Tetrahedron, Vol. 37, pp. 1607 to 1611, 1981
Printed in Great Britain

0040-4020/81/081607-05$02.00/0
Pergamon Press Ltd.

THE pH DEPENDENCE OF PHENOLPHTHALEIN

A ^{13}C NMR STUDY

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(*Received in Germany* 2 *September* 1980)

Abstract—The pH dependence of the ^{13}C NMR spectra of phenolphthalein has been measured and interpreted. The spectrum of the neutral compound **1** is compared with the spectra of the dianion **4**, the trianion **5** and the carbocation **7**. At the first time spectroscopic evidence for the carbinol **6** is given.

Despite the widespread use of phenolphthalein, both as a titration indicator and as a laxative agent, the spectroscopic investigation of this important compound seems to have ceased more than 20 years ago. After the discovery of phenolphthalein by Baeyer,[1] intensive discussion as to the structure and the acid-base equilibria of this dyestuff continued until in the early 1940s[2] the now common textbook knowledge[3] was settled. These investigations were mainly based on chemical arguments, such as the results of derivatisation, and the physical method extensively used was, of course, UV spectroscopy. The only ^{1}H NMR study of value appeared more than 10 years ago,[4] demonstrating unambiguously for the first time the parallel existence of two forms in solution.

Phenolphthalein is believed to exist in the following equilibria:[3] The neutral form **1** is deprotonated to **2**, which opens to **3** being further deprotonated to **4** giving cause for the intensive dark red colour above pH 9. In strong alkaline solutions the colour facts and a hydroxylated trianion **5** is formed. It was assumed already by Green and Perkin[5] that titrating a solution of **5** with acetic acid at low temperature yields the carbinol **6**. Furthermore it was observed by Baeyer[6] that phenolphthalein can be dissolved in conc H_2SO_4 giving rise to an intensive red colour, which after standing turns to orange. Since ^{13}C NMR spectroscopy would possibly be the best method to follow the pH dependent changes of this compound in somewhat more detail we have undertaken a ^{13}C NMR investigation covering the entire pH scale.

RESULTS AND DISCUSSION

1. The ^{13}C *spectrum of the neutral compound*. The ^{13}C spectrum of the neutral compound **1** in DMSO-d$_6$ (Table 1) gives rise to twelve signals, six of which are from quarternary C atoms. The signals are assigned with the help of the proton coupled ^{13}C spectrum. At lowest field the lactonoid C atom C-1 resonates at 170.2 ppm, its signal is split into a broadened doublet by H-7. At 158.6 ppm the two equivalent C atoms 4′ and 4″ resonate and can be identified by their typical chemical shift, their double intensity and their splitting by the ortho and meta protons. The signal at 153.6 ppm is assigned to C-4a based on chemical shift increments[7] and by comparison

