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Prototropic processes in benzaurins. ^{19}F and ^{1}H NMR spectra of fluoro- and methylsubstituted 4-hydroxyphenyl-diphenylcarbinols, related fuchsones and benzaurins

Research Article

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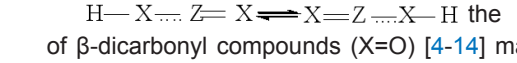
Abstract: Tautomerism of benzaurins and hydration are studied. ^{1}H and ^{19}F chemical shifts have been determined for a number of substituted 4-hydroxyphenyl-diphenyl carbinols containing fluorine in a 3-, 3*- or 4*-position, and for similar compounds containing additional methyl groups in a position of 3, 3** or 4**. The same data have been obtained for the fuchsones prepared by dehydration of the above carbinols. On this basis chemical shifts of fluorine in different positions have been evaluated as a monitor of the transformation of 4-hydroxyphenyl group to the semiquinone moiety. The ^{19}F NMR can be used to monitor the transformation of 4**-fluorobenzaurin and the related 3,3*-disubstituted and 3,3*,5,5*-tetramethylsubstituted compounds to the corresponding carbinols due to the addition of a water molecule and to study the tautomerism of the two latter benzaurins as well as that of 3,3*,4**trifluorobenzaurin. Furthermore, fluorine and methyl group chemical shifts are sensitive to *syn-anti*-isomerism in substituted fuchsones.

The prototropic process of these compounds may be slow or fast on a ^{1}H NMR time scale depending on the solvent and may be catalyzed by water or carbonic acids. On the basis of kinetic and thermodynamic data obtained by dynamic NMR studies, a mechanism for the process has been proposed.

Keywords: *^{19}F NMR • Prototropic tautomerism • Syn-anti isomerism • Fluoro- and methyl substituted benzaurins • Fuchsones*

1. Introduction

Prototropic tautomerism as illustrated below has attracted much attention for intermolecular [1-3], but especially for intramolecular cases [4-14]. In the latter category



the enol forms of β-dicarbonyl compounds (X=O) [4-14] may serve as a model for the intermolecular case studied herein. The prototropic transitions in these systems proceed at high rates because the oxygen atoms are sterically drawn together, and the geometry of the six-membered chelate ring is optimal for the formation of the intramolecular hydrogen bond. It should be noted that in the literature the possible structure of these compounds is discussed as a fast migration of the proton between the two oxygen atoms in the potential with two wells, [4-10] or the mesomeric structure arising due to the presence of only one well [11,12]. Examples of prototropic transfer for other systems with the oxygen atoms as cation accepting centres are nitrone-hydroxylamine tautomerism in the methyl ester of N-hydroxyindolecarbonic acid [13] and the tautomerism of 3-hydroxyflavone [14].

Investigations of the prototropic tautomerism in systems involving remote cation accepting oxygen atoms (intermolecular exchange) are more rare. Tautomerism of nitrone-hydroxylamine type in 4-hydroxypyrimidine oxide [15] and nitroso-oxime tautomerism in 4-nitrosophenol and related substituted compounds were based on NMR evidence. A quantitative investigation of the proton transfer rate in these non-degenerated tautomeric systems was not conducted [16,17].

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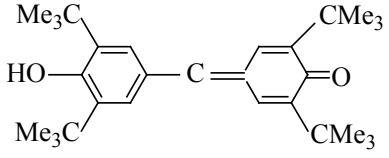
Deceased: The paper is dedicated to the memory of Professors D.N. Kravtsov, L.S. Golovchenko and E.V. Borisov

The so called degenerate systems (Z is the symmetric framework of the tautomeric system) are most suitable for the investigation of the influence of different outer and inner structural factors on the mechanism of tautomeric transformations. Degenerate systems can be studied by NMR. The use of isotopic perturbation of equilibrium is well demonstrated for intramolecularly hydrogen bonded systems [18-20]. NMR has in general the advantage of having a number of reporter atoms which makes it useful in the study of degenerate systems. Furthermore, NMR studies allow a broad range of solvents to be used, and the effects of water addition can easily be monitored as well.

In literature there are two examples of such degenerated tautomeric systems, the structures of which are discussed on the basis of NMR data. The first example is hydrogalvinoxyl:



In aqueous acetone-d_6 or in aqueous DMSO-d_6 dynamic changes in the ^{1}H and ^{13}C NMR spectra with changes in the concentration of all three components of the mixture – hydrogalvinoxyl, solvent and water were observed [21]. The authors have interpreted these results due to cluster formation (for a more detailed discussion see below) [21]. Another example is ethyl ester of 3*,3**,5*,5**-tetrabromophenolphtalein [22].

Benzaurins represent prototropic systems with remote cation-accepting centers. This type of benzaurin tautomerism can be studied by the NMR technique provided that reference data are available. In order to facilitate the detection of tautomerism reporter groups are introduced into benzaurins at the 3,3* and 4** positions (Fig. 1).

The substituents in positions 3 and 3* are necessary to monitor the prototropic process in the framework of a simple two-site exchange, whereas the indicator in the position 4** will help to detect a possible transformation of substituted benzaurins to substituted bis-(4-hydroxyphenyl)-phenylcarbinols as a result of addition of a H_2O molecule [24]. Substitutents in these positions have only a small steric effect.

Fluorine atoms or the methyl group are used as indicators [25,26], whereas the CF_3-group seems less suitable due to the lower synthetic accessibility of the corresponding model compounds.

In the present investigation 4-hydroxyphenyl-diphenylcarbinols and corresponding substituted fuchsones (4-diphenylmethylene-2,5-cyclohexadien-1-ones) (Scheme 1) containing fluorine or methyl group tags in appropriate positions are used as model compounds .

