Deuterium isotope effects on ^{13}C chemical shifts of intramolecularly hydrogen-bonded Schiff bases

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Received (in Cambridge, UK) 21st April 1999, Accepted 27th September 1999

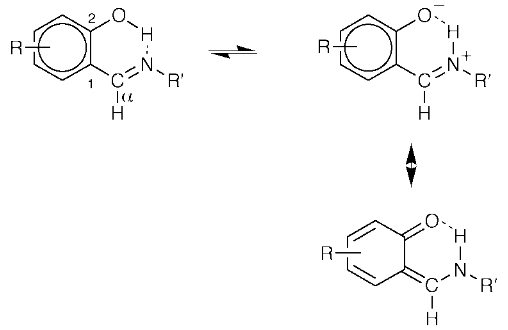
The proton transfer equilibrium in a series of Schiff bases derived from substituted salicylic aldehydes and aliphatic amines has been investigated by means of variable temperature multinuclear magnetic resonance and the deuterium isotope effect on ^{13}C nuclear shielding. Most of the compounds exist in two tautomeric forms in $CDCl_3$. The populations of the tautomeric forms have been estimated using ^3J(NH,H) and ^1J(^{15}N,H) coupling constants. One goal is to describe the characteristics of both tautomers. Deuterium isotope effects on ^{13}C chemical shifts ($^n\Delta$C(XD)) are shown to depend on the position of the tautomeric equilibrium. $^n\Delta$C-2(XD) and $^n\Delta$C-1′(XD) are found to be a sensitive non-monotonic function (S-shape) of the mole fraction. The pattern of the dependence seems also to be general for other tautomeric compounds with intramolecular hydrogen bonds, but with much lower barriers to interconversion like β-diketones and piroxicam as well as organic acid–pyridine complexes with intermolecular hydrogen bonds. This new feature is a valuable tool in the characterisation of tautomeric and other equilibrium systems.

Introduction

The Schiff bases derived from aromatic *ortho*-hydroxyaldehydes have received considerable attention due to their interesting photo-physical properties,[1] role played in biological systems[2] and other applications.[1c,3] The intramolecular hydrogen bond and proton transfer equilibrium have been considered to be major factors controlling the properties of these Schiff bases.[1–3] Thermochromism exhibited by some *N*-salicylideneanilines is directly related to the thermally activated intramolecular proton transfer.[1] The proton transfer process is connected to the hydrogen bond potential energy surface with a double minimum. In the Schiff bases the potential barrier and the energy difference between the two minima may be lowered by several factors such as: an increase of the acidity of the phenol OH group and the basicity of the proton acceptor N atom, an extension of the π-electron delocalisation over the whole molecule and favourable intermolecular interactions in the solid state or in polar solutions.[4] The activation barriers have been found in *N*,*N*′-bis(salicylidene)phenylenediamine to be 10 and 25 kJ, respectively.[4i] In addition, the ΔS of the reaction is negative and relatively large, −48.5 J mol^{-1} K^{-1}.[4e] The existence of such an equilibrium has been proven for Schiff bases derived from *o*-hydroxynaphthaldehyde[4a–i] and in a few cases from *N*-salicylideneanilines.[2d,4j–q]

One of the aims of the present work is to study intramolecular hydrogen bonding and related proton transfer equilibria in Schiff bases derived from salicylic aldehydes and aliphatic amines (Fig. 1) and to establish standard parameters for both the OH and the NH type of tautomer. Several compounds exist in the OH-form, whereas the NH form is more difficult to reach. A few solid state structures have been determined by X-ray crystallography.[4r,s]

The stronger basic properties of aliphatic amines compared to aniline have led to a lowering of the proton potential barrier in comparison with the *N*-salicylideneanilines.[4] We have used measurements of secondary isotope effects on ^{13}C chemical shifts, as this method is known to be very useful in studies of intramolecular hydrogen bonds and tautomerism in Schiff bases[5] and other systems.[6] Previous studies have indicated that equilibrium isotope effects on chemical shifts depend on the equilibrium constant,[6e,h] but one of the difficulties is to find compounds to cover the full range of equilibrium constants. This trend will be dealt with in depth. The Schiff bases form a very suitable set as the equilibrium can be tailored by change of substituents.



R = H; CH_3; OCH_3; Cl; Br; 3,5-diCl; 3,5-diBr; 3,4,5,6-tetra-Cl; 3-NO_2; 5-NO_2

R′ = CH_3; C_3H_7; t-C_4H_9;CH_2-C_6H_5

Fig. 1 Tautomeric structures of Schiff bases.

A very important feature is the investigation of many kinds of deuterium isotope effects on chemical shifts and the correlations between these internally and with coupling constants and chemical shifts. The relevance of such studies is much stressed by the increased interest in and studies of isotope effects of low barrier systems such as β-diketones,[6h] *o*-Mannich bases[7] and organic acid–pyridine complexes.[8]

Experimental

Materials

Salicylaldehyde, 3,5-dichloro-, 3-methoxy-, 4-methoxy-, 5-methoxy-, 4,6-dimethoxysalicylaldehyde and 2-hydroxy-1-naphthaldehyde were purchased from Aldrich Chemicals;

5-chloro-, 5-bromo- and 3,5-dibromosalicylaldehydes were obtained from I. Bogdanska. 3-Methyl-, 3-nitro- and 3,4,5,6-tetrachlorosalicylaldehydes were prepared according to literature procedures.[9] Schiff bases were prepared by standard methods, condensation of the substituted salicylic aldehydes with aliphatic amines in refluxing ethanol.[10] The products were purified by distillation or crystallisation. The purity of the compounds was verified by melting points, ^{1}H NMR spectroscopy and elementary analysis. Deuteriation of the compounds was done by heating the Schiff bases in a CH_3OD solution and evaporation of the solvent under reduced pressure. The degree of the deuteriation was estimated from ^{1}H NMR spectra.

NMR Experiments

The ^{1}H and ^{13}C NMR spectra of samples of non-deuteriated and deuteriated species, containing mixtures of both isotopomers as well as HETCOR and COLOC experiments were measured on 0.1 M solutions in $CDCl_3$ and CD_2Cl_2 using a Bruker DPX-400 Avance or a Bruker AC 250 spectrometer. Parameters were used as in previous studies.[6e] ^{1}H and ^{13}C chemical shifts were measured relative to internal TMS and those of ^{15}N relative to external nitromethane. The temperatures were maintained and measured by Eurotherm BV-T 2000 with an accuracy of 1 K and calibrated *vs.* methanol.