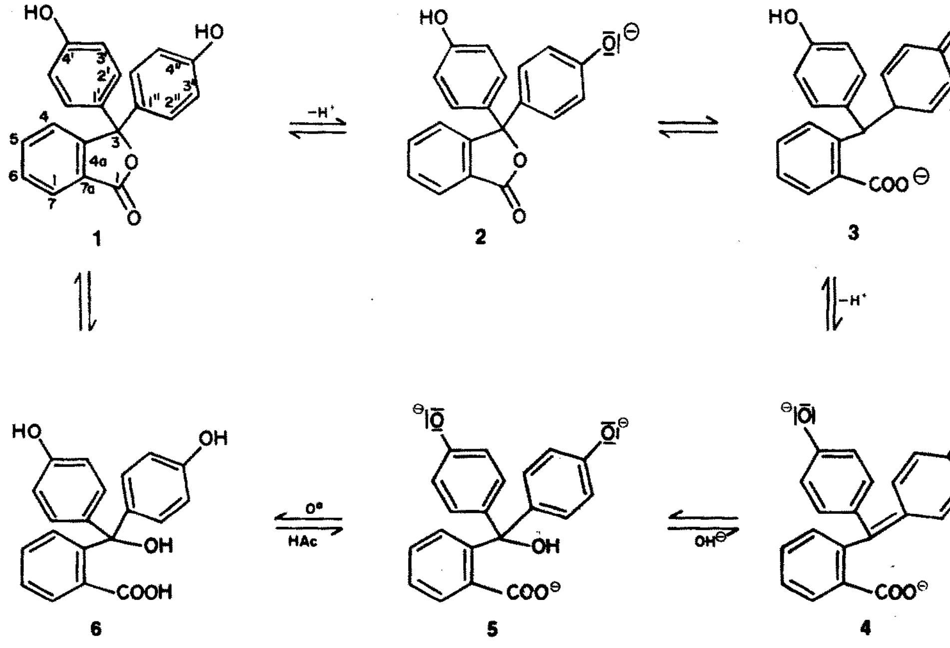


Table 1. ^{13}C chemical shifts of the different forms of phenolphthalein[a]

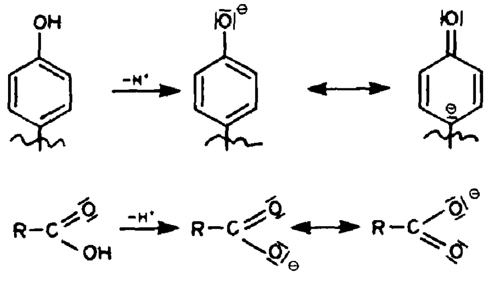
C Atom	**1** a)	**4** a)	**5** b)	**6** c)	**7** d)
1	170.2	172.6	179.2	178.6	176.3
3	92.5	100.7	83.2	82.7	194.1
4	125.5 g)	125.7	128.3	e)	134.1 f)
5	135.8	135.4	131.2	e)	136.0 f)
6	130.5	130.1	130.5	e)	137.3 f)
7	126.4	126.3	129.7	e)	136.0 f)
4a	153.6	154.6	147.3	146.9	141.4
7a	125.5 g)	126.5	140.2	140.5	130.8
1'/1''	132.3	124.8	134.0	139.6	134.1
2'/2''	129.2	129.8	130.5	129.6	145.5
3'/3''	116.3	119.6	118.5	115.3	120.4
4'/4''	158.6	169.9	166.0	156.0	170.9

a) measured in DMSO-d_6 containing as internal standard dioxane, values given in ppm vs TMS with $\delta_{TMS} - \delta_{dioxane} = 67.4$ ppm, values of **4** measured in the same solution but with 2 equivalents NaOH/H_2O added. b) measured in 10n NaOH, reference to a capillary containing D_2O as lock solvent and three drops of dioxane as standard. c) measured in CD_3OD at 0° with excess acetic acid present, referenced to the solvent CD_3 peak, values given in ppm vs TMS with $\delta_{TMS} - \delta_{CD_3OD} = 49$ ppm. d) measured in H_2SO_4, lock and reference as b). e) for sensitivity reasons not observed. f) lines broadened, relative assignment tentative. g) in CD_3OD solution the signals are separated.

with the spectrum of isobenzofuranone.[8] The signal of C-4a is split into a broadened triplet due to the protons at C-5 and C-7. From the remaining three quarternary C atoms the signal of C-1′ and C-1″ shows double intensity and resonates at 132.3 ppm, typical for a *para* substituted phenol,[9] whereas the chemical shift increment for a substitution by a carboxyl group is in accordance with the assignment for C-7a at 125.5 ppm. Finally the spiro atom C-3 resonates at 92.5 ppm. From the remaining six signals for the C atoms bearing an H atom, the assignment of the phenolic C atoms C-3′, C-5′ and C-3″, C-5″ as well as C-2′, C-6′ and C-2″ and C-6″ at 116.3 and 129.2 ppm is straight forward on account of their fourfold intensity and comparison with the values of substituted phenols.[9] The signals of the C atoms C-4, 5, 6 and 7 are first divided into two groups according to the pattern analysis by Günther.[10] The signals at 135.8 and 130.5 ppm show sharp doublets of doublets of doublets in the CH coupled spectrum, whereas the signals at 126.4 and 125.5 ppm show broadened doublets of doublets. Therefore the first group belong to C-5 and C-6 and the signal at 135.6 ppm is assigned to C-5 in accordance with the values found for isobenzofuranone.[8] A distinction between the two closely resonating signals at 126.3 and 125.4 ppm can be achieved by selective decoupling of the proton at C-7, it being the lowest field resonating proton of the ABCD spin system of phenolphthalein.[11]