2. Experimental Procedure

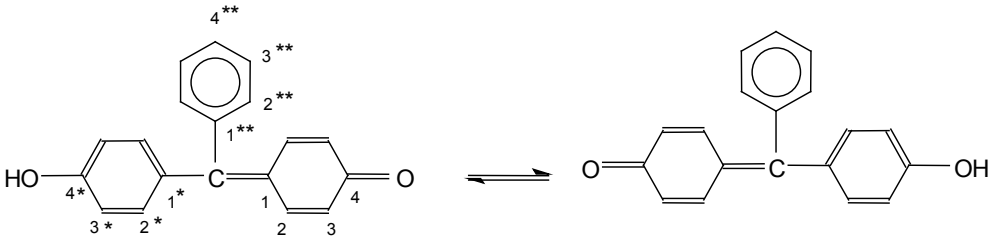
2.1 Compounds

The hydroxyphenyl carbinols **1, 3, 5, 7, 9, 11, 13** were obtained by the reactions of substituted 4-hydroxybenzophenones with the corresponding arylmagnesium bromides. Fuchsones **2, 4, 6, 8, 10, 12, 14** were obtained by the dehydration of the corresponding substituted 4-hydroxyphenyl-diphenylcarbinols. 3,3*,5,5*-tetramethyl-4**-fluorobenzaurin (**15**), 3,3*-dimethyl-4**-fluorobenzaurin (**16**) and 4**-fluorobenzaurin (**18**) have been prepared by condensation 4-fluorobenzotrichloride with 2,6-dimethylphenol, 2-methylphenol and phenol, respectively. 3,3*,4**-trifluorobenzaurin (**17**) was obtained by the reaction of 4-fluorophenylmagnesium bromide with 3,3*-difluoro-4,4*-dihydroxybenzophenone.

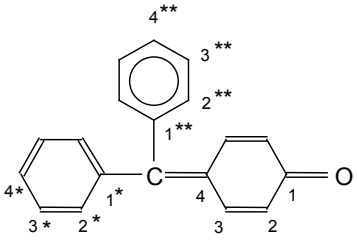
The typical methods of synthesis of the obtained compounds are presented below.

Diphenyl-(3-fluoro-4-hydroxyphenyl)-carbinol (1): To the solution of Grignard reagent prepared from 10.16 g (0.065 M) of PhBr and 1.56 g (0.066 GA) of Mg in 50 mL of absolute THF and stirred in the argon current the solution of 3.5 g (0.016 M) of 3-fluoro-4-hydroxybenzophenone in 15 mL of the same solvent was added. The same solvent was added absolute THF and stirred in the argon current the solution of 3.5 g (0.016 M) of 3-fluoro-4-hydroxybenzophenone in 15 mL of After having been boiled and stirred for 5 hours, the reaction mixture was cooled to room temperature and decomposed with a 5% aqueous solution of NH_4Cl . The organic layer was separated, washed with water and dried over Na_2SO_4. The yellow viscous substance which remained after the distillation of the solvent was dissolved in a 5% aqueous NaOH solution, filtered and precipitated with a 5% aqueous solution of NH_4Cl. This procedure was repeated twice. The precipitate was washed with water and dried over Na_2SO_4. 1.77 g (37%) of (**1**) was obtained as a yellow solid. M.p. 126-128^{0}C. $C_{19}H_{15}FO_2$ (MW 294): calcd. C 77.55, H 5.10, F 6.46; found C 76.75, H 5.36, F 5.92.

(3-Fluorophenyl)-(4-hydroxyphenyl)-phenylcarbinol (3) was obtained from PhMgBr and 3*-fluoro-4-hydroxybenzophenone using a similar method with a 96% yield as a dark yellow solid. M.p. 125 - 127 ^{0}C. $C_{19}H_{15}FO_2$ (MW 294): calcd. C 77.55, H 5.10, F 6.46; found C 77.45, H 5.38, F 5.39.

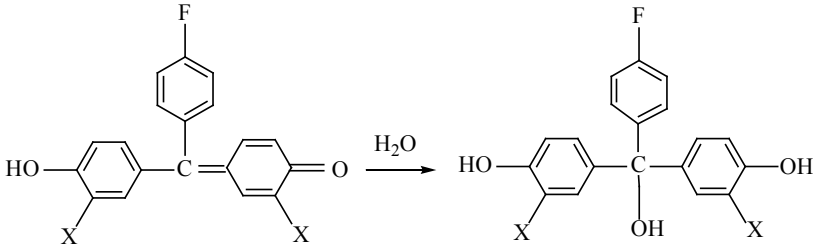


benzaurin



fuchsone

Figure 1. Tautomeric scheme and numbering of compounds



X=CH_3 **16**; X=F **17** and X=H **18**

Figure 2. Water addition

(4-Fluorophenyl)-(4-hydroxyphenyl)-phenylcarbinol (5) was obtained from PhMgBr and 4*-fluoro-4-hydroxybenzophenone using a similar method with a 72% yield as an orange solid. M.p.110 - 112^{0}C. $C_{19}H_{15}FO_2$ (MW 294): calcd. C 77.55, H 5.10, F 6.46; found C 77.57, H 5.51, F 6.24.

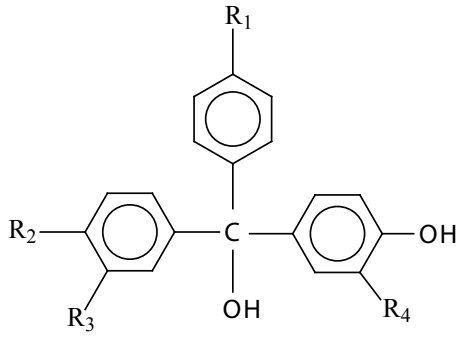
(4-fluorophenyl)-(3-fluoro-4-hydroxyphenyl)-phenylcarbinol (7) was obtained from PhMgBr and 3,4*-difluoro-4-hydroxybenzophenone using a similar method with a 21% yield as an orange solid. M.p. 113 - 119^{0}C. $C_{19}H_{14}F_2O_2$ (MW 312): calcd. C 73.08, H 4.49, F 12.18; found C 72.20, H 4.45, F 10.21.

(4-Fluorophenyl)-(4-hydroxy-3-methylphenyl)-phenylcarbinol (9) was obtained from PhMgBr and 4*-fluoro-3-methyl-4-hydroxybenzophenone using a similar method with a 97% yield as an yellow solid. M.p. 68 – 78^{0}C. $C_{20}H_{17}FO_2$ (MW 308): calcd. C 77.92, H 5.52, F 6.17; found C 77.45, H 5.38, F 5.39. ^{1}H NMR (C_6D_6): 2.17, 3H.

