

2-ARYL DERIVATIVES OF CONDENSED FIVE-MEMBERED N-HETEROCYCLIC COMPOUNDS. I.

DISSOCIATION CONSTANTS OF 2- AND 4-SUBSTITUTED PHENOLS AND NAPHTHOLS

J. DURMIS^a, M. KARVAŠ^a and Z. MAŇÁSEK^b

^a Research Laboratory, Dimitrov Chemical Works and

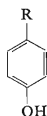
^b Institute of Polymers, Slovak Academy of Sciences, Bratislava

Received May 17th, 1971

Dissociation constants, in 50% aqueous dioxane, of 16 phenols and 2 naphthols substituted in positions 2 and 4 with condensed N-heterocyclic group and of 10 substituted phenols were determined spectrophotometrically. The observed linear dependence of dissociation constants on Hammett σ_p^- -constants (ρ 2.548) was used to calculate substitution constants for 2-benzotriazolyl, 2-naphtho[1,2-*d*]triazolyl, 2-indazolyl, 2-indolyl, 2-benzimidazolyl, N-methyl-2-benzimidazolyl, 2-benzoxazolyl, 2-benzthiazolyl and benzoyl groups. The effect of intramolecular hydrogen bonding on dissociation constants of 2-substituted derivatives is discussed.

Five-membered N-heterocyclic compounds, along with salicylic acid derivatives and benzophenone, are one of the well-known UV-absorbers for plastics. The importance of intramolecular hydrogen bond in photostabilizers was stressed by several authors¹⁻⁴. Dissociation constants of the systems with intramolecular hydrogen bonds are, in addition to steric and field effects, influenced also by hydrogen bonds⁵. These cause that hydrogen of hydroxyl group, when bonded by such bond, is abstracted less easily than in the absence of this bond. 2-Hydroxy compounds containing substituents which act as proton acceptors are therefore weaker acids than analogous compounds having these substituents in position^{6,7} 4. Dissociation constants of derivatives of 2-(2-benzotriazolyl)phenol were studied by Karvaš and coworkers⁸ who were interested in the effect of substituents in benzotriazol ring on the strength of intermolecular hydrogen bond.

In the present work dissociation constants, in 50% aqueous dioxane, of a series of 2- and 4-substituted phenols and naphthols I-XXVIII were determined spectrophotometrically. The study was undertaken with the aim to calculate σ_p^- -constants for condensed N-heterocyclic 2-yl groups and for benzoyl group, and on the basis of differences between dissociation constants of 2- and 4-substituted phenols and naphthols, to estimate the strength of intramolecular hydrogen bond.



- I, R = NH₂
- II, R = CH₃
- III, R = H
- IV, R = Cl
- V, R = CHO
- VI, R = NO₂

EXPERIMENTAL

Melting points, measured with Boetius apparatus, are uncorrected. Studied compounds were dried over P_2O_5 at 100 to 200°C under the pressure 1 Torr. Spectrograde dioxane was freshly distilled prior to use. Other chemicals were of analytical purity.

Compounds Used

Derivatives *I–IV* were commercial products and were purified to constant melting (boiling) point. The purity of the liquids was checked by gas chromatography. Compounds *V*, *VII–X*, *XIV*, *XVI*, *XVIII*, and *XXI–XXIV* were prepared according to known procedures. The other compounds were synthesized by modified procedures of the preparation of analogous compounds described in literature (Table I, II). Melting points of the prepared compounds agreed well with literature data, except the cases specified in the tables.

4-(2-Benzimidazolyl)phenol (*XVII*). A mixture of 5 g (0.036 mol) 4-hydroxybenzoic acid and 5 g (0.036 mol) 2-nitroaniline was melted at 170°C and 2 g PCl_3 were added in portions, while stirring. The crude product was dissolved in 10% aqueous NaOH, precipitated with dilute hydrochloric acid and dried (63.6%). The twofold crystallization of the product from ethanol gave 2-nitroanilide of 4-hydroxybenzoic acid (*XVIIa*) melting 193–194.5°C. For $C_{13}H_{10}N_2O_4$ (258.2) calculated: 60.60% C, 3.89% H, 10.83% N; found: 60.53% C, 3.75% H, 10.77% N. To a mixture of 2.58 g (0.01 mol) *XVIIa* and 38 ml conc. HCl were added 10 g of tin powder over 10 min period, and the mixture was then heated to 60°C for 5 h. After removal of the water, neutralization with dilute Na_2CO_3 solution, washing with water and drying, the crude product was extracted with ether. Twofold crystallization from ethanol–water afforded *XVII* (15%) melting 286–287°C (lit.⁹ 286–297°C).

Determination of Dissociation Constants

Dissociation constants of substances *I–XXVIII* in the range of concentrations $1.5 \cdot 10^{-4}$ mol/l were determined spectrophotometrically^{10,11} with Spektronom 202 spectrophotometer (MOM, Budapest). The measurements were carried out with solutions of the compounds in Britton–Robinson acetate buffers. pH of buffers was measured with pH-meter PHM 4 (Radiometer, Copenhagen) with the use of K-100 standard calomel electrode. The glass electrode was standardized by a buffer of pH 6.5 and a borax buffer (pH 9.18). The measurements were carried out at $25 \pm 0.1^\circ C$. Dissociation constants were calculated as arithmetic mean of five measurements. As the allowance for small effect of ionic strength¹² has not been made, the dissociation constants so obtained are primed. The described procedure enabled to carry out the measurements with all the studied compounds at approximately equal ionic strength. The accuracy of the determination was ± 0.05 .

Calculation of Hammett constants. Substituent constants of 4-substituted phenols containing benzoyl, 2-indolyl and 2-(4,5)-aryleneazoyl groups were calculated from their dissociation constants and the equation expressing the dependence of dissociation constants of phenols *I–VII* on σ_p^- -constants¹³ of their substituents.

RESULTS AND DISCUSSION

Dissociation constants of all the studied compounds are summarized in Tables I and II. Dissociation constants, in 50% aqueous dioxane, of derivatives *I–VII* correlate with σ_p^- constants according to Eq. (I),

$$pK' = 11.622 - 2.548\sigma_p^-; \quad s = 0.153, \quad r = 0.997, \quad n = 7, \quad (I)$$

where s is the standard deviation, r is the correlation coefficient and n is the number of the compounds used in calculation.

The reaction constant ρ (2.548) is greater in absolute value than that found by Cohen and Jones¹¹ for 4-substituted phenols in aqueous medium (2.23) and slightly smaller than in 50% aqueous ethanol (2.67). The pK'_0 is by contrast greatest in the aqueous dioxane. This demonstrates the sensitivity of ionization constants toward polarity of the medium. Dioxane forms with phenols comparatively strong intermolecular hydrogen bond of the type O—H...O which is obviously stronger than the similar bond with ethanol, due to greater basicity of the oxygen of dioxane, compared with ethanol. As found by Dearden²⁹, in hydrogen bonding with water ethanol acts predominantly as proton acceptor. Water, on the other hand, acts as proton donor²⁹, stabilizing thus the anion formed by dissociation. As the