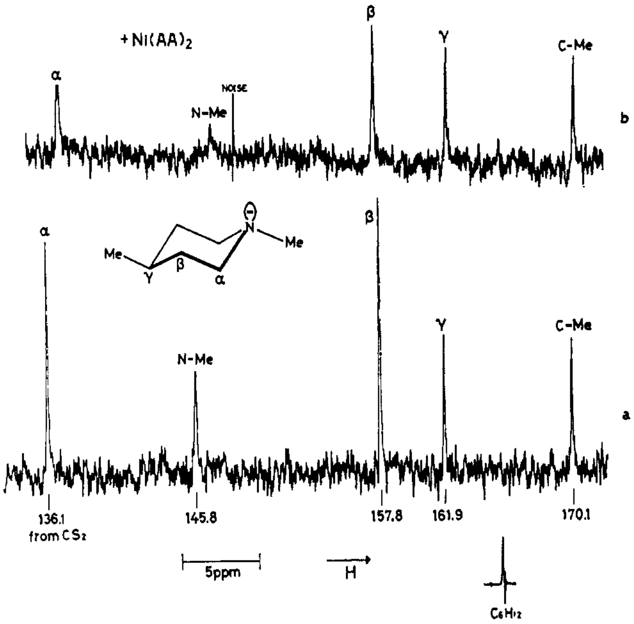

Figure 2. Completely proton-decoupled ^{13}C nmr spectra at 25.1 MHz for 1,4-dimethylpiperidine: (a) in the neat liquid; (b) in the presence of 0.025 *M* $Ni(AA)_2$ in this solution.

Experimental Section

Materials. Compounds I, II, III, and V were obtained from commercial sources.[6] 1,4-Dimethylpiperidine (IV) was prepared by N methylation of III.[13] 1-Azaadamantane (VI) was provided by Dr. Speckamp of the University of Amsterdam. Commercially available $Ni(AA)_2$ was dried *in vacuo* over 30 hr at 60°.

Nmr Measurements. Completely proton-decoupled ^{13}C nmr spectra were obtained at 25.1 MHz on a JEOL-4H-100 spectrometer equipped with an IS-100 field-frequency synchronous sweep system of the proton irradiation frequency and an SD-HC heteronuclear spin decoupler. Spectra were also measured with the external field locking mode. Samples were made in 50 v/v % $CDCl_3$ solution in 8-mm sample tubes. For the diamagnetic solution, spectra of I–IV were recorded in a single scan, and for the paramagnetic solution, 4–64 scans were accumulated, using the JEOL S/N booster, to obtain enhanced *S/N* values. The spectra were taken at room temperature (24°) in the presence of varying amounts of $Ni(AA)_2$. The concentration of $Ni(AA)_2$ ranged from 0.2 to 2 *M*. For quinuclidine (V) and 1-azaadamantane (VI) we used moderately dilute solution (*ca.* 1 *M*) and accumulated 200–300 scans for diamagnetic and paramagnetic solutions. The ^{13}C chemical shifts were measured with respect to external CS_2.[14] The observed paramagnetic shift is relative to the free ligand.

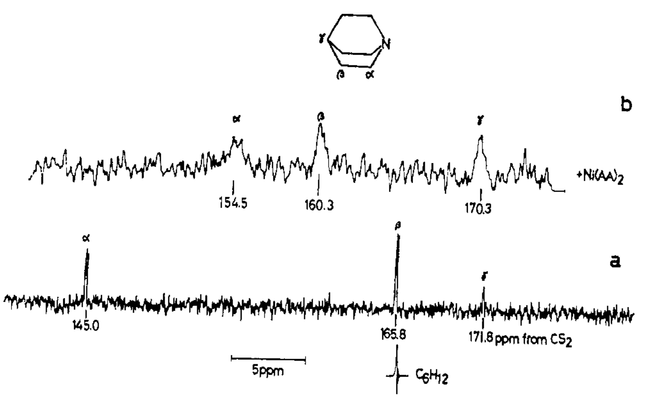

Figure 3. Completely proton-decoupled ^{13}C nmr spectra at 25.1 MHz for quinuclidine: (a) in $CDCl_3$ solution (1 *M*); (b) in the presence of 0.014 *M* $Ni(AA)_2$ in the solution (with 16 accumulations).