(4-Fluorophenyl)-(4-hydroxyphenyl)-(3-methylphenyl)-carbinol (11) was obtained from 3-$CH_3C_6H_4$MgBr and 4*-fluoro-4-hydroxybenzophenone using a similar method with a 84% yield as a pale yellow solid. M.p. 130 –132 ^{0}C. $C_{20}H_{17}FO_2$ (MW 308): calcd. C 77.92, H 5.52, F 6.17; found C 77.75, H 5.61, F 5.59. ^{1}H NMR (C_6D_6): 2.12, 3H;

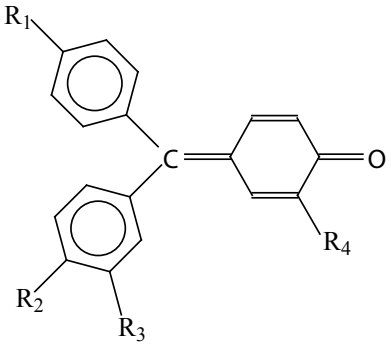
(4-Fluorophenyl)-(4-hydroxyphenyl)-(4-methylphenyl)-carbinol (13) was obtained from

Hydroxyphenyl carbinols



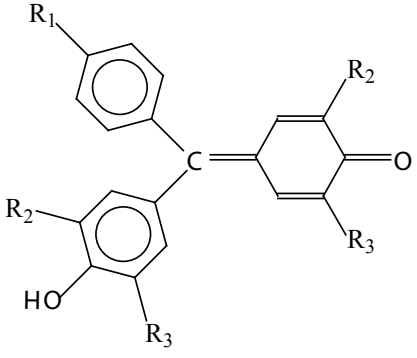
1 and **2** R_1=R_2=R_3=H; R_4=F
3 and **4** R_1=R_2=R_4=H; R_3=F
5 and **6** R_1=R_3=R_4=H; R_2=F
7 and **8** R_1=R_4=F; R_2=R_3=H

Fuchsones



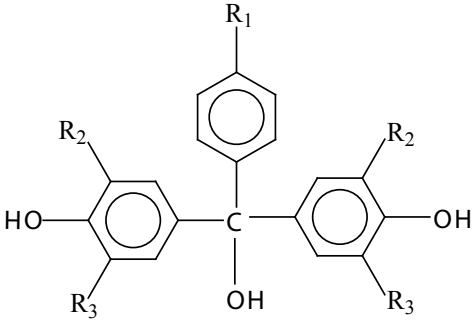
9 and **10** R_1=F; R_2=R_3=H; R_4=CH_3
11 and **12** R_1=F; R_2=R_4=H; R_3=CH_3
13 and **14** R_1=F; R_3=R_4=H; R_2=CH_3

Benzaurins



15 R_1=F; R_2=R_3=CH_3
16 R_1=F; R_2=H; R_3=CH_3
17 R_1= R_3=F; R_2=H
18 R_1=F; R_2=R_3=H

Di(hydroxyphenyl) carbinols



19 R_1=F; R_2=R_3=CH_3
20 R_1=F; R_2=H; R_3=CH_3
21 R_1= R_3=F; R_2=H
22 R_1=F; R_2=R_3=H

Scheme 1. Investigated compounds. Even numbers are fuchsones.

4-$CH_3C_6H_4MgBr$ and 4*-fluoro-4-hydroxybenzophenone using a similar method with a yield of 65 % as a yellow solid. M.p. 101^{0}C. $C_{20}H_{17}FO_2$ (MW 308): calcd C 77.92, H 5.52, F 6.17; found C 77.90, H 5.96, F 4.89. ^{1}H NMR (C_6D_6): 2.14, 3H;

2,4*-Difluorofuchsone (8): 0.4 g (0.0013 M) of (4-fluorophenyl)-(3-fluoro-4-hydroxyphenyl)-phenyl-carbinol (**7**) was dissolved in 15 mL of acetic acid and heated until the boiling of the solvent. After removing acetic acid on the rotating evaporater, the remaining oil was triturated with a small quantity of ether. 0.21 g (56%) of the compound (**8**) was obtained as red crystals. M.p. 162 – 164^{0}C. $C_{19}H_{12}F_2O$ (MW 294): calcd.: C 77.55, H 4.08, F 12.92; found C 77.41, H 4.24, F 12.05.

4*-Methyl-4-fluorofuchsone (14)** was obtained by boiling a toluene solution of (4-fluorophenyl)-(4-hydroxyphenyl)-(4-methylphenyl)-carbinol (**13**) for 20 hours. After recrystallization from m-xylene **14** was obtained as orange-red crystals. M.p.78-80^{0}C. $C_{20}H_{15}FO$ (MW 290): calcd. C 82.76, H 5.17; found: C 82.16, H 5.93. ^{1}H NMR (C_6D_6): 2.11, 3H.

2-Methyl-4*-fluorofuchsone (10) was obtained by heating in the argon current a small quantity of carbinol (**9**) without a solvent for 4 hours at 110^{0}C . The red product that formed had m.p. 60 – 62^0. $C_{20}H_{15}FO$ (MW 290): calcd. C 82.76, H 5.17; found C 81.30, H 5.23. ^{1}H NMR (C_6D_6): 2.05, 3H; 2.09, 3H.

The heating of carbinols **1**,**3**,**5** and **11** for several hours under an argon atmosphere led according to NMR to the formation of the corresponding fucsones **2**,**4**,**6** and **12**. The reaction mixture contains considerable quantities of starting carbinols. The element analysis of these products corresponds to the mixtures of fuchsone – carbinol or fuchsone – water.

