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Hydrogen bonding in fluoroanilines studied by means of a nitroxide radical probe☆

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Abstract

^{1}H, ^{13}C and ^{15}N NMR chemical shifts were measured for aniline and its five fluoro derivatives dissolved in CCl_4. The EPR spectrum of the 2,2,6,6-tetramethylpiperidine nitroxide (TMPN) radical was used as a probe to study the changes in hydrogen bonding between the aniline NH_2 group after fluorine substitution and the O–N group of the radical. The coupling constant A(^{14}N) increases with the number of fluorine atoms substituted in aniline. NMR contact shifts indicate a positive spin density of C4 and C2,6 aniline atoms and a negative spin density on the C1 atom and on the hydrogen atoms of the NH_2 group.

1. Introduction

The interaction between electron acceptors and nitroxyl groups is of theoretical and experimental interest and has been studied by NMR and EPR methods. Stable nitroxide radicals form short-lived complexes with OH···ON hydrogen bonds in water and alcohols [1–5]. Relatively few papers have reported interactions involving the NH group. ^{1}H contact shifts and relaxation times T_1 have been measured [6] in solutions of aniline containing the 2,2,6,6-tetramethylpiperidin-ol-4-oxyl (TANOL) radical.

Fluoroaromatics are of increasing utility in medicinal and agricultural chemistry [7]. Halogen substituents on the aromatic ring of aniline are interesting since they produce electron attraction and electron release (delocalization of the nitrogen lone electron pair, also called "back-bonding") effects. Especially interesting is the behaviour of the fluorine substituent as its p orbital is of comparable size to the π orbitals in aromatic compounds and strongly influences the electron density distribution in the molecule. It seemed worth investigating the ability of the NH_2 group to form hydrogen bonds in the case when several fluoro substituents are present in an aromatic ring.

The 2,2,6,6-tetramethylpiperidine nitroxide (TMPN) radical is an electron donor and forms hydrogen-bonded complexes with amines. In EPR spectroscopy the observables are the g-factor, the lineshape and the coupling constant $A(^{14}\mathrm{N})$. The first two do not change significantly upon varying the composition of TMPN/aniline solutions, but the coupling constant $A(^{14}\mathrm{N})$ appears to be sensitive to the strength of hydrogen bonds formed by

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☆ Dedicated to Professor C.N.R. Rao on the occasion of his 60th birthday.

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the nitroxide radical. $A(^{14}N)$ was measured in EPR spectra of this radical in the presence of aniline and its mono-, di-, tri-, tetra- and pentafluoro derivatives. The semiempirical AM1 and MNDO methods were applied to calculate the electron density distribution in the fluoroanilines.

2. Experimental

Aniline was distilled at reduced pressure. Crystalline fluoroanilines from Aldrich were used without further purification. Solvents were dehydrated over molecular sieves and freshly distilled. Solutions were prepared in a dry glove box using microsyringes.

NMR spectra were recorded: ^1H at 100 MHz on a Tesla FT spectrometer with 90° pulse and repetition time 15 s; ^{13}C on a Jeol FX 90 Q with 35° pulse, repitition time 2 s, spectral width 5000 Hz, 3000–8000 scans accumulated; ^{15}N spectra at 20.2 MHz on a Bruker WP 200 spectrometer using the INEPT technique optimized for a $^{15}N-^{1}H$ coupling constant of about 90 Hz; ^{14}N spectra at 30.1 MHz on a Bruker AM500 spectrometer with the program LORE applied to simulate lineshapes.

EPR spectra in the X-band were recorded by an SE/X 2452 spectrometer from Radiopan. The coupling constant $A(^{14}N)$ was measured with a Radil JTM-48 magnetometer with an accuracy of ± 0.001 mT.

The TMPN radical was prepared from 2,2,6,6-tetramethylpiperidine by oxidation and purified by sublimation.

The AM1 and MNDO calculations with electrostatic potential maps (program POZIOMICE) were carried out on IBM AT personal computer.