2. *Titration with* NaOH. A DMSO solution of phenolphthalein was titrated with small amounts of NaOH in H_2O. As the diagram in Fig. 1 shows there are three groups of signals distinguishable by their response to the pH change: C-4′/C-4″, C-1′/C-1″ and C-3 change their chemical shifts by about 7–11 ppm, C-1, C-7a, C-4a and C-3′/C-3″ change their chemical shifts by about 1–3 ppm and finally C-4, C-5, C-6, C-7 and C-2′/C-2″ remain more or less at their chemical shift position at pH 7. The behaviour of C-4′/4″ and C-1′/1″ (strong deshielding for C-4′ and shielding for C-1′) could be explained by Scheme 1 indicating higher electron density in the phenolate anion for C-1′/1″ and contribution of a CO like structure for C-4′/4″. However, the deshielding of C-4′/4″ can be seen in connection with the deshielding of the CO group of carboxylic acids on deprotonation.[12]

As in carboxylic acids the ring opening and anionization of the lactonoid ring C atom in phenolphthalein causes a deshielding. This is predicted by INDO calculations in spite of the fact, that the C atoms in question have higher electron density.[13] In phenol the electron density of the oxygen bearing C atom does not change significantly be deprotonation, although the chemical shift is altered by 12 ppm as in phenolphthalein. Whether electric field effects can be used to explain this behaviour sufficiently is still under debate.[14] Since the spiro C atom C-3 becomes olefinic by this structural change its deshielding is expected and similar to the central C atom in triphenyl carbanions.[15] The titration diagram does not reveal two distinct deprotonation steps and it was shown



Scheme 1.