3,3*,5,5*-Tetramethyl-4-fluorobenzaurin (15):** 7.32 g (0.06 M) of 2,6-dimethylphenol were placed in a three-necked flask, fitted with a stirrer, reflux condenser and dropping funnel. The flask was heated to 85^{0}C, and 2.14 g (0.01 M) of 4-fluorobenzotrichloride were dropped into the flask. The reaction mixture was stirred at 80^{0}C for 7 hours and then decomposed with an aqueous solution of sodium acetate. The by-products were separated by water steam distillation. The remaining brown substance was filtered, washed several times with hot water and dried to constant weight. The product was recrystallized from chlorobenzene and dried in the pistol. 2.68 g (76.8%) of **15** was obtained as a red solid. M.p. 220-222^{0}C. $C_{23}H_{21}FO_2$ (MW 348): calcd. C 79.31, H 6.03, F 5,46; found C 79.41, H 5.88, F 4.98. ^{1}H NMR: ($CDCl_3$) 2.02, 3H; 2.04, 3H and 2.28, 6H. (dioxane-d_8) 2.06, 3H, 2.07, 3H and 2.34, 6H. (DMF-d_7) 2.17, 12H. (dioxane-d_8+D_2O, 2.05, 12H. (dioxane-d_8+HCOOH) 2.28, 9H. (dioxane-d_8+CF_3COOH) 2.29, 12H.

3,3*-Dimethyl-4-fluorobenzaurin (16)** was obtained from 2-methylphenol and 4-fluorobenzotrichloride using a similar method with the yield of 69% as a red solid. After recrystallization from p-dichlorobenzene m.p. 268 – 270^{0}C. $C_{21}H_{17}FO_2$ (MW 320): calcd. C 78.75, H 5.31, F 5.93; found C 78.72, H 5.19, F 5.31. ^{1}H NMR: (dioxane-d8) 2.06, 3H; 2.31, 3H.

2.2 NMR spectroscopy

^{1}H NMR spectra were recorded at room temperature at 400.1 MHz on a Bruker AMX-400 or at 300 MHz on a Bruker Avance™ 300, respectively. ^{19}F NMR spectra were recorded at 188.3 MHz on a Bruker WP-200 SY spectrometer. For ^{19}F NMR, the fluorine chemical shifts values were measured relative to the external fluorobenzene dissolved in the same solvent as the compounds. The stabilization of resonance conditions regarding ^{19}F NMR was performed using an external D_2O lock.

2.3 Analysis of spectra

The mean lifetimes were determined by correlating the experimental PMR spectra to the theoretical curves. The theoretical spectra were calculated by employing the Bloch equations which were modified with regard to the dynamic processes [27] of the 3-site exchange with 2:1:1 populations of the three states (in dioxane-d_8, Tables 2 and 3) or a 2-site exchange with 1:1 populations (DMF-d_7, Table 4). The linewidth $\nu^0_{1/2}$ of 3 Hz for dioxane-d_8 was used. In regard to DMF-d_7, the linewidth $\nu^0_{1/2}$ of the solvent signal at near 8 ppm wass used, which varied from 3-4 Hz at a moderate temperature to 9 Hz at -50^{0}C. The experimental error in the case τ values did not exceed ±4% in their concentration and temperature dependence.

In general, for the exchange reaction:

$$n\mathrm{A} + m\mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} p\mathrm{C} + q\mathrm{D}$$

the mean life time τ_A of the exchange species in state A between two successive exchanges can be expressed by the following relation [28]:

$$1/\tau_A = 1/[\mathrm{A}]\, d[\mathrm{A}]/dt = k_{obs}[\mathrm{A}]^{n-1}[\mathrm{B}]^m$$

where *n* and *m* are the orders of the exchange reaction in A and B respectively. A similar expression can be written for τ_B. Moreover, in our case k_{obs} is equal to $k_1/2$ [29]. Hence, knowing the τ_A and τ_B for some values of [A] and [B], one can calculate *n* and *m*. In this work the τ_A and τ_B values were obtained in varying [B] or [A] and keeping, respectively, [A] or [B] constant (Table 2). For a two-site exchange as demonstrated in Fig. 8, a similar result was obtained using Spinworks 3.1.7 [30].

3. Results and Discussions

3.1 Substituted 4-hydroxyphenyl-diphenylcarbinols and fuchsones.

The fluorine chemical shift (δ ^{19}F) values of compounds in the benzene solution have been determined relative to external fluorobenzene in the same solvent (Table 1).

For the hydroxyphenyl carbinols the fluorine atom in an *ortho* position to the hydroxy group resonates in the range of –26.88 to –25.00 ppm as seen from the data of compounds **1** and **7**. Fluorines in 4*or 4** positions fall in a different chemical shift range from -2.87 to -3.41 ppm (compounds **5**, **7** and **9**). For the fluorofuchsones **6**, **8**, **10, 12** and **14**a fluorine in *para* position fall in a range from 1.97 to 3.71 ppm. For the fluorines next to

Table 1. ^{19}F [a] chemical shifts of fuchsones, benzaurins and their corresponding carbinols.

	δ^{19}F, ppm	Solvent		δ^{19}F, ppm	Solvent
	Hydroxyphenyl carbinols			**Fuchsones**	
1	-26.88	C_6H_6	**2**	-13.25	C_6H_6
3	0.10	C_6H_6	**4**	0.59	C_6H_6
5	-3.05	C_6H_6	**6**	3.02	C_6H_6
7	-25.00(3-F) -3.41(4*-F)	C_6H_6	**8**	-14.29;-14.41(2-F) 2.86; 2.87(4*-F)	C_6H_6
9	-2.87	C_6H_6	**10**	1.97; 2.12	C_6H_6
11	-2.88	C_6H_6	**12**	3.35	C_6H_6
13	-3.01	C_6H_6	**14**	3.71	C_6H_6
	Benzaurins			**Di(hydroxyphenyl) carbinols**	
15	2.20 1.55 1.03 2.88 1.90	$CHCl_3$ THF Dioxane DMF Pyridine	**19**	no data available	
16	1.83;1.85 1.50;1.55 2.40 2.41	THF Dioxane DMF Pyridine	**20**	-4.57 -4.37 -4.16	THF Dioxane Pyridine
17	-19.29(3,3*-F) 3.20(4**-F) -18.97(3,3*-F) 3.66(4**-F)	THF Pyridine 	**21**	-24.86(3,3*-F) -3.41(4**-F) -23.09(3,3*-F) -3.27(4*-F)	THF Pyridine
18	2.35 2.40 3.00 2.87	THF Dioxane DMF Pyridine	**22**	-4.39 -4.13 -3.97 -4.10	THF Dioxane DMF Pyridine

a) For ^{1}H chemical shifts see experimental part

the C=O group the fluorine resonates in a range from -13.25 to -14.41 ppm (compounds **2** and **8**). This type of fluorine is therefore an excellent reporter group to monitor the change from a C=O to a C-OH functional group, as is in a tautomeric equilibrium (Fig. 4) or by addition of water as seen in Fig. 2.