3. Results and discussion

The coupling constant $A(^{14}N)$ was measured in EPR spectra for the nitroxide radical TMPN in three non-polar solvents: cyclohexane, *n*-hexane and carbon tetrachloride in the concentration range from 2×10^{-2} down to 1×10^{-4} mol dm^{-3} (Fig. 1). The EPR spectrum of this radical is a triplet (due to coupling of the unpaired electron with the ^{14}N nucleus, $I = 1$) and $A(^{14}N)$ was measured as half the distance in mT between the downfield and upfield components of the signal.

At a radical concentration of 1×10^{-4} mol dm^{-3} the change of solvent gives only a 0.02 mT difference in $A(^{14}N)$ but a larger effect appears on increasing the radical concentration. The mechanism of spin exchange decreases the signal width, causing its hyperfine structure to vanish in the solid state. Usually, this mechanism was considered to be effective in solutions with a high concentration of the radical. We have found, however, that in diluted solutions as well, in the concentration range 10^{-3}–10^{-4} mol dm^{-3}, radical–radical exchange interaction is still responsible for the changes in $A(^{14}N)$. It should be stressed that in experiments where the nitroxide radical is applied as a probe for intermolecular interactions, the nitroxide radical concentration has to be rigorously constant and generally low. In the present work the concentration of the radical was kept at 1.05×10^{-3} mol dm^{-3}.

An important question to be answered is whether the lifetime of the hydrogen-bonded complex of aniline with the nitroxide radical is longer than the correlation time of motion.

An attempt has been made to estimate the correlation times for 4-fluoroaniline and pentafluoroaniline from ^{14}N NMR data. The ^{14}N signal widths are mainly determined by quadrupolar relaxation. In the extreme narrowing conditions the equation $T_1 = T_2 = T_q = (\pi\Delta)^{-1}$ holds, where Δ is the signal width at half-height ($\Delta = 300$–600 Hz, whereas field inhomogeneity or modulation broadening is below 1 Hz).

The quadrupolar relaxation times are 1.06 ms for 4-fluoroaniline and 0.57 ms for pentafluoroaniline at 297 K. Correlation times τ_q were estimated to be 3.0–3.8 and 5.1–6.7 ps for 4-fluoro- and pentafluoroaniline respectively in the temperature range 297–317 K.[1] Increasing the temperature makes τ_q shorter and the activation energy obtained from the temperature dependence of τ_q

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[1] Estimated from the expression for isotropic motions of molecules [8], neglecting the asymmetry parameters (contributions below 5%) and assuming that the quadrupolar coupling constant for liquid fluoroaniline is 4.1 MHz, and 4.117 MHz for 4-chloroaniline.