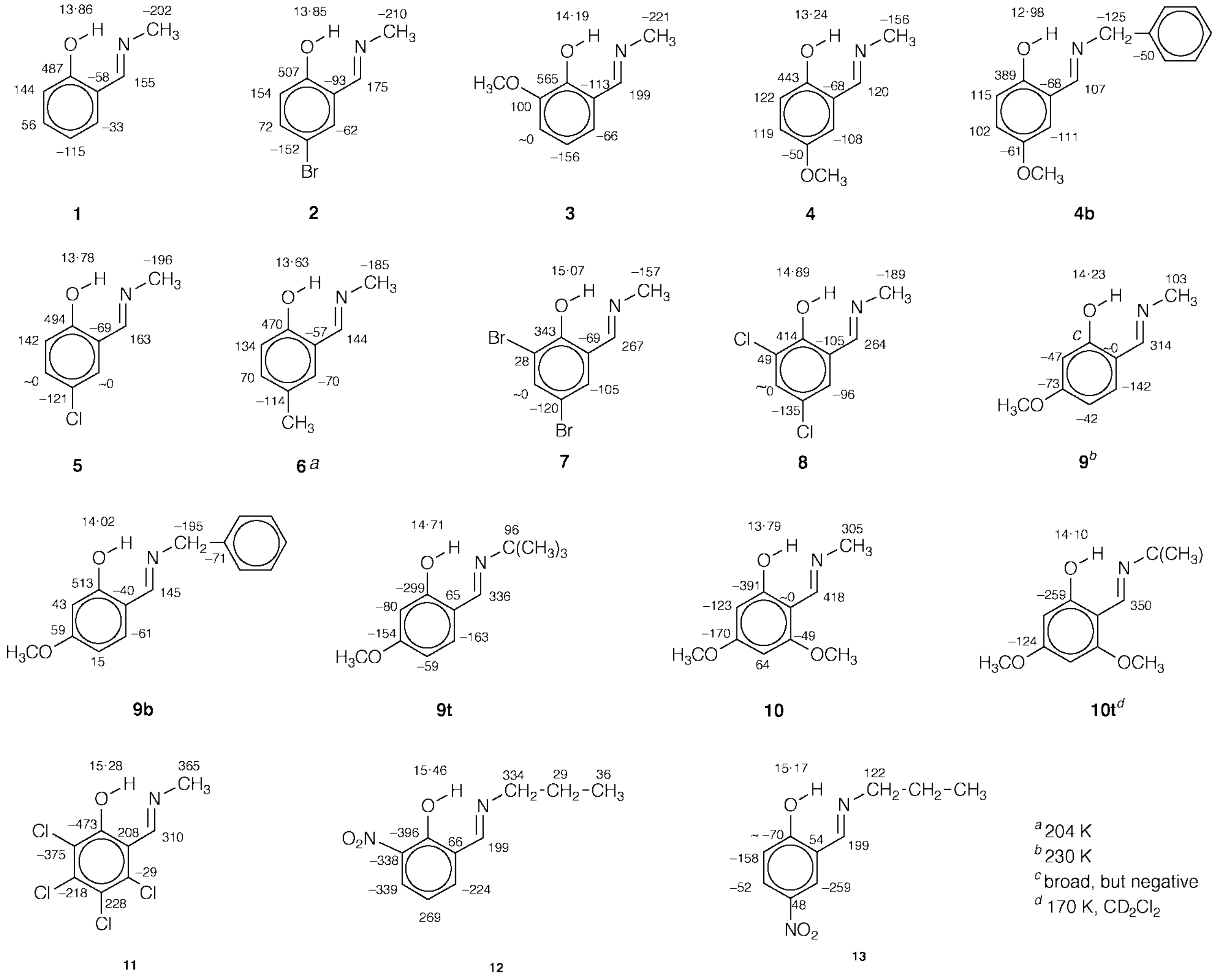
Results

The Schiff bases **1**–**13** are presented in Scheme 1. They were obtained by condensation of substituted salicylic aldehydes with methylamine (**1**–**11**), propylamine (**12** and **13**), *tert*-butylamine (**9t** and **10t**) and benzylamine (**4b** and **9b**). Propylamine, *tert*-butylamine and benzylamines were used either to increase solubility at low temperatures or to vary the strength of the base part. *N*-(2-Hydroxy-1-naphthylidene) *tert*-butylamine (**14**) was recorded at low temperature to give coupling constants for the NH-form.

The ^{1}H, ^{13}C and ^{15}N NMR spectra

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 250 K and for some representative compounds **1**, **4b**, **9t**, **10** and **11** at lower temperatures down to 220 and 170 K in $CDCl_3$ and CD_2Cl_2, respectively. The ^{1}H and ^{13}C chemical shifts are given in Tables 1–3. The assignments of the ^{1}H and ^{13}C NMR spectra of *N*-salicylidenealkylamines were made on the basis of substituent effects and ^{1}H–^{13}C correlation (COSY). The ^{13}C chemical shift assignments for compounds **5**, **7** and **8** were verified by isotope effect values, and for compounds **2**, **5**, **6**, **9**, **10** by COLOC experiments.

O^{1}H chemical shifts. The signals of the protons involved in the intramolecular hydrogen bonds δ(XH) (X = O or N) are found between 12.81–15.65 ppm (see Fig. 2). Lowering of the temperature led to a slight low frequency shift for compounds **1**–**9b**. For compounds **10**–**13** the reverse effect was observed (Tables 1–3). In the case of **9t** the proton resonance shifted to higher frequency with decreasing temperature down to 230 K, then shifted back to lower frequency. No distinct concentration dependence of δ(XH) was observed.



Scheme 1 Deuterium isotope effects on chemical shifts[a] and XH chemical shifts, δ(XH). [a] In ppb. [b] At 230 K.

Table 1 ^{1}H and ^{13}C chemical shift assignments in compounds **1**–**13** at 300 K

			Position								
Compound	Substituents	δ (ppm)	1	2	3	4	5	6	α	1′	Others
1		C	118.87	161.16	116.99	132.00	118.42	130.96	166.17	46.02	—
		H	—	—	6.95	7.29	6.86	7.23	8.34	3.48	13.50
2	5-Br	C	120.23	160.33	119.07	134.70	109.84	133.12	164.95	45.98	—
		H	—	—	6.85	7.36	—	7.34	8.26	3.49	13.49
3	3-OCH$_3$	C	118.64	152.19	148.57	113.80	117.67	122.70	166.27	45.58	56.10
		H	—	—	—	6.91	6.78	6.86	8.32	3.48	13.85, 3.90
4	5-OCH$_3$	C	118.56	155.13	117.62	118.83	151.87	114.69	165.85	46.21	55.91
		H	—	—	6.90	6.90	—	6.75	8.29	3.48	12.95, 3.77
4b^a	5-OCH$_3$	C	118.80	155.43	117.66	119.45	152.29	115.15	165.68	63.45	138.68
		H	—	—	6.95	6.95	—	6.88	8.46	4.84	12.81, 7.40, 3.81
5	5-Cl	C	119.59	159.81	118.56	131.83	122.94	130.12	165.03	45.94	—
		H	—	—	6.88	7.21	—	7.16	8.22	3.46	13.44
6	5-CH$_3$	C	118.52	158.83	116.70	132.78	127.46	131.02	166.15	46.10	20.35
		H	—	—	6.86	7.09	—	7.01	8.28	3.46	13.20, 2.28
7	3,5-diBr	C	119.57	159.33	112.97	137.70	108.72	132.47	164.55	44.44	—
		H	—	—	—	7.68	—	7.29	8.18	3.51	14.66
8	3,5-diCl	C	119.21	157.72	123.20	132.22	122.02	128.73	164.72	44.76	—
		H	—	—	—	7.39	—	7.12	8.22	3.51	14.48
9	4-OCH$_3$	C	112.25	166.76	101.39	163.77	106.28	132.40	164.95	43.85	55.30
		H	—	—	6.40	—	6.35	7.06	8.12	3.39	13.94, 3.80
9b^a	4-OCH$_3$	C	112.84	164.04	101.17	163.22	106.12	132.91	164.60	62.35	138.83
		H	—	—	6.98	—	6.48	9.23	8.38	4.78	13.83, 3.84, 7.37
9t	4-OCH$_3$	C	112.3	168.1	101.6	164.1	105.9	133.1	158.9	55.7	55.3, 29.54
		H^b	—	—	6.29	—	6.29	7.12	8.15	—	14.78, 3.80, 1.36
10	4,6-diOCH$_3$	C	102.38	176.71	95.59	167.20	87.49	160.76	159.37	39.08	55.34, 55.30
		H	—	—	5.87	—	5.57	—	8.29	3.29	14.03, 3.77
10t^a	4,6-diOCH$_3$	C									
		H	—	—	5.81	—	5.52	—	8.33	—	14.58, 1.41, 3.77
11	tetra-Cl	C	112.07	166.50	125.73	138.38	118.23	131.92	163.90	40.39	—
		H	—	—	—	—	—	—	8.63	3.52	15.43
12	3-NO$_2$	C	119.54	164.61	139.88	132.19	113.32	138.89	164.61	56.23	23.34, 11.32
		H	—	—	—	8.11	6.64	7.46	8.28	3.64	15.65, 1.79, 1.03
13	5-NO$_2$	C	115.94	171.44	119.94	128.52	138.03	128.79	164.06	58.62	23.63, 11.48
		H	—	—	6.93	8.17	—	8.24	8.33	3.64	15.01, 1.79, 1.03