The data in the experimental section indicates that the sensitivity of δ^{1}H values of the methyl group regarding the transformation of the carbinol to the corresponding fuchsone is rather low. The changes in δ^{1}H vary from -0.12 ppm for the methyl group in position 2 (for numbering see Fig. 1) to 0.03 ppm for the methyl group in position 3**, and the decrease in absolute values depends on the position in the sequence: 2 > 4** > 3**. In two cases the changes in the shieldings are unexpected. Thus, the shielding of the methyl group in 4*-fluoro-2-methylfuchsone **10** and 4*-fluoro-4**-methylfuchsone **14** are decreased with respect to that of the methyl group in the corresponding carbinol; however, in going from carbinol to fuchsone the neighboring electron-donating hydroxyl group is transformed to the electron-accepting carbonyl group. This may be connected to the dominating contribution from the anisotropy effects.

3.1.1 Syn/anti

For 2,4*-difluorofuchsone **8** and 4*-fluoro-2-methylfuchsone **10** two fluorine signals for the fluorine in the 4-fluorophenyl group are observed. For the former compound, two signals also appear for the fluorine which is adjacent to the carbonyl group. This is consistent with the existence as a mixture of *syn*- and *anti*-isomers, in which the 4-fluorophenyl group can be oriented in the direction of fluorine or in the direction of the methyl group in position 2 or in the direction of the hydrogen atom in position 6 (Fig. 3). This observation shows clearly that

the interconversion of the two isomers is slow on the NMR time-scale.

The δ ^{1}H values of the methyl group in position 2 of fuchsone is likewise sensitive to the *syn-anti* isomerism, as may be seen from the data of **10**. The δ^{1}H values of methyl groups in the position 3* of 2,3*-dimethylfuchsone and position 4* of 2,4*-dimethylfuchsone will be also sensitive to the *syn-anti* isomerism. The methyl resonances are therefore useful in detecting the extent of dimerisation and *syn-anti* isomerism.

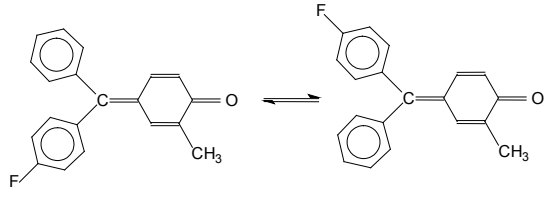
Further the δ ^{1}H values have been studied for the methyl groups in substituted 4-hydroxyphenyl-diphenylcarbinols **9**, **11** and **13** as well as for the corresponding fuchsones **10**, **12** and **14** containing methyl groups in positions 2, 3** or 4** and fluorine in position 4*. The results show that the use of only a methyl indicator group for the study of benzaurin tautomerism may be insufficient. The more suitable approach is to use jointly, fluorine and methyl group tags as reporters.

3.2 Substituted benzaurins.

The tautomeric process of 3,3*,5,5*-tetramehyl-4*-fluorobenzaurin (**15**), of 3,3*-dimethyl-4**-fluorobenzaurin (**16**) and of 3,3*,4**-trifluorobenzaurin (**17**) as shown in Fig. 4 were the focus of this work.

In this connection **15 - 17** and for comparison, the 4**-fluorobenzaurin **18** have been studied (Fig. 4). In addition to a prototropic process as described in Fig. 4 water addition may also occur as shown in Fig. 2.

The δ^{19}F values in different solvents for **15** – **18** and the corresponding carbinols**, 20 - 22,** which are formed due to the addition of water molecule to **16**-**18**, are presented in Table 1. This Table shows that for **15** - **18** the fluorine resonances are observed in the range from 3.66 to 1.03 ppm. According to the results that were obtained for fuchsones, they may safely be assigned to the benzaurin form. The slight shift to lower frequency (higher field) may be connected with the electron-donating effect of the hydroxyl group and methyl substituents. It should be noted that in the case of 3,3*-dimethyl-4**-fluorobenzaurin **16** the signal of fluorine appears as two closely lying resonances at 1.83 and 1.85 ppm (Table 1) in THF and at 1.50 and 1.55 ppm in dioxane. According to the data obtained for fuchsones, this means that for the above compound the mutual transformation of *syn*- and *anti*-forms is slow in these solvents on the ^{19}F NMR time scale (see Fig. 3 for an example).



syn-isomer *anti*-isomer

Figure 3. Syn- and anti-isomers as illustrated by **10**.

3.2.1 Water addition

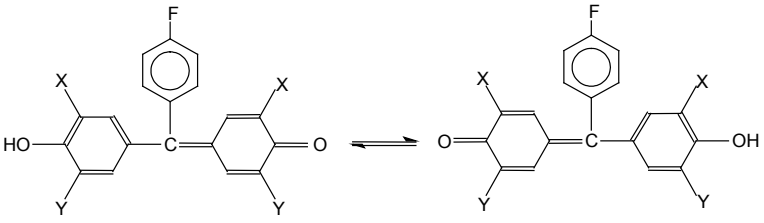
In addition to the two closely lying resonances described above, a signal in the range from –3.27 to -4.57 ppm appears in the spectra of **17** and **18** and the 3,3*-dimethylsubstituted analogue **16** in solvents such as dioxane, DMF, pyridine and THF. This position is in the range close to that observed for the substituted diphenyl-(4-hydroxyphenyl)-carbinols **7**, **9**, **11** and **13** containing a 4-fluorophenyl group. It can be expected that the electron-donating effect of the additional HO-group in 4*-position will increase the electron density on the carbon atom in 4**-position and in the fluorine shielding (see above). Thus, the above signals ranging from –3.27 to -4.57 ppm may be assigned to the carbinol form of the corresponding benzaurin which was formed as a result of the addition of a water molecule. Therefore, ^{19}F NMR spectroscopy allows the monitoring of the transformation of benzaurins and the corresponding carbinols. As water addition readily occurs it may be difficult to record the spectra of pure benzaurins.