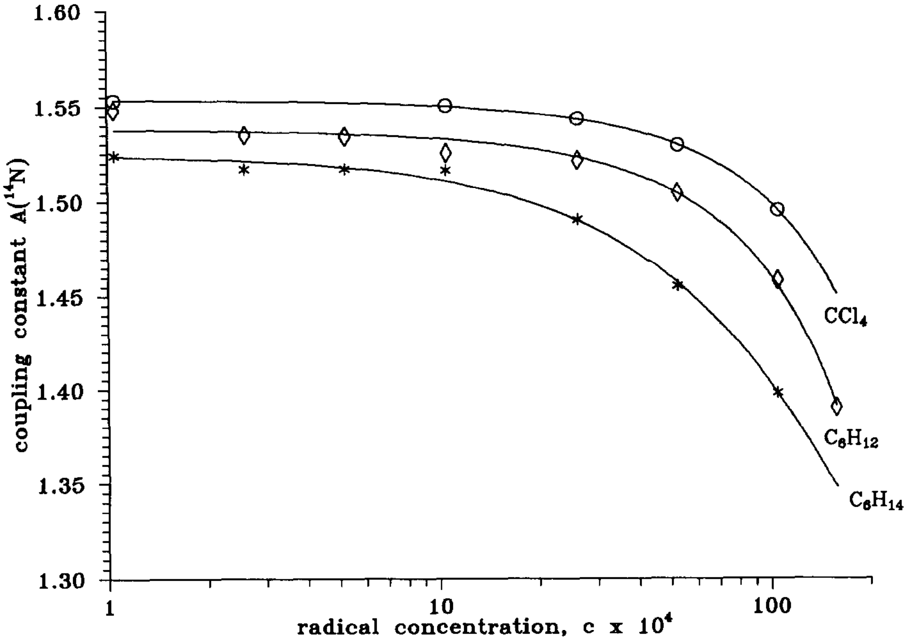

Fig. 1. Dependence of the coupling constant $A(^{14}N)$ on the concentration of the TMPN radical in *n*-hexane, cyclohexane and carbon tetrachloride.

is 9.8 kJ mol^{-1} for 4-fluoroaniline and 10.3 kJ mol^{-1} for pentafluoroaniline; the E_a values lie in the 8.5–12.5 kJ mol^{-1} region [8] and increase with molecular size, as expected.

In solutions of aniline containing the nitroxide radical the spin–lattice relaxation of the aniline protons is governed by dipolar interactions with the unpaired electron spin and the rotational tumbling of the hydrogen-bonded associate [6]. The lifetime of aniline complexes NH···ON was assumed to be 10^{-11} s, similar to those with OH···ON hydrogen bonds in alcohols and significantly longer than reorientation of 4-fluoro- or pentafluoroaniline (10^{-12} s).

Hydrogen-bond formation between NH_2 and some electron donor in a diamagnetic system is expected to produce a downfield shift of the ^1H NMR signal of the amino protons. However, the shift induced by the nitroxide radical, as found to occur in nature [5], is to the higher field.

Contact shifts for NH_2 protons (in ^1H NMR) and for aromatic carbons (in ^{13}C NMR) reflect the spin density transfer through the interaction of aniline with the radical. The electron spin density transferred to the NH_2 group of aniline is thus less than in the OH···ON systems [6].

On increasing the concentration of the radical, the signals of C1 and of the NH_2 protons are shifted upfield (Fig. 2) showing that a negative spin density is produced, whereas at C4 and C2,6 the sign of the spin density is positive (downfield shift of the respective ^{13}C signals).

On the basis of IR results [10], where the equilibrium constants of the formation of pentafluoroaniline complexes with one and two electron donor molecules have been determined, one can assume that the concentration of 1:2 complexes is negligibly low.

The investigation of NH···ON complexes was carried out by means of EPR, following the spin density changes within the NO group of the radical formation of a hydrogen bond with fluoroaniline. The coupling constant of the TMPN radical is found to depend on the solvent [4,11,12] and the value of $A(^{14}N)$ increases in polar, protic solvents.

The XH proton of alcohols and amines when forming hydrogen bonds with TMPN attracts two bonding π electrons of the NO group towards