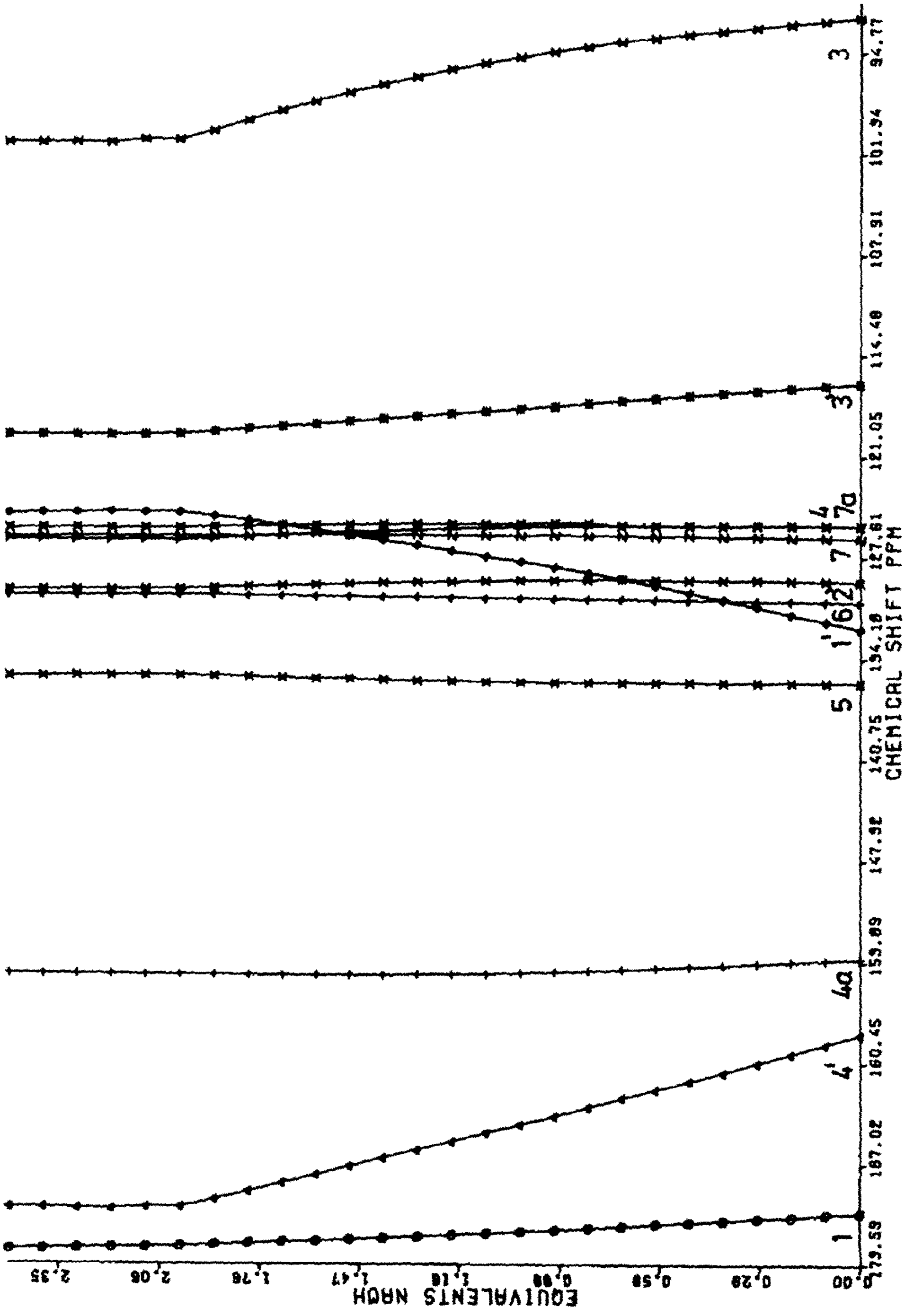

3
3'
4
7a
7
2'
6'
1'
5
4a
4'
1
94.77
101.34
107.91
114.48
121.05
127.61
134.18
140.75
147.32
153.89
160.45
167.02
173.59
CHEMICAL SHIFT PPM
EQUIVALENTS NAOH
0.00
0.29
0.58
0.88
1.18
1.47
1.76
2.06
2.35

Fig. 1.

earlier,[16] that the pk$_a$ values of the forms 1 and 3 must be very close.

As shown in Fig. 1 the C atoms of phenolphthalein do not change their chemical shift position after two equivalents of base have been added. However, the signals start to disappear after this point and another set of twelve ^{13}C signals appears. When three equivalents of base are added, the ratio of the form 4 and 5 is about 1:9. If the solution at this point is made more acidic, the conversion of 5 into 4 is completely reversible.

3. *The ^{13}C spectrum in strong alkaline medium.* If one dissolves phenolphthalein in 5 m NaOH solution one obtains the same set of twelve signals which forms during the titration after more than two equivalents of base have been added. The assignment of these twelve signals (Table 1) follows the same arguments and experiments as described for the neutral compound. There are several typical chemical shift changes compared with the neutral compound 1 and the dianion 4 which strongly support the trianion structure 5 for these solutions.

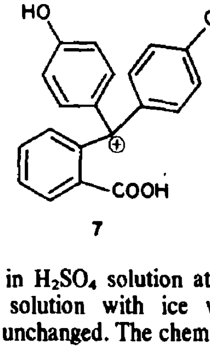
The hydroxylation at C-3 is clearly revealed by the shielding of this C atom to 83.2 ppm, the chemical shift region of tertiary alcohols. Whereas C-1' resonates nearly at the chemical shift position it maintains in the neutral compound, C-4' resonates at lower field than in the neutral compound but at higher field than in the dianion 4 indicating that no quinoid resonance structure is present. Due to the hydroxylation at C-3 the carboxyl group is less likely to be coplanar with the aromatic ring. This is seen by a typical downfield shift of 7 ppm for C-1, an effect already described by Leibfritz[17] and the large downfield effect for C-7a (14 ppm). For the same reason, loss of resonance with the carboxyl group, C-5 is shielded by 4 ppm. The effect for C-4a is large (7 ppm upfield) as is expected since C-4a now bears a diphenylcarbinol group.[7] The ipso C atom in aromatic carboxylic acids is deshielded by 10 ppm on deprotonation.[14] This deshielding can now be seen for C-7a, although one would have already expected it in 4. Presumably due to charge delocalisation in 4 this effect was restrained.

The chemical shifts of this trianion 5 once formed, do not change by varying the pH of the solution. On back titration of the solution with HCl the signals stay at their resonance position and start to disappear accompanied by the appearance of the twelve signals for 4, showing the complete reversibility of these reactions.