^{a} In CD$_2$Cl$_2$. ^{b} At 270 K.

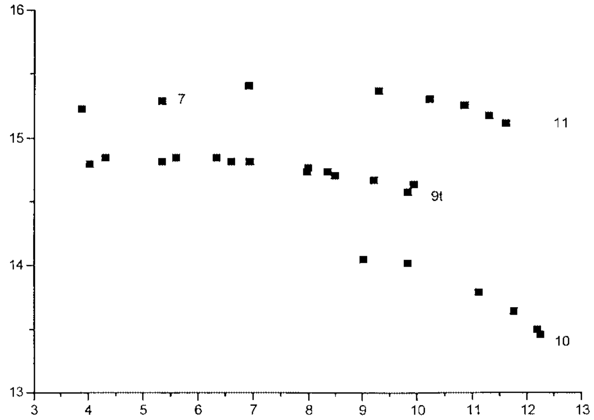


Fig. 2 Plot of XH chemical shifts *vs.* ^3J(NH,H-α).

Temperature effects on ^{13}C chemical shifts. The ^{13}C chemical shifts for compounds **1**–**6** display small variations as a function of temperature; the temperature coefficient for C-2 varied from 0.002 to 0.006 ppm K^{-1}. More important variations were observed for compounds **7**–**13**, the temperature coefficient varied from 0.02 to 0.06 ppm K^{-1} (300–250 K CDCl$_3$) and the C-2 resonance shifted to low frequency at lower temperature. For the C-α atoms of **9**, **10**, **12** and **13** the temperature coefficients were 0.009–0.015 ppm K^{-1}. Other ^{13}C signals displayed little variation with temperature.

^{15}N Chemical shifts. The ^{15}N chemical shifts increased at lower temperature.

Coupling constants ^3J(NH,H). The three bond coupling constants were measured at low temperature (Table 4). Values of 3.98 and 5.35 Hz were observed for **3** at 230 and 220 K. An increase in ^3J(NH,H) with lowering of the temperature was observed for **9**, **9t**, **10** in CDCl$_3$ and CD$_2$Cl$_2$ (Table 3), **10t** (from 12.01 Hz at 230 K up to 12.57 Hz at 170 K) and for **11** (from 6.93 at 270 K up to 10.23 at 250 K). For **12** this coupling constant equals 10.76 at 250 K. For **14** a constant value of 12.6 Hz was determined in a mixture of CD$_2$Cl$_2$ and CDCl$_3$ at 170 K. At 160 K the resonances were too broad to yield accurate values. The maximal values of ^3J(NH,H) for **14** are close to those found for some Schiff bases with the XH proton localised at the N atom.[4a–f] It is difficult to measure the small values of coupling constants probably due to intermolecular exchange of the NH proton. The value of ^3J(NH,H) for **9b** (1.34 Hz) was extrapolated from the relationship between ^1J(^{15}NH) and ^3J(NH,H) (Fig. 3A). From the values of the ^3J(NH,H) the mole fractions (χ) of the N-tautomeric form for each compound were estimated.

The proton resonances of the chelate protons (XH) were broad. This broadness is partly due to exchange at high temperature and partly due to unresolved couplings to the H-7 protons and to the protons at the C-1′ carbon. Lowering the temperature to 250 K led to a resolved XH resonance (X = O or N or both if a tautomeric equilibrium exists).

Coupling constants ^1J(^{15}N,H). One-bond coupling constants were measured for **9b** and **9t** at low temperature in the ^{15}N NMR spectra in CD$_2$Cl$_2$. The linear correlation between the ^{15}N chemical shift (in Hz) and ^1J(^{15}N,H) is presented in Fig. 3B. This is similar to the one found in ref. 6*i*. The plot of ^1J(^{15}NH) *vs.* ^3J(NH,H) is shown in Fig. 3A. Assuming a value of 12.6 Hz

Table 2 ^{1}H and ^{13}C chemical shift assignments in compounds **1**–**13** at 250 K

			Position					
Compound	Substituents	δ (ppm)	1	2	3	4	5	6
1		C	118.56	160.91	116.85	131.95	118.39	130.9
		H	—	—	6.99	7.33	6.90	7.28
2	5-Br	C	119.89	160.13	118.97	134.56	109.70	132.9
		H	—	—	6.88	7.38	—	7.37
3	3-OCH$_3$	C	117.99	152.07	148.21	112.66	117.43	122.3
		H	—	—	—	6.91	6.82	6.91
4	5-OCH$_3$	C	118.25	154.79	117.52	118.49	151.43	114.0
		H	—	—	6.93	6.93	—	6.78
4b[a]	5-OCH$_3$	C	118.15	154.62	117.25	118.81	151.45	114.1
		H	—	—	6.94	6.94	—	6.87
5	5-Cl	C	119.26	159.60	118.43	131.71	122.64	129.9
		H	—	—	6.90	7.23	—	7.16
6	5-CH$_3$	C	118.21	158.57	116.54	132.72	127.45	130.9
		H	—	—	6.89	7.13	—	7.06
7	3,5-diBr	C	118.58	160.71	113.63	137.83	107.80	132.5
		H	—	—	—	7.70	—	7.30
8	3,5-diCl	C	118.34	158.86	123.34	132.34	121.14	128.7
		H	—	—	—	7.42	—	7.14
9	4-OCH$_3$	C	111.29	169.64	101.36	164.15	106.27	132.7
		H	—	—	6.36	—	6.31	7.07
9b[a]	4-OCH$_3$	C	112.08	164.11	100.56	163.08	105.98	132.5
		H	—	—	6.46	—	6.46	7.21
9t	4-OCH$_3$	C	110.14	174.25	101.88	165.23	106.11	133.3
		H	—	—	6.27	—	6.27	7.10
10	4,6-diOCH$_3$	C	101.81	179.26	95.81	167.58	86.65	160.6
		H	—	—	5.84	—	5.51	—
10t[a]	4,6-diOCH$_3$	C	101.43	179.93	96.09	167.60	86.34	160.7
		H	—	—	5.81	—	5.49	—
11	tetra-Cl	C	111.05	168.34	126.37	138.69	116.98	131.8
		H	—	—	—	—	—	—
12	3-NO$_2$	C	118.88	167.70	139.87	134.00	111.87	140.7
		H	—	—	—	8.21	6.58	7.55
13	5-NO$_2$	C	114.43	174.56	121.35	129.21	136.47	130.0
		H	—	—	6.88	8.19	—	8.29