Results and Discussion

^{13}C Contact Shifts in the $Ni(AA)_2$ Complex System. The perturbation of the ^{13}C nmr spectrum by the addition of $Ni(AA)_2$ is exemplified for piperidine (I), 1,4-dimethylpiperidine (IV), and quinuclidine (V) in Figures 1–3. In the spectrum of the diamagnetic solution a, each carbon signal is easily assigned. Addition of $Ni(AA)_2$ to the diamagnetic solution shifts the carbon resonances upfield or downfield, and is accompanied by signal broadening. γ-Carbon and 4-methyl carbon resonances are hardly perturbed by $Na(AA)_2$. The various carbon resonances are shifted from their normal diamagnetic values by an amount which is proportional to the concentration of added $Ni(AA)_2$. This linear relation implies that the exchange of ligand between complexed and uncomplexed sites is rapid on the nmr time scale and that the spectra are time averaged.[3] Thus the ^{13}C resonances of the ligand shift toward the resonance position of the complex as $Ni(AA)_2$ is added to the diamagnetic solution and the relative values of these paramagnetic shifts are of significance in the present study; these relative values for various carbons in a ligand molecule were obtained from the slopes of the linear plot of the paramagnetic shifts *vs.* the concentration of $Ni(AA)_2$, with the value for the α-carbon normalized to 1.00. Figure 4 gives an example of this linear plot for IV. The relative ^{13}C contact shifts for various ligand molecules are summarized in Table I. The plus and the minus signs of these values denote the upfield and the downfield shifts which correspond to the negative and the positive spin densities, respectively, induced in the ligand carbon

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[13] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshans, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

[14] The use of an internal reference is more advisable when we discuss the small ^{13}C contact shift, less than 1 ppm. However the susceptibility shift is negligible.

s atomic orbital. Table I also contains the proton contact-shift data.[4]

Alternating ^{13}C contact shifts were obtained for all the ligand molecules. This is quite different from the proton contact shifts in the corresponding molecules in which most of the protons experience downfield contact shifts[4] and this has been interpreted in terms of a dominant mechanism of electron spin delocalization through the σ orbitals (predominantly through the lone-pair orbital).[3,4] Alternating ^{13}C contact shifts indicate the relative importance of spin polarization in the mechanism of electron spin transfer through the carbon skeleton. Since electron spin delocalization through the σ bond is due to the delocalized nature of the lone-pair electrons,[3] the attenuation and the alternating sign of the ^{13}C contact shifts imply that the carbon 2s atomic orbital contribution to the lone-pair orbital is minor, unlike the proton, and thus the electron spin reaches the carbon 2s atomic orbital *via* a spin polarization mechanism. This is also confirmed by the molecular orbitals (INDO–MO) of the free ligand molecules studied here. The proton 1s AO contribution to the lone-pair orbital is quite large for piperidine (both for lone-pair equatorial and axial conformers) and positive spin density reaches each proton *via* this lone-pair orbital to an extent proportional to the square of the hydrogen contribution to the lone-pair orbital.[3] The carbon 2s contribution is small, resulting in a minor contribution of electron spin delocalization through the lone-pair orbital.

Conformational Dependence of ^{13}C Contact Shifts. Inspection of Table I shows that the relative ^{13}C contact shifts of α-, β-, and γ-carbons are astonishingly different between N–H piperidines I and II and *N*-methylpiperidines III and IV. The most striking difference is the relative ^{13}C contact shifts at the β-carbon; for III and IV, quite rapid attenuation of the contact shifts, compared with those for I and II, was observed. Methyl substitution at the γ-carbon, which lowers the rate of the ring inversion,[3] has no effect on this mode of the relative ^{13}C contact shifts which were also encountered for 2-methyl-, 3-methyl-, 1,2-dimethyl-, and 1,3-dimethylpiperidines.

As clearly shown in Figure 1, the β-carbon signal for piperidine (I) is broadened most rapidly. This observation is also the case for II. The extent of the broadening is approximately proportional to the shift. This observation shows that ^{13}C line broadening is due to ^{13}C contact interaction.[14] For *N*-methylpiperidines III and IV, the extent of the signal broadening (see Figure 2) is in the order of $NCH_3 > \alpha\text{-C} > \beta\text{-C} > \gamma\text{-C} > 4\text{-CH}_3$ which is in agreement with the order of ^{13}C contact shifts. This difference in the signal broadening of the β-carbon between N–H piperidines I and II and *N*-methylpiperidines III and IV also implies different features of ^{13}C contact shifts for the β-carbon in these molecules. For quinuclidine (V) and 1-azaadamantane (VI), the signal broadening effect is in the order of $\alpha\text{-C} > \beta\text{-C} > \gamma\text{-C}$, in agreement with the order of ^{13}C contact shifts. Accordingly, the ^{13}C signal broadening in the $Ni(AA)_2$ complex system may also serve as a sensitive probe for measuring the extent of the ^{13}C contact shifts for various carbons in a molecule.