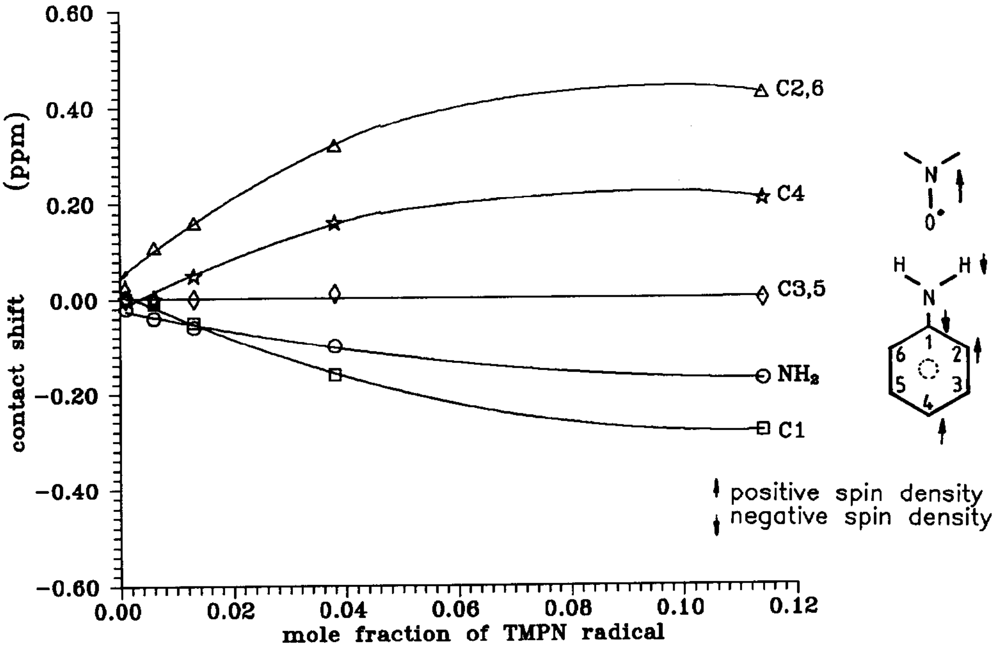

Fig. 2. ^1H and ^{13}C contact shifts (ppm) of aniline in three-component solutions (aniline + cyclohexane + TMPN) versus mole fraction of the radical.

oxygen, whereas the unpaired electron is shifted towards the nitrogen atom. As a result the spin density at the nitrogen and thus the coupling constant increase. The value of $A(^{14}N)$ can serve as a measure of the strength of XH···ON hydrogen bond interaction [11].

The dependence of $A(^{14}N)$ on the concentration of fluoroanilines was measured in a series of solutions in CCl_4. The concentration of TMPN was kept constant at 1.05×10^{-3} mol dm^{-3} and that of the respective fluoroaniline varied from 0.025 to 0.195 mol dm^{-3}. The results are collected in Table 1.

The coupling constants were found to increase with increasing amounts of aniline because the concentration of the hydrogen-bonded complexes increases. The exchange of proton within the complex and the process of its formation/decay are fast compared to the EPR time scale and the value of $A(^{14}N)$ of the radical with and without hydrogen

Table 1
Hyperfine coupling constants of the TMPN radical ($c_R = 1.05 \times 10^{-3}$ mol dm^{-3}) in solutions of aniline (An) and fluoroanilines in CCl_4; (without aniline $A(^{14}N) = 1.550$ mT)

c (mol dm^{-3})	$A(^{14}N)$ (mT)					
	An	2F	2,6F	2,4,6F	2,3,5,6F	2,3,4,5,6F
0.025	1.568	1.567	1.570	1.569	1.570	1.571
0.050	1.570	1.570	1.572	1.572	1.574	1.573
0.075	1.570	1.571	1.574	1.573	1.576	1.575
0.100	1.573	1.573	1.576	1.576	1.577	1.577
0.125	1.575	1.575		1.577		1.579
0.150	1.576	1.577			1.580	1.581
0.195	1.577	1.579	1.581	1.583	1.590	1.592

Table 2
Net charges within the C1–NH_2 fragment and C–N bond lengths as obtained from AM1 calculations and NMR chemical shifts

	C1	N	H	H′	C–N (nm)	δ^{13}C1^{a} (ppm)	δ^{15}N^{b} (ppm)
An	0.0548	−0.3270	0.1823	0.1823	0.1399	147.1	−324.2
2F	0.0314	−0.3218	0.1879	0.1944	0.1397		−327.9
2,4F							−329.8^{c}
2,6F	0.0051	−0.3170	0.2004	0.2004	0.1393		
2,4,6F	−0.0064	−0.3148	0.2026	0.2026	0.1393		
2,3,5,6F	0.0745	−0.3307	0.2196	0.2196	0.1384		
2,3,4,5,6F	0.0650	−0.3288	0.2218	0.2218	0.1383	125.1	−350.0

[a] 0.5 M solutions in $CDCl_3$.
[b] 1 M solutions in C_6D_6.
[c] Ref. [16].

bonding to aniline is not observed separately. The measured $A(^{14}N)$ is a function of the equilibrium constant and of the strength of the NH···ON interaction.