[a] In CD$_2$Cl$_2$.

for ^3J(NH,H) in the NH-tautomer, an averaged maximal value of $^1J(^{15}$NH) = 91.3 Hz was extrapolated from this plot. This is very close to the value of 91 Hz estimated by Dudek and Dudek[4p] and the 92.6 Hz reported by Kurkovskaya *et al.*[4d] This also shows that the value extrapolated from azo compounds[4f] is less useful.

^{13}C chemical shifts. The chemical shift of C-2 varies linearly as a function of the mole fraction (Fig. 4). The ^{13}C chemical shift difference between carbons, C-*x*, of the OH and the NH forms may be estimated from the plot of δC-*x vs.* ^3J(NH,H) (see *e.g.* Fig. 4). ΔC-2 = ΔC-2$_{OH}$ − ΔC-2$_{NH}$ = −16.4 ppm. Similarly, ΔC-4 = −2.7 ppm, ΔC-6 = 1.4 ppm and ΔC-α = 1.5 ppm. These trends are also reflected in the differences in the ^{13}C chemical shifts of Tables 1 and 2. Notice the small values for δC-α except for **9**, **9t** and **10** explaining why the equilibrium isotope effects in general are small (see later).

Deuterium isotope effects at hydrogen $^n\Delta$H-α(XD). Deuterium isotope effects at the hydrogen atom of the imine group $^n\Delta$H-α(XD) are observed in the ^{1}H NMR spectra of compounds **9**, **9t**, **10**–**13**. They vary in magnitude from 0.02 to 0.04 ppm. For **9t** in CDCl$_3$ or in CD$_2$Cl$_2$ a plot of $^n\Delta$H-α(XD) *vs.* mole fraction showed a maximum around 10 Hz and a shape for the measured segment similar to that of Fig. 8 (see later).

Deuterium isotope effects on ^{13}C chemical shifts, $^n\Delta$C(XD). Deuterium isotope effects on ^{13}C chemical shifts caused by deuterium substitution of the proton involved in the intramolecular hydrogen bond were measured as the difference between the chemical shifts at ^{13}C signals in partially deuteriated compounds in CDCl$_3$ and CD$_2$Cl$_2$ solutions. The isotope effects are defined as $^n\Delta$C(XD) = ΔC(XH) − δC(XD), where *n* is the number of bonds between the deuterium and the carbon in question. We have adopted the nomenclature, $^n\Delta$C(XD), for isotope effects of all carbon atoms as both the OH- and NH-forms exist in equilibrium. In most cases the isotope effects were not observed at ambient temperature, in spite of a high yield of deuteriation (except for **1**–**4** and **11**). For this reason standard measurements were performed at 250 K in CDCl$_3$ solution and for some compounds at lower temperature if required. The $^n\Delta$C(XD) values at 250 K (except **9** at 230 K and **10t** at 170 K) are given in Scheme 1, all others in Table 4. Large positive $^n\Delta$C-2 (XD), $^n\Delta$C-α (XH) and large negative $^n\Delta$C-1′(XD) isotope effects are observed for compounds **1**–**8** and **9b**. These results are in good agreement with those obtained before for anils of salicylaldehyde.[5a] For compounds **9**, **9t**, **10**, **11** and **13** isotope effects of opposite signs on C-2 and C-1′ compared to the just mentioned compounds were observed, the values of $^n\Delta$C-2(XD) are large and negative, while the values of $^n\Delta$C-1′ (XD) are large and positive. Large positive and negative values of the long-range isotope effects are observed for aromatic carbon atoms. The positive $^n\Delta$C-3(XD), $^n\Delta$C-4(XD) changes to negative going from Schiff bases **1**–**8** to **9**–**13**, whereas the opposite happens for $^n\Delta$C-1(XD) and $^n\Delta$C-5(XD). **9b** is an exception. A linear relationship between the $^n\Delta$C-2(XD) and $^n\Delta$C-1′(XD) is observed (Fig. 5) for all Schiff bases, except for **9t** and **10t**. Likewise, a reasonable linearity is found between $^n\Delta$C-2(XD) and the isotope effects at C-4. For other aromatic carbons the relationship is less well defined. No linear relationship between the $^n\Delta$C-2(XD) and the $^n\Delta$C-*α*(XD) or between this parameter and δ(XD) was found.

The secondary isotope effects $^n\Delta$C-2 (XD) measured for compounds **1** and **4b** display only small variations with tem-

Table 3 $^n\Delta$C(OD) at variable temperature for compounds **1**–**13**[a]

		Position									
Compound	*T*/K	C-1	C-2	C-3	C-4	C-5	C-6	C-α	C-1′	δOH	Other
1	260	~0	481	134	~0	−116	~0	153	−191	13.76	
	270	~0	473	90	~0	−93	~0	106	−181	13.68	
	300[c]	~0	372	~0	~0	~0	~0	68	−97	13.50	
4b	200	−52	397	122	106	−61	−120	108	−129	13.12	−44
	220	−57	391	121	104	−66	−114	109	−124	13.08	−45
	300	n.m.[d]	382	104	96	−59	−110	104	−120	12.81	−38
7	240	−56	292	~0	~0	−82	−121	273	−126	15.14	
	260	−104	397	78	~0	−141	−97	262	−190	14.98	
	300	−37	503	47	~0	−162	~0	239	−194	14.66	
8	230	−65	293	~0	~0	−89	−115	279	−130	15.07	
	300	−127	495	111	~0	−166	−61	227	−225	14.48	
9b[b]	160	n.m.	440	~0	n.m.	~0	−83	190	−137	14.28	−47
	180	−43	497	~0	42	~0	−78	~171	−178	14.24	−64
	200	−64	508	36	57	~0	−72	159	−195	14.17	−69
	240	−45	573	41	59	−15	−64	145	−199	14.06	−72
	300	n.m.	490	n.m.	n.m.	n.m.	n.m.	72	−163	n.m.	n.m.
9t	230	94	−444	−110	−191	−51	−177	345	112	14.64	
	260	n.m.	−225	−61	−127	−50	−152	327	77	14.72	
9t[b]	180	121	−459	n.m.	−205	n.m.	−203	324	119	14.60	
	200	87	n.m.	−90	n.m.	n.m.	−187	328	96	14.73	
	230	n.m.	~−50	n.m.	−101	n.m.	−155	312	n.m.	14.81	
	250	n.m.	~120	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	14.81	
	260	n.m.	~178	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	14.79	
10	230	~0	−340	−114	−154	60	−51	395	283	13.67	
	250	~0	−391	−123	−170	64	−49	418	305	13.79	
10[b]	160	n.m.	−220	n.m.	n.m.	n.m.	n.m.	n.m.	224	13.39	
	170	n.m.	−247	n.m.	−122	n.m.	−52	348	249	13.46	
	180	n.m.	−279	n.m.	−131	n.m.	−52	374	263	13.50	
	200	n.m.	−349	−113	−152	70	−60	392	293	13.64	
	220	n.m.	−397	−124	−173	78	−62	419	312	13.79	
	250	n.m.	−377	−120	−166	70	−59	434	295	14.02	
	260	n.m.	br.	−107	−158	n.m.	n.m.	433	268	14.05	
11	230	203	−456	−357	−211	230	−28	300	358	15.15	
	300	n.m.	−297	n.m.	n.m.	n.m.	n.m.	305	245	15.43	
11[b]	185	157	−271	−266	−149	176	−45	273	270	14.73	
	200	177	−318	−298	−164	193	−46	278	287	14.82	
	230	207	−398	−353	−191	243	−28	291	347	15.05	
	250	301	−427	−353	−203	252	−29	301	358	15.17	
	270	309	−407	n.m.	n.m.	232	~0	309	339	15.29	
	300	209	−319	n.m.	n.m.	n.m.	n.m.	299	270	15.36	
13	230	131	−271	−257	−98	116	−337	184	243	15.12	