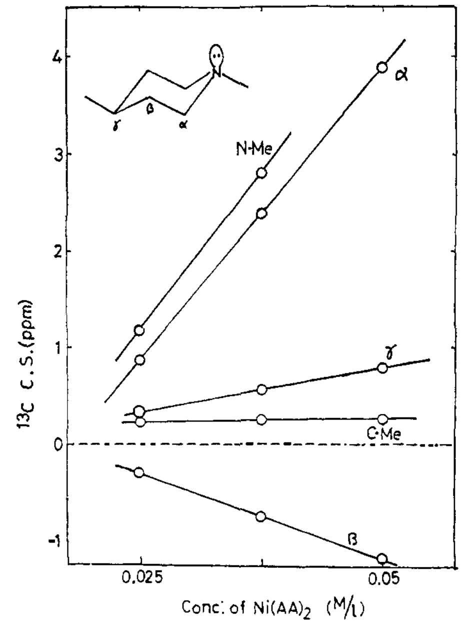
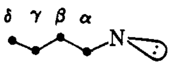


Figure 4. Plots of ^{13}C contact shifts *vs.* concentration of $Ni(AA)_2$ for 1,4-dimethylpiperidine.

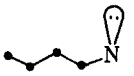
These different features of the ^{13}C contact shifts are most probably due to the effect of different lone-pair orientations. The nitrogen lone pair has a greater preference for the equatorial position in N–H piperidines while the lone-pair electrons in *N*-methylpiperidines preferentially occupy the axial position.[3,4] It has also been shown[3] that these lone-pair orbital orientations are not affected significantly by the presence of $Ni(AA)_2$.[3,4] Therefore, perhaps the odd electron distributes itself on the ligand carbons along a "zigzag path" for I, II, and VI while electron spin reaches the carbon through a "folded path" for III and IV.

zigzag path



I, II, VI

folded path



III, IV

Electron spin reaches β-carbon to a greater extent by a "zigzag path" than a "folded path." This trend is similar to nuclear spin coupling constants.[6] However, in VI, having a rigid carbon skeleton and zigzag paths, the β-carbon contact shift is slightly smaller than the α-carbon shifts, but the rate of attenuation is still slow compared with *N*-methylpiperidines. The difference in the β-contact shifts between N–H piperidines I and II and 1-azaadamantane (VI), in both of which the nitrogen lone-pair electrons are located most dominantly or fixedly at the equatorial position, is probably due to the effect of carbon substitution at the β-axial position in VI. 4-Methyl carbon (δ-carbon), which is expected to be located predominantly at the equatorial position, experiences a greater contact shift for I and II than for III and IV. This is also due to the preference of electron spin transfer through a

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Table II. Calculated Electron Spin Densities on the Carbon 2s Atomic Orbital

Ligand molecule	Position	ρ_{2s}	Relative values of ρ_{2s}	Rel values of ^{13}C contact shift	
Piperidine (lone-pair eq)	α	-0.00787	-1.00	$+1.00^a$	$+1.00^b$
	β	0.00439	$+0.56$	-1.60^a	-0.75^b
	γ	-0.00237	-0.30	$+0.10^a$	$+0.13^b$
Piperidine (lone-pair ax)	α	-0.00787	-1.00	-1.00	
	β	0.00159	$+0.20$	-0.35	
	γ	-0.00072	-0.09	$+0.20$	
Quinuclidine	α	-0.00754	-1.00	$+1.00$	
		0.00479	$+0.64$	-0.63	
	γ	-0.00291	-0.38	-0.07	

[a] Data for piperidine. [b] Data for 1-azaadamantane (VI).