A comparison of $A(^{14}N)$ at one concentration, e.g. at 0.195 mol dm^{-3}, reveals the differences between the fluoroanilines. The value of $A(^{14}N)$ goes from 0.027 mT for aniline up to 0.042 mT for pentafluoroaniline (Table 1). Generally, $A(^{14}N)$ increases with the number of fluorine atoms in the aromatic ring:

aniline < difluoroaniline < trifluoroaniline
< tetrafluoroaniline < pentafluoroaniline.

The role of the fluorine atom in the ortho position of the aromatic ring is notable in the interaction of the amino group with the nitroxide radical, in spite of the fact that the space-filling model with van der Waals spheres of the ortho-fluoro-substituted aniline shows that there is still enough room to approach both NH_2 protons.

3.1. Calculation of electrostatic potentials

The semiempirical AM1 method was found recently [13] to be good for predicting properties of aniline and its derivatives. AM1 was used therefore to calculate the optimal geometry and net atomic charges (Table 2), and to determine the distribution of the negative and positive electrostatic potentials around the molecules of fluoroanilines according to the procedures described by

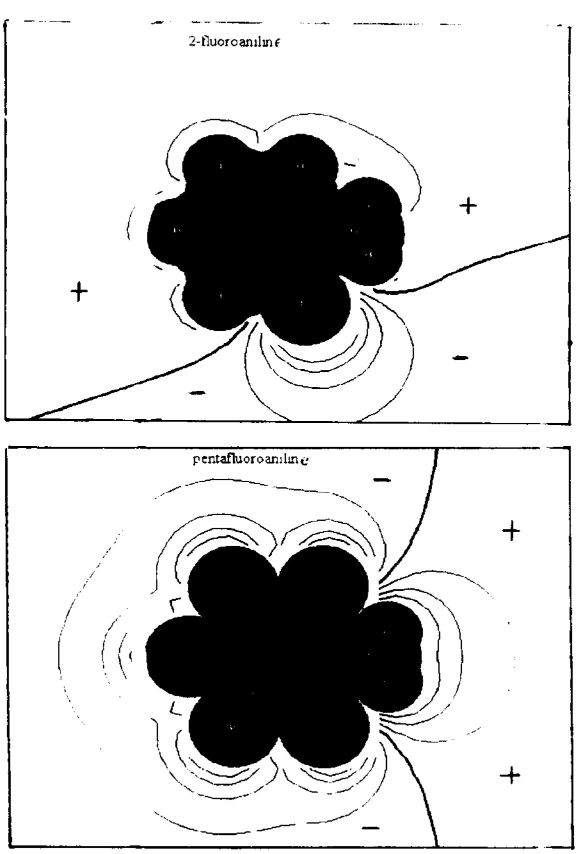

Fig. 3. Electrostatic potential maps in the vicinity of (a) 2-fluoroaniline and (b) pentafluoroaniline. The space inside the van der Waals spheres of atoms is shadowed; the thick line corresponds to zero energy of interaction and other contour lines mark energies of ±25, 50, 75 and 100 kJ mol^{-1}.