[a] For more isotope data see Scheme 1. [b] CD_2Cl_2. [c] Concentrated solution. [d] n.m. means not measured.

perature. For compounds **7** and **9b** a decrease with decreasing temperature was observed, whereas for **9t** in CD_2Cl_2 a change of the sign of the $^n\Delta$C-2 (XD) with variation of temperature is seen: from +170 ppb at 260 K through −50 ppb at 230 K to −459 ppb at 180 K. For $CDCl_3$ solutions lowering the temperature led to an increase in the negative value of $^n\Delta$C-2(XD) (Table 3). In compounds **10** and **11** in CD_2Cl_2 lowering of the temperature down to 230 and 250 K, respectively, caused an increase of the negative values of $^n\Delta$C-2 (XD). Further lowering of the temperature led to a decrease in these values. The isotope effects for other carbon atoms displayed small variations with temperature (Table 4).

Discussion

Deuterium isotope effects on ^{13}C chemical shifts $^n\Delta$C(OD) have proven to be a valuable tool in the study of resonance assisted intramolecular hydrogen bonding (RAHB).[5,6] The $^2\Delta$C(OD) values have been found to correlate with the δ(OH) values[5a,6] and the OH distance and the O · · · O distance.[11] For such types of hydrogen bonds linear correlations between $^2\Delta$C(OD) and $^4\Delta$C(OD) have been observed.[6d] The intrinsic isotope effect clearly is important as this always will contribute to the total isotope effect including equilibrium systems. For the hydrogen bond with double minimum proton potential (tautomeric situation) the replacement of proton by deuterium in the hydrogen bridge therefore produces both intrinsic and equilibrium effects. In these cases the $^2\Delta$C(OD) values are large, temperature dependent, and do not correlate with δ(OH) or with four-bond isotope effects.[6] Intramolecular hydrogen bonding in Schiff bases has been investigated by Hansen[5b] and Katrizky *et al.*[5a] by measurements of the deuterium isotope effect on ^{13}C chemical shifts and recently also by deuterium isotope effects on ^{15}N chemical shifts.[6i] For a series of substituted salicylideneanilines linear relations log $^2\Delta$C(D) *vs.* δ(OH) and $^2\Delta$C(D) *vs.* $^4\Delta$C(D) were found,[5a] taken as evidence that these compounds exist exclusively in the OH-form. We have adopted the isotope effect method to investigate the intramolecular hydrogen bond in Schiff bases of substituted salicylaldehydes with aliphatic amines (**1**–**13**).

Factors affecting the equilibrium

The resonance assisted intramolecular hydrogen bond (RAHB) OH · · · N is present in Schiff bases of substituted salicylaldehydes and aliphatic amines under study (**1**–**13**) (Fig. 1). In these Schiff bases the N atoms exhibit stronger proton acceptor properties in comparison to aniline, so the existence of a proton transfer equilibrium (Fig. 1) in the ground state is facilitated in comparison to the *N*-salicylidenes. The position of the proton transfer equilibrium OH · · · N ⇔ O^- · · · H^+N (see Fig. 1) is known to depend strongly upon the ΔpK_a value. (ΔpK_a =

Table 4 Selected data for chemical shifts (ppm) and coupling constants (Hz)

Compound	Temp./K	^3J(NH,H-α)	C-2	C-4	C-6	C-α	OH
9t[a]	230	9.95	176.07	165.51	133.53	157.66	14.64
	240	9.21	175.09	165.35	133.46	157.78	14.67
	250	8.49	174.27	165.23	133.38	157.83	14.71
	260	7.98	173.52	165.08	133.29	157.90	14.74
9t[b]	180	9.84	174.93	164.59	133.13	157.59	14.58
	200	8.36	173.23	164.37	133.04	157.81	14.74
	240	6.61	171.21	164.14	132.96	158.12	14.82
	250	5.35	170.08	164.15	132.94	158.33	14.82
	260	4.03	169.56	164.05	133.15	158.45	14.80
9t[b,c]	205	8.0	172.96	164.39	133.16	158.01	14.77
	220	6.95	171.76	164.22	133.08	158.15	14.82
	230	6.35	171.10	164.15	133.05	158.24	14.85
	240	5.60	170.42	164.08	133.07	158.34	14.85
	250	4.31	169.89	164.05	133.02	158.45	14.85
10[b]	170	12.26	178.92	166.54	159.73	157.56	13.48
	180	12.20	178.91	166.65	159.85	157.71	13.53
	200	11.76	178.67	—	—	—	13.66
	220	11.12	178.12	166.84	160.24	157.98	13.80
	230	10.68	—	—	—	—	13.88
	240	10.31	—	—	—	—	13.93
	250	9.83	176.75	166.76	160.48	158.93	13.97
	260	9.02	176.14	166.88	160.64	159.18	14.05

[a] In $CDCl_3$. [b] In CD_2Cl_2. [c] Diluted solution.