4. *The ^{13}C spectrum of the carbinol* 6. Following the observation of Green and Perkin[5] that on slow back titration of 5 with icecold acetic acid the dark red colour of 4 is not observed, we tried to measure the endproduct of this titration, presumably the carbinol 6 which has not so far been characterized. For this purpose a CD$_3$OD solution of phenolphthalein was first made alkaline and then quenched at 0° with icecold acetic acid; the carbon[13] spectrum was taken immediately afterwards at 0°.

The spectrum obtained should, to some extent, be a composite of the spectra of the forms 1 with respect to the phenolic part of the molecule, and of 5 with respect to the benzo-carboxylic part of the molecule. This is indeed the case, as an inspection of Table 1 shows. Whereas for example C-1, C-3, C-4a and C-7a resonate close to their resonance position in 5, the phenolic C atoms 4'/4" resonate close to their resonance position in 1. Due to the instability of the compound under these conditions (half-life time about 2 hr) we were not able to get clear signals for C-4, 5, 6 and 7. On warming the solution the signals due to 6 disappear and the signals of 1 are formed. This is to our knowledge the first time that concrete evidence for the existence of 6 is given.

5. *Phenolphthalein in concentrated* H$_2$SO$_4$. Following the observation of Baeyer[6] that phenolphthalein can be dissolved in H$_2$SO$_4$ with a bright red colour, we have taken the ^{13}C spectrum of phenolphthalein in H$_2$So$_4$ solution, at 10° to prevent sulfonation of the carbocation formed, since it is known that on standing the bright red solution turns into yellow-orange. Again a set of twelve signals is obtained which are assigned with the same arguments and methods as for the neutral compound. Due to the viscosity of the solution the resonances of C-4, C-5, C-6 and C-7 are very broad and a detailed assignment is prevented, the assignment given in the table for these C atoms is therefore only tentative. As Table 1 shows, the signal of C-3 has disappeared from its usual shift region and instead a new signal at 194.1 ppm is formed. This is the typical chemical shift for the central C atom of a similar substituted triphenylcarbonium ion.[18] Therefore we ascribe structure 7 for phenolphthalein in H$_2$SO$_4$ solution at low temperature. Quenching the solution with ice water precipitates phenolphthalein unchanged. The chemical shifts for C-1', C-2', C-3' and C-4' are also very close to those of *p*-methoxytriphenylcarbonium ion.[18] On warming the solution the signals of the cation 7 start to disappear and again different sets of new signals appear. However, as expected, the resulting mixtures are complex and further work is needed to assign structures for the different compounds which can be seen in the spectra.



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CONCLUSIONS

It has been shown in this work that the assumed picture of the different forms of phenolphthalein in alkaline solutions is in agreement with the results of ^{13}C spectroscopy. The characterization of the carbinol 6 and the cation 7 demonstrate nicely the applicability of ^{13}C NMR spectroscopy for investigating pH dependent structural changes.[19]

EXPERIMENTAL

For the diagram of Fig. 1 typically solns of 300 mg phenolphthalein (9.43×10^{-4} m) in 2 ml DMSO-d$_6$ were measured and subsequently treated with 50 μl portions of a 3.775×10^{-3} m NaOH/H$_2$O soln from a syringe. A drop of dioxane served as internal standard. The spectra in 10 n NaOH/H$_2$O as well as the spectra in H$_2$SO$_4$ were taken with a 5 mm capillary containing D$_2$O and three drops of dioxane as lock and external standard. To obtain spectra of 6 2 ml solns of phenolphthalein in CD$_3$OD containing LiOH were prepared. By ^{13}C measurement it was assured that the trianion 5 was formed. Thereafter the solns were cooled to 0° and treated with cold AcOH. The measurements were performed directly after neutralisation at 0°.

The NMR measurements were performed both on a VARIAN XL-100-15 with a disc accessory and on a VARIAN CFT-20. For the proton coupled spectra 32 k FT NMR spectra were obtained.

Chemical shifts are reported relative to TMS with $\delta_{TMS} - \delta_{dioxane} = 67.4$ ppm. No correction for external standardisation was made.

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