3.2.2 Tautomerism

Of special interest is 2,4*,4**-trifluorobenzaurin (**17**). The ^{19}F NMR spectrum in THF consists of two resonances in an estimated ratio of 2:1 at -19.29 and 3.20 ppm in addition to resonances belonging to the carbinol (-3.41 and –24.86 ppm) and some very minor impurities. The chemical shift of –19.29 ppm for the fluorine next to the C=O/COH groups clearly shows that a prototropic process is at play.

The absence of the carbinol resonance in the spectra of solutions of 3,3*,5,5*-tetramethyl-4**-fluorobenzaurin **15** may be explained by the electron-donating effect of two additional methyl groups which increases the electron density at the central carbon atom, whereby hindering the attack of the hydroxyl anion. For **15** dissolved in THF, dixoane or pyridine even addition of water to the point of precipitation did not lead to the appearance of a ^{19}F signal corresponding to the carbinol. The same result has been obtained for **16** in DMF.

The ^{1}H NMR spectra of methyl-substituted benzaurins have been studied in connection with the possibility of prototropic tautomerism in benzaurins. The corresponding data are presented in the experimental section. The ^{1}H NMR spectrum of 3,3*,5,5*-tetramethyl-4**-fluorobenzaurin **15** in $CDCl_3$ contains three signals



X=Y=CH_3 **15;** X= H; Y= CH_3 **16;** X=H, Y=F **17;** X=Y=H **18**

Figure 4. Tautomers of **15 - 18**

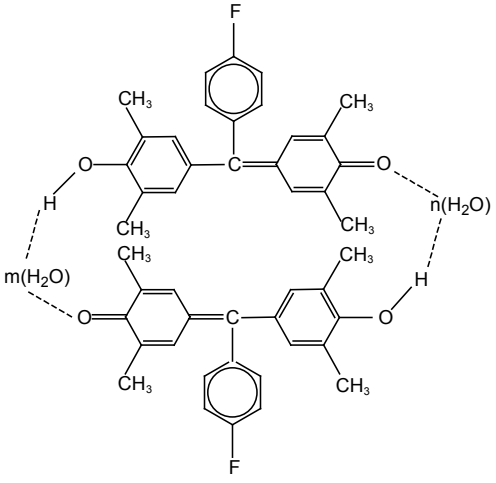


Figure 5. Water catalysis model involving two molecules of **15**.

in the CH_3 region, a doublet like feature at 2.02 and 2.04 ppm and a singlet like feature at 2.28 ppm, the intensities of these signals being at a ratio of 1:1:2. On the basis of the general considerations and the data on the chemical shifts of methyl protons in 4-fluorophenyl-(4-hydroxy-3-methylphenyl)-phenylcarbinol **9** and 4*-fluoro-2-methylfuchsone **10,** it may be concluded that the doublet belongs to the methyl groups in the vicinity of the carbonyl group, whereas the singlet arises from the methyl groups in the *ortho*-position to the HO-group. A similar picture is observed in dioxane-d_8. These data indicate that the prototropic process (Fig. 4) in benzaurin **15** is slow on the ^{1}H NMR time scale in chloroform and dioxane.

However, only one broadened signal is observed in the ^{1}H NMR spectrum of **15** in DMF-d_7. This indicates that in this case the prototropic process on the ^{1}H NMR time scale occurs at a moderate rate. In addition it has been determined that water and carbonic acids catalyze the prototropic process in 3,3*,5,5*-tetramethyl-4**-fluorobenzaurin (**15**) in dioxane-d_8. Thus, the addition of water resulting in a concentration of 14 mol L^{-1} in dioxane-d_8 leads to the appearance of only one peak for the methyl groups in the ^{1}H NMR spectrum of this compound. The same is observed when formic or trifluoroacetic acids are added, resulting in a concentration of 4 mol L^{-1} of the above benzaurin in dioxane-d_8. A similar picture is found for **16**.

It may be tentatively proposed that the prototropic process is accelerated due to the formation of cyclic reactive complexes containing two molecules of benzaurin and one or more molecules of water (Fig. 5) or other HO-acid. In these complexes, the molecules of water or HO-acid can act as bridges for the transfer of two hydrogen atoms from oxygen atoms of two HO-groups to those of two carbonyl groups. The inspection of molecular models show that in the case of benzaurin or 4**-fluorobenzaurin, the *syn* and *anti* forms of 3,3*,4**-trifuorobenzaurin and the *anti* form of 3,3*-dimethyl-4**-fluorobenzaurin two molecules may be joined without steric hindrance arising in the hydrogen-bonded complex involving hydroxyl and carbonyl groups. In contrast, 3,3*,5,5*-tetramethyl-4**-fluorobenzaurin **15** steric hindrance does not allow the formation of a complex without water or carbonic acid participation.

A similar effect of water on the ^{1}H and ^{13}C NMR spectra of a hydrogalvinoxyl in acetone-d_6 has been described [21]. The coalescence of ^{1}H or ^{13}C signals of *t*-Bu groups as well as corresponding nuclei of aromatic and methine moieties has been observed. The authors [21] interpreted their results using the formation of a three-components system **(**Fig. 6**)** in which the broadening of signals takes place due to the increase in correlation time caused by the transition of anisotropic state to a liquid-crystal state and does not discuss the possible tautomeric process similar to those shown in Fig. 4. We carried out some kinetic experiments in dioxane-d_8 as well as in DMF-d_7 to make the distinction between the model as shown in Fig. 6 or in Fig. 5 or even a more complicated one involving chains of solvent molecules.