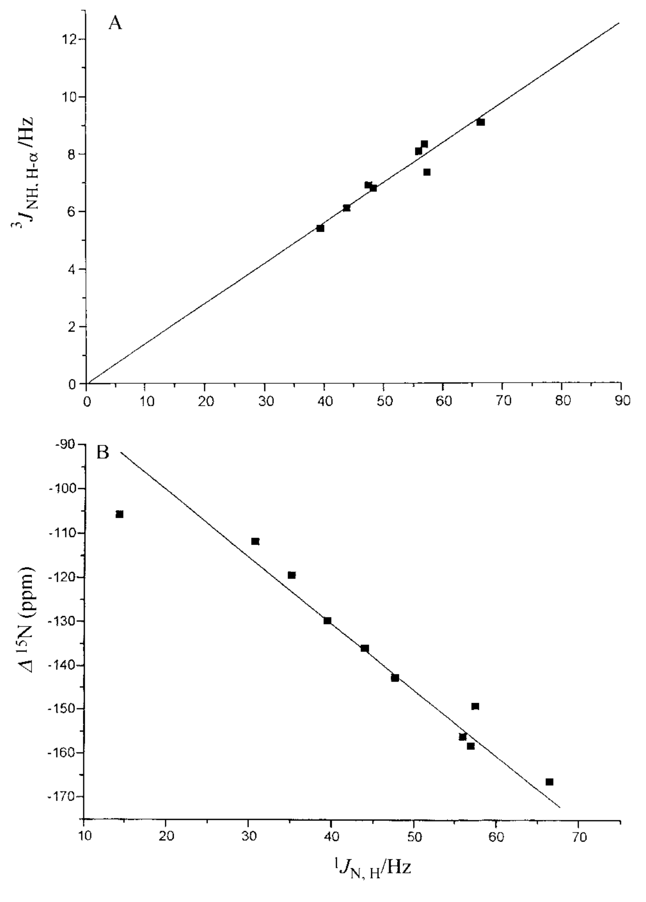


Fig. 3 A. ^3J(NH,H-α) *vs.* ^1J(N,H). Regression constants, slope = 0.13, constant = 0.27. Correlation coefficient, r = 0.962. B. ^{15}N chemical shifts *vs.* ^1J(N,H). Regression constants, slope = 1.29, constant = 79.5. Correlation coefficient, r = 0.971.

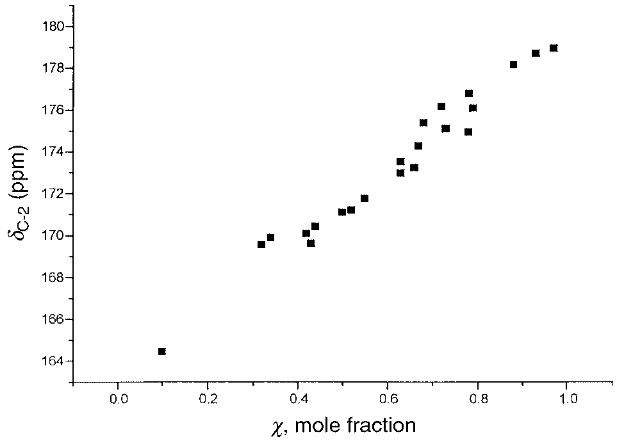


Fig. 4 Plot of C-2 chemical shifts *vs.* mole fraction. Regression constants, slope = 16.33, constant = 163.3. Correlation coefficient, r = 0.985.

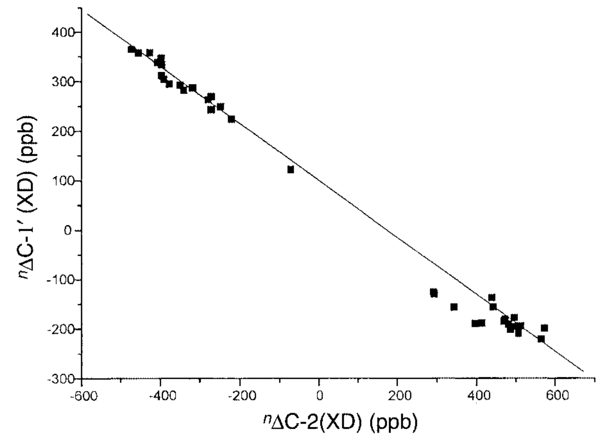


Fig. 5 Plot of ^{n}ΔC-2(XD) isotope effects *vs.* ^{n}ΔC-1′(XD). Regression constants, slope = 0.59, constant = 90.16. Correlation coefficient, r = 0.996.

pK_a(NH^+) − pK_a(OH), where pK_a(NH^+) and pK_a(OH) are for the respective amines and phenols). The substituents introduced into the aromatic ring of the Schiff bases under study (Fig. 1 and Scheme 1), through mesomeric and steric effects, cause a change in the acidity of the phenolic group, or alternately (4-OCH_3 and 4,6-di-OCH_3) in the basicity of the nitrogen atom. The ΔpK_a values change from −0.83 for **4b** up to +4.27 for **11**. In the case of **9** and **10** it is difficult to estimate the ΔpK_a values, as the basicity of the N atom is increased by the mesomeric effect of the methoxy groups. We have changed the hydrogen bond strength in these compounds by replacing methylamine (pK_a = 10.66) by benzylamine (pK_a = 9.38) or by the bulky *tert*-butylamine (pK_a = 10.79).

The obtained results, such as the large and temperature dependent $^n\Delta$C-2(XD) values, varying from ~+0.5 to ~−0.5 ppm (Table 4), as well as positive and negative values of $^n\Delta$C(XD) for C-1′ and other carbon atoms far from the centre of deuteriation[6] indicate the presence of the proton transfer equilibrium $OH\cdots N \Leftrightarrow O^-\cdots N^+H$ in the series of Schiff bases under study (Fig. 1). This is supported by the lack of linear dependence between $^n\Delta$C-2(XD) and δ(XH). For estimates of the position of equilibria, see later. The equilibrium may be perturbed by several factors. For some thermochromic Schiff bases aggregation has been shown to exist in rigid non-polar glasses at 70 K.[12] There is also some evidence[13] of association of *N*-salicylideneisopropylamine in the liquid state, also of an aggregation of the Schiff bases derived from diazafluorenone[14] in $CDCl_3$ solution, but at a concentration above 0.3 mol dm^{-3}. Self association of the proton transferred zwitterionic form of some Mannich bases in CD_2Cl_2 solution has been shown.[7b] However, none of these factors seem very important in the present case.

Two-species equilibria

For simple two-species tautomeric equilibria, the observed chemical shifts of the carbon atoms as well as the coupling constants are given by a weighted average of the respective values of both the OH- and NH-tautomers [eqn. (1)].

$$\delta^{13}C_{OBS} = (1 - \chi)\delta^{13}C_{OH} + \chi\delta^{13}C_{NH} \qquad (1)$$

A similar relationship can be written for ^{1}H and ^{15}N chemical shifts. For coupling constants, either ^1J(N,H) or ^3J(NH,H), the equations can be formulated generally as eqn. (2), where χ is the molar fraction of the NH-tautomer.

$$J_{OBS} = (1 - \chi)J_{OH} + \chi J_{NH} \qquad (2)$$

This obviously implies that chemical shifts and coupling constants have linear relationships. The above condition of proportionality between chemical shifts and coupling constants is fulfilled for the Schiff bases under study. The linear relationships between the $^1J(^{15}$N,H) and δ^{15}N (Fig. 3B) and between ^3J(NH,H) and δ^{13}C (Fig. 4) have been obtained for individual compounds. The slight spread of the points of Fig. 4 results from the influence of the substituent effect, as we have compared the data for different compounds and different solvents. The lack of the concentration dependence of δ(XH) at 300 K confirms the absence of strong intermolecular interactions. However, for all the Schiff bases with an intramolecular hydrogen bond studied in $CDCl_3$ the proton transfer process along the intramolecular hydrogen bond can be considered as a simple equilibrium between two species (see later).