"zigzag path" rather than a "folded path." A similar conformational dependence has also been encountered for proton resonances in the corresponding piperidine derivatives I–VI.[4]

One can see quite a different feature of relative ^{13}C contact shifts for quinuclidine (V) with a rigid σ skeleton; the γ-carbon unexpectedly shows a downfield contact shift, contrary to the case of piperidines I–IV and 1-azaadamantane (VI). The negative spin density on the γ-carbon for I–IV and VI may result from spin polarization in the electron spin transfer through σ bonds. However, the positive spin density on the γ-carbon 2s orbital, characteristic of a downfield contact shift, for V should be attributable to the spin delocalization mechanism. The lone-pair electrons are highly delocalized onto the γ-carbon 2s orbital, which facilitates delocalization of positive spin density to the γ-carbon by *through-space spin transfer*. In the actual case, both the spin polarization and the spin delocalization mechanisms would be cooperative. Anyhow, direct spin delocalization onto the γ-carbon gives the evidence of through-space participation of lone-pair electrons to the γ-carbon.

The very substantial sensitivity of ^{13}C contact shifts to conformational changes suggests that there should be considerable utility of ^{13}C contact shifts in the studies of molecular conformations associated with the orientation of lone-pair electrons, not readily accessible by other means.

Molecular Orbital Calculations of Electron Spin Densities on the Carbon. In order to substantiate theoretically the observed trend of ^{13}C contact shifts, we attempted to carry out molecular orbital calculations of electron spin densities on the carbon atoms. The method adopted here takes into account spin polarization by using the unrestricted Hartree-Fock self-consistent field (UHF–SCF) MO calculation.[12] We obtained spin densities from the INDO–MO calculations for the cation radical in which an electron is eliminated from the free ligand molecule.[15] This method corresponds to the model calculations of electron spin transfer from the ligand to $Ni(AA)_2$. This method has been shown to be successful in the interpretation of proton contact shifts in piperidine derivatives,[4] and of ^{13}C contact shifts in pyridine derivatives complexed with $Ni(AA)_2$.[10,16]

INDO–MO calculations were performed for lone-pair axial (a conformer) and lone-pair equatorial (e conformer) conformers of N–H piperidine.[17] Bond lengths and bond angles were the same as in the previous work.[3] The results are summarized in Table II. Spin densities for the e conformer are compared with observed ^{13}C contact shifts for I, II, and VI in which the nitrogen lone-pair electrons are situated most dominantly at the equatorial position. Calculated spin densities on the carbon a conformer are compared with ^{13}C contact shifts for III and IV in which lone-pair electrons have a greater preference for axial position. We did not take into account the populations of a and e conformers for N–H and *N*-methylpiperidines in the estimation of calculated spin densities to be compared with experiments (see Table II).[15] The attenuation of calculated spin densities is faster for the a conformer than for the e conformer. This trend agrees qualitatively with experiments. However, the greater value of spin density for the β-carbon rather than for the α-carbon in N–H piperidines cannot be reproduced by theoretical calculations. The agreement between theoretical and experimental results is excellent for 1-azaadamantane (VI). For quinuclidine, MO calculation reproduces the observed trend of ^{13}C shifts well except for γ-carbon contact shift, as in the case of proton contact shifts.[4,17a]

Acknowledgment. The authors are grateful to Dr. W. N. Speckamp for providing us with some 1-azaadamantane. They are also indebted to Dr. H. Nakatsuji and Mr. K. Hirao for the use of the INDO–MO program.

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(15) R. J. Kurland and B. R. McGarrey, *J. Magn. Resonance*, 2, 286 (1970).

(16) For a detailed discussion on the ^{13}C signal broadening effect in the paramagnetic solution containing $Ni(AA)_2$, see ref 9 and 10.

(17) Previously[4] we have obtained the populations of a and e conformers of piperidine complexed with $Ni(AA)_2$ (P_a = 12% and P_e = 88%). Consideration of these populations in the estimation of calculated spin densities for piperidine does not change significantly the spin densities for the lone-pair equatorial conformer of piperidine.

(17a) Note Added in Proof. The mode of electron spin distribution for N-containing molecules complexed with $Ni(AA)_2$ is more plausibly reproduced by INDO–MO calculations of the corresponding σ radical in which the nitrogen lone pair is replaced by the carbon radical (I. Morishima, K. Okada, and T. Yonezawa, submitted for publication). For example, the relative spin densities on the carbons are $\alpha:\beta:\gamma = -1.00:1.57:-0.20$ for the cyclohexyl radical in which the radical orbital lobe is in the equatorial position, while in the cyclohexyl radical with the axial radical lobe the corresponding values are $-1.00:0.32:-0.06$. These values explain satisfactorily the observed ^{13}C contact shifts for piperidine and *N*-methylpiperidine.