In dry dioxane-d_8 the ^{1}H NMR spectrum of **15** at room temperature reveals one signal at 2.339 ppm (6H) and two nearby signals at 2.071 (3H) and 2.059 (3H) ppm (Me-protons), singlet at 6.971 ppm (2H - aromatic protons), two signals at 7.172 (1H) and 7.303 (1H) ppm from quinone protons, the last one is overlapped by the multiplet (4H) from the p-FC_6H_4 group. In addition,

a singlet due to the OH-proton is are observed at 7.585 ppm. All signals are rather sharp. This spectrum corresponds to the slow prototropic process. The spectral pattern does not depend on concentration of **15** in the range from 0.03 M to 0.12 M and on temperature (up to 80°C). Some changes in chemical shifts have been observed.

The addition of surplus water, up to 4 moles with respect to **15,** does not change the spectrum very much with one exception as the signal of the OH-proton disappears. The addition of 10 moles of H_2O gives rise to the broadening of methyl signals as well as of those of CH-aromatic and quinone protons. The addition of the 13-15 moles of H_2O leads to the coalescence of the Me and of the CH signals. The spectra are reproduced for different samples with the same ratio of water to compound **15**. The above data show that the prototropic process is catalyzed by water.

The analysis of the kinetic data (Table 2) performed in the framework of dynamic NMR method (three-site exchange) [23] (see Experimental Procedure) reveals that in dioxane-d_8 the reaction is second order in **15** and 6.5 in H_2O. These data suggest that the transition state includes two molecules of **15** and 6-7 bridging molecules of water (m+n=6-7) (Fig. 5).

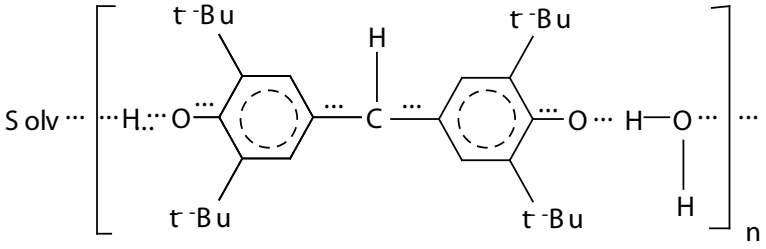


Figure 6. Hydroxygalvinoxyl and suggested three component system from [4]

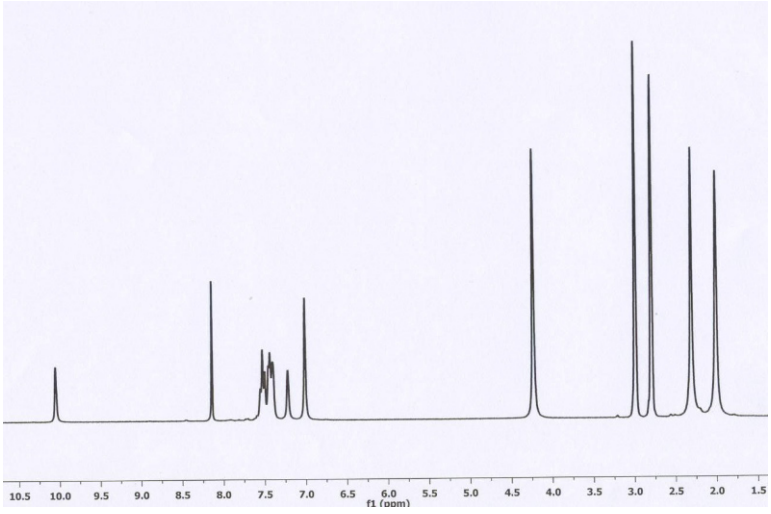


Figure 7. ^1H spectrum of **15** at -50°C.

Table 2. The concentration dependence of mean life time τ for system 15 + H_2O in dioxane-d_8 at 20°C

Concentration of 15, M	Concentration of H_2O, M	τ×10³ , sec
0.05	0.5	17.2
0.05	0.05	1.94
0.1	1.0	8.7

Table 3. The temperature dependence of mean life time τ for system 15 + 10 M H_2O in dioxane-d_8

T, K	τ×10³ , sec	T, K	τ×10³ , sec
293	17.2	335	5.8
310	11.0	345	5.1
320	8.0	350	4.8
325	7.3	355	4.5
330	6.3	360 [a]	4.2