A small dependence on the concentration has been observed in low temperature studies of **9t**. An increase of the concentration leads to a small increase in ^3J(NH,H) and in the ^{13}C chemical shift. As the value of ^3J(NH,H) is a measure of the mole fraction of the NH-form this result indicates that intermolecular interactions favour the NH form.

For a discussion of the effect of the substituents on the position of the proton transfer equilibrium in the Schiff bases under study it is important to determine the mole fraction (χ) of the NH form for individual compounds. This can in principle be done using ^{1}H, ^{13}C and ^{15}N chemical shifts or coupling constants as indicated in eqns. (1) and (2). In order to use these approaches the chemical shifts or the coupling constants of the two species, the OH and the NH form, must be known. This is not the case for the chemical shifts, although estimates of the ^{13}C chemical shifts of C-2 may possibly be extracted from data for 2-hydroxynaphthylidenetoluidine[4f]

^1J(N,H) has been found to vary only little for a series of amides and amines.[15] Kurkovskaya *et al.* found a value of 92.5 Hz for the NH-form[4d] and one of 1.55 Hz for the OH-form.[4c] From the present study a value of 91.3 Hz is obtained for ^1J(N,H). This is very close to that obtained by Dudek and Dudek for Schiff bases of primary amines.[4b]

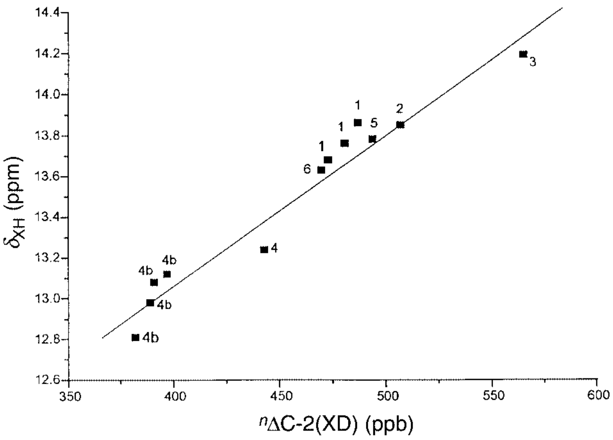


Fig. 6 Plot of XH chemical shifts *vs.* $^n\Delta$C-2(XD). Regression constants, slope = 0.007, constant = 10.12. Correlation coefficient, r = 0.977.

^3J(HN,H-α) is another useful parameter to determine the mole fraction of compounds primarily in the NH-form. Salman *et al.*, using a ^1J(N,H) of 96 Hz, estimated a ^3J(HN,H-α) of 11.6.[4f] Similarly to the $^1J(^{15}$N,H) values couplings through three bonds, ^3J(NH,H), change with the polarity of the NH group and hydrogen bond strength.[4a–d] From the study of **14** the ^3J(HN,H-α) coupling for the pure NH-form is close to 12.6 Hz. We adopt this value as a reference to estimate the mole fraction, χ, of the NH-tautomers from eqn. (3).

$$^3J(\text{NH,H-}\alpha) = 12.6 * \chi\,[\text{Hz}] \qquad (3)$$

As this coupling constant cannot be measured for values below 4 Hz, we have used $^1J(^{15}$N,H) as a measure of the mole fraction for compounds primarily in the OH-form, assuming a value of 91.3 Hz for the NH-form as described earlier.

Populations

The populations of the NH tautomer in the Schiff bases under study have been found to increase from about 0 up to 1.0. Compound **4b** is fully in the OH form ($\Delta pK_a = -0.83$). Compounds **1** to **6**, with ΔpK_a ranging from +0.43 to +1.3, exist mainly as OH tautomers in $CDCl_3$ solution. The small temperature dependence of the chemical shifts and isotope effect (Tables 1, 2 and 4) and the linear relationships between the $^n\Delta$C-2(XD) and δ(HX) (r = 0.98) (Fig. 6) as well as that between $^n\Delta$C-2(XD) and $^n\Delta$C-α(XD) (r = 0.98) are very characteristic of localised or nearly localised hydrogen bonds.[5a,6]

The results obtained for compounds **7** ($\Delta pK_a = 2.87$), **8** ($\Delta pK_a = 2.77$) and **9b** (see previously) (Tables 1–4) indicate the existence of a tautomeric equilibrium, with the OH tautomer prevailing. The χ values estimated from ^3J(NH,H) are ~0.15 for **9b** and ~0.3 (at 230 K) and ~0.4 (at 220 K) for **7**. Compounds with the highest ΔpK_a values, **11** (4.26), **12** (3.37), **13** (3.44), **10** and **10t**, form a group of compounds existing mainly as NH-tautomers in $CDCl_3$ and CD_2Cl_2 solutions; χ equals about 0.8 at 250 K and increases up to 1.0 with decreasing temperature. Compound **9t** occupies the middle position with χ changing from ~0.3 up to ~0.8, depending on solvent and temperature (Table 4). The increase in the mole fraction on going from CD_2Cl_2 to $CDCl_3$ indicates that, in accord with other results,[4a,b] the interactions with the solvent stabilise the NH (proton transferred) form. Lowering of the temperature shifts the equilibrium in the same direction. Summing up, by increasing the ΔpK_a values in the series of *N*-salicylidenealkylamines, lowering the temperature and increasing the polarity of the

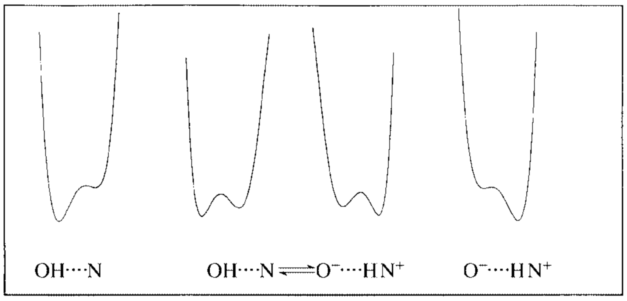


Fig. 7 Changes of the potential energy surface with the position of the tautomeric equilibrium.

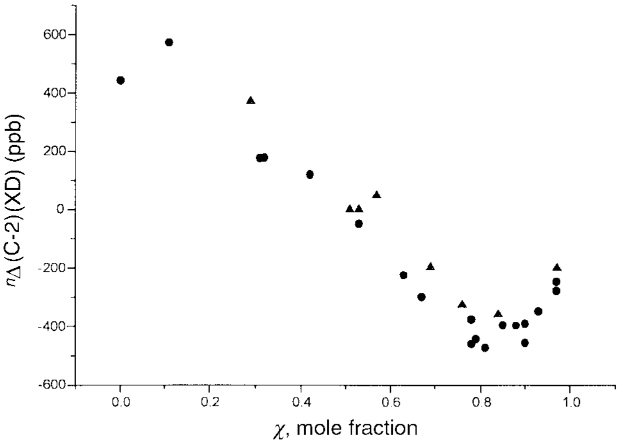


Fig. 8 Plot of $^{n}\Delta$C-2(XD) *vs.* mole fraction. ● Data from present work. ▲ Data from ref. 4*q*.

solvent shift the position of the proton, from i) a situation where the proton is located much closer to the oxygen atom, to ii) an equilibrium situation with proton transfer, OH···N ⇔ O^{-}···$^{+}$HN, and finally to iii) localisation of the proton at the nitrogen atom; the corresponding changes of potential energy surface are presented in Fig. 7. For those compounds for which ^{3}J(HN,H-α) or ^{1}J(N,H) have been measured in order to obtain the mole fraction, a proportionality between chemical shifts of ^{13}C or ^{15}N and mole fraction has been observed showing that for the Schiff bases with intramolecular hydrogen bonds taking part in an equilibrium, the equilibrium can be described as a simple two-state one as shown in Fig. 1.

Deuterium isotope effects

The unusual dependence of $^{n}\Delta$C-2 (XD) on mole fraction is presented in Fig. 8. For monitoring the position of the equilibrium we have used ^{3}J(NH,H) values, as these values are proportional to χ. A similar shape is also obtained for C-1′ (not shown) as $^{n}\Delta$C-2 (XD) is proportional to $^{n}\Delta$C-1′(XD) (Fig. 5). Also isotope effects at C-4 show similar trends. There is a striking resemblance to the dependence determined by Hansen *et al.*[6e] for β-diketones, in particular the local maximum at $\chi <$ ~0.1–0.2 and the local minimum at $\chi =$ ~0.8. The large variation of $^{n}\Delta$C-2(XD) as a function of the mole fraction χ, being similar to that found for diketones,[6e] may be explained in a similar way by a change of the equilibrium isotope effect with the position of the tautomeric equilibrium.[6b] The observed deuterium isotope effect on the ^{13}C chemical shift may be divided into two contributions as described earlier: an intrinsic ($^{n}\Delta\text{C(XD)}_{\text{INT}}$) and an equilibrium part ($^{n}\Delta\text{C(XD)}_{\text{EQ}}$). For C-2 we can present it as eqn. (4), in which $\Delta\chi$ is the change in the mole fraction upon deuteriation.

$$^{n}\Delta\text{C-2(XD)}_{\text{OBS}} = (1-\chi)^{n}\Delta\text{C-2(XD)}_{\text{INT}} + \chi^{n}\Delta\text{C-}\alpha\text{(XD)}_{\text{INT}} + \Delta\chi(\text{C-2}_{\text{OH}} - \delta\text{C-2}_{\text{NH}}) \quad (4)$$

The intrinsic effects depend on the hydrogen bond energy and the transmission of the effect along the transmission pathway, while the equilibrium part depends on the difference in chemical shifts of the two tautomers and the change in the equilibrium constant K upon deuteriation ($K_{\text{D}} = K_{\text{H}}^{(1+\alpha)}$). Hansen *et al.*,[6e] following Bordner's[6h] suggestion, found that the relationship of $^{n}\Delta$C(XD) *vs.* mole fraction phenomenologically could be described this way.

Low barrier systems

Isotope effects of low barrier systems, *o*-Mannich bases[7a,b] and the organic acid–pyridine system[8] show a pattern similar to what is observed for the Schiff bases. It has been suggested that the barrier to interconversion in the organic acid–pyridine system is so low that the zero point vibration for the H-species is above the barrier, whereas that of the D-species is below and this possibly could be the cause of the unusual behaviour.[8] However, a good resemblance to systems like Schiff bases in which this is not the case, is described below.

Comparison of systems

The finding that for Schiff bases both coupling constants, ^{1}J(N,H) and ^{3}J(HN,H-α), and ^{1}H, ^{13}C and ^{15}N chemical shifts are proportional and behave in the same manner supports a two-species tautomeric equilibrium (Figs. 3A,B and 4). A linear change in ^{1}J(N,H) with ^{15}N chemical shift was also found in organic acid–pyridine complexes.[8] The ^{15}N chemical shift was taken as a parameter for N–H bond stretching,[8] but in the present paper it is considered proportional to the mole fraction. A linear behaviour of the one-bond coupling constant has by many authors been considered to prove the presence of a two-species equilibrium,[15,16,17a,b] as shown in eqn. (2). Organic acid–pyridine complexes and Schiff bases are clearly different in that the latter have a much more rigid hydrogen bond skeleton. The former may clearly change the O···N distance depending on the strength of the hydrogen bond, which is much less possible in the Schiff bases as is also evidenced by the difference in the behaviour of the XH resonance. For organic acid–pyridine complexes a large variation in the XH chemical shift as a function of the ^{15}N chemical shift is observed and a maximum is seen for $\chi = 0.5$, whereas for the Schiff bases the variation in the chemical shift of the XH proton is very modest (Fig. 2). The very slight variation of δXH *e.g.* for **4b** with $^{n}\Delta$C-2(XH) indicates that the hydrogen bond strength of the OH···N bond varies only little. Similarly for the NH···O bond (Fig. 2), so relatively little variation in O–H, N–H or OH···N or NH···O bond lengths is expected. To sum up, in the Schiff bases both chemical shifts and coupling constants are shown to be proportional proving the presence of a system that to a first approximation can be described by a simple two-species tautomeric equilibrium as described in Fig. 1. The Schiff base system gives an S-shaped dependence of all deuterium isotope effects on ^{13}C chemical shifts (except for C-4 and C-α, which are constant because they are dominated by the intrinsic effects) on the mole fraction, a finding similar to those for low barrier systems like β-diketones,[6e] but also for very low barrier systems like organic acid–pyridine complexes[8] and possibly also for Mannich bases, which show a temperature behaviour similar to the Schiff bases. Other systems showing similar trends are the intramolecularly hydrogen bonded *ortho*-hydroxyazocompounds,[6g] β-thioxoketones[6g] and piroxicam.[6h] In other words this is behaviour common to a broad series of compounds involving hydrogen bonding and proton transfer equilibria.

Conclusions

The existence of the proton transfer equilibrium OH···N ⇔ O^{-}···H^{+}N in a series of Schiff bases derived from salicylic aldehydes and aliphatic amines has been evidenced by measurement of the deuterium isotope effect on ^{13}C NMR spectra. The population of the NH-tautomer has been estimated by ^3J(NH,H) coupling constants. The equilibrium is shifted gradually to the right by increase of the ΔpK_a values, by introducing substituents into the aromatic ring and having aliphatic groups at the N-atom. Similarly, lowering of the temperature and increasing the proton-donor properties of the solvent have been found to favour the NH-tautomer.

An S-shaped relationship between $^n\Delta$C-2(XD) and ^3J(NH,H-α), and thereby the mole fraction of the NH-tautomer, χ, is observed. A similar trend is seen for $^n\Delta$C-1′-(XD). The variation of the $^n\Delta$C-2(XD) value with χ for the Schiff bases under study is quite similar to that found for β-diketones,[6e] and may likewise be explained by the changes in the equilibrium isotope effect with the position of equilibrium. A similar dependence of deuterium isotope effect seems to be a common behaviour for a broad series of compounds involving proton transfer along the hydrogen bond. The study has confirmed that deuterium isotope effects on chemical shifts are a powerful tool in establishing the presence and also the position of an equilibrium especially as several different kinds of isotope effects can support the conclusions.

Acknowledgements

The authors wish to thank Anne Lise Gudmundsson for recording some of the spectra and I. Bogdanska for a gift of some of the aldehydes. Z. R. wishes to thank the Foundation for Polish Science for financial support.

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