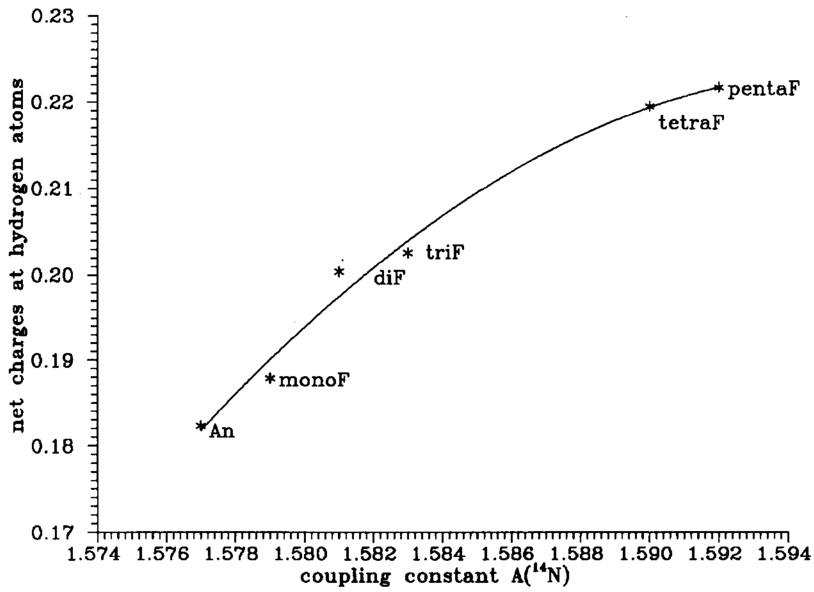

Fig. 4. Relationship between net charges at hydrogen atoms of the NH_2 group (as obtained from AM1) versus the EPR coupling constant $A(^{14}N)$ of the TMPN radical in the solutions of the respective fluoroaniline ($c_{TMPN} = 1.05 \times 10^{-3}\,mol\,dm^{-3}$, $c_{FAn} = 0.195\,mol\,dm^{-3}$).

Mizerski and Kalinowski [14] for MNDO results. The energy of interaction (in kJ mol^{-1}) with an elementary point charge was used as a measure of this potential and the interaction with negative point charge ($z = -e$) can simulate the interaction with the nitroxide radical. The potential is a function of the spatial coordinates and can be illustrated in-plane as a section with contour lines connecting points of the same values of energy. Electrostatic potential maps in the vicinity of (a) 2-fluoro-, and (b) pentafluoranilines are shown in Fig. 3. The NH proton in the proximity of fluorine has less suitable conditions to attract the radical and to form a hydrogen bond because it is near to the zero potential line and to the field with negative charge where the nitroxide radical will not approach. Compounds with 2,6-fluoro substituents have similar potentials as in Fig. 3(b). The repulsion between the electron-rich fluorine atoms in the proximity of NH_2 and the negative charge on the nitroxyl group of the radical restrict the frequency and the distance of approach of the radical, thus reducing the amount of $NH \cdots ON$ complexes and causing the decrease of $A(^{14}N)$.

The opposite effect is observed, i.e. $A(^{14}N)$ also increases in di-ortho-substituted fluoroanilines. The calculated trends in electron density changes within the C1–N–H fragment are expected to reproduce the electron acceptor properties of fluoroanilines and this correlates with the NMR shielding data and the $A(^{14}N)$ from EPR spectra. Net charges at hydrogen atoms are plotted versus $A(^{14}N)$ for fluoroanilines (Fig. 4). It is evident that the strength of the hydrogen bond with the radical (measured by the $A(^{14}N)$) increases because the hydrogen atoms in fluoroanilines bearing many fluorine atoms are more positively polarized. The lone pair electron delocalization (back-bonding effect) was accepted as an explanation of the decrease of nitrogen shielding in aniline (−324.2 ppm) compared to NH_2 nitrogen in the aliphatic amines (about −370 to −380 ppm).

In aniline derivatives, an ortho-halogen effect was observed. Replacing one ortho-hydrogen by fluorine produces an increase of nitrogen shielding of −11.8 ppm (in ortho-chlorine −3.4 ppm) [15]. Fluorine is best able to reduce the back-bonding.

Reduction of lone electron pair delocalization is most pronounced in pentafluoroaniline. As compared to unsubstituted aniline the increase in nitrogen shielding amounts to 25.8 ppm (Table 2) and is followed by the increase of shielding by 22 ppm of the C1 carbon directly bonded to nitrogen.

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