[a] *near collapse*

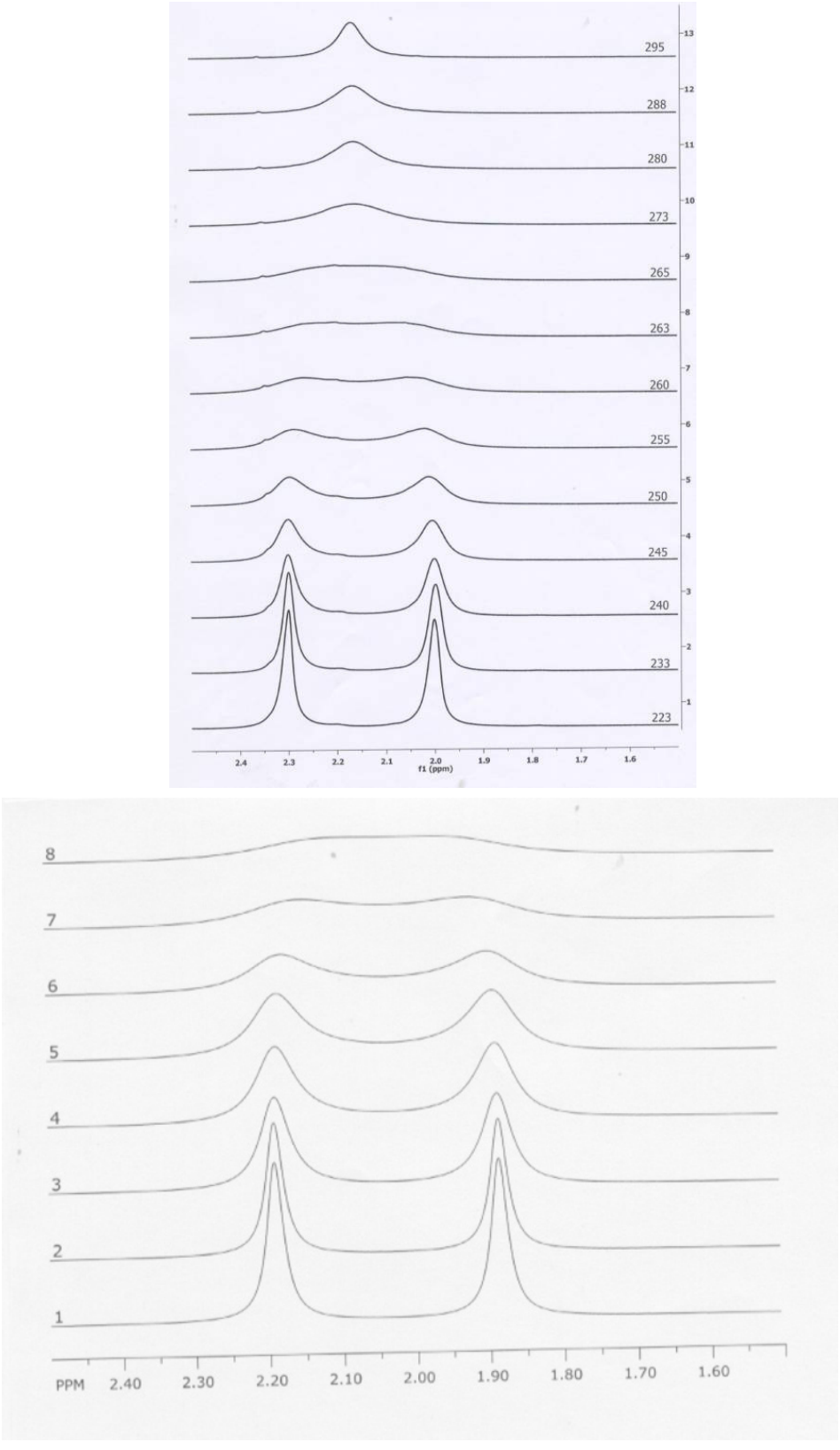


Figure 8. ^{1}H spectrum of **15** with 2.5 moles of water added; (a) experimental traces, (b) simulated traces for temperatures from 223 K to 263 K.

Table 4. The temperature dependence of mean life time τ for the solution of 15 in DMFA-d_7 with 2.5 moles of water added.

T, K	τ×10³ , sec	T, K	τ×10³ , sec
240	25.0	263	5.8
245	19	273	2.6
250	13.5	280	1.8
255	9.4	288	1.6
260	6.9	295	1.0

For the analysis of the temperature dependence the system involving 0.05 M **15** and 0.5 M H_2O in dioxane-d_8 was selected because for this system the full dynamic picture from three Me signals at room temperature to one broad signal at 90^0 was observed (Table 3).

The following thermodynamic parameters of the process have been obtained.

E_a=4.4±0.2 kcal mol^{-1}, $\Delta H^{\neq}$ = 3.8±0.2 kcal mol^{-1},
$\Delta S^{\neq}$ = -38e.u., $\Delta G^{\neq}_{293}$ = 15.0±0.2 kcal mol^{-1}.

The large negative entropy of activation suggests that the transition state has a greater steric hindrance in comparison with the initial starting state. This is consistent with the proposed mechanism.

The ^{1}H NMR spectrum of the solution of **15** in DMF-d_7 at room temperature reveals one broad signal of Me-groups at 2.15 and one broad signal of CH-protons at 7.20 ppm. On lowering the temperature to -50^0 the methyl signals split into two relatively broad signals at 2.001(6H) and 2.302(6H) ppm. The CH-signals split into three relatively broad signals at 6.97(2H), 7.18(1H) and 7.38 ppm(1H) (Fig. 7).

^{1}H NMR spectra of **15** in DMF-d_7 and 2.5 moles of water per mole benzaurin at different temperatures are shown in Fig. 8a. A comparison of experimental and simulated spectra is shown in Fig. 8b. The following thermodynamic parameters have been obtained for 11 temperatures from the analysis of the temperature dependence of rate constants (Table 4):

E_a=8.45±0.24 kcal mol^{-1}, R= -0.996
$\Delta H^{\neq}$=7.85±0.2 kcal mol^{-1}, $\Delta S^{\neq}$=-18 e.u.,
$\Delta G^{\neq}_{293}$ =13.6±0.2 kcal mol^{-1} .

Addition of 18 moles of water based on 9 temperatures:

E_a=6.98±0.14 kcal mol^{-1}, R= -0.998:
$\Delta H^{\neq}$=6.44±0.15 kcal mol^{-1}, $\Delta S^{\neq}$=-21 e.u.,
$\Delta G^{\neq}_{293}$ =12.6±0.2 kcal mol^{-1}.

At room temperature the width of the averaged Me signal does not depend on the concentration of **15** in the range from 0.03 to 0.15 M. The above data suggest that in DMF-d_7 the mechanism is monomolecular in **15,** but from the present study it cannot be excluded that one or two molecules of water are involved in the process or that it may involve close connected ionic pairs or ionic pairs disconnected by the solvent.

4. Conclusions

The benzaurins **16** –**18** appear to add water to form carbinols in solvents like dioxane, THF and pyridine. Fuchsones **8** and **10** exist on syn and anti forms in benzene, and the conversion rate is slower than 10 times per second. For the less hydrophilic compound, **15**, no carbinol formation is observed. Compounds **15** – **18** are shown to be prototropic (see Fig. 4) in DMF. **17** is also found to be prototropic in solvents like THF and pyridine. For **15** a prototropic exchange is found in DMF and in solvents such as dioxane. In the latter case this is observed only after adding considerable amounts of water or carbonic acids. Kinetic experiments revealed that a chain of 6-7 bridging water molecules are involved in the process. Thermodynamic parameters show that the transition state is sterically more hindered than the initial state.

For **15** in DMF kinetic experiments, the process is monomolecular or possibly involves one or two molecules of water**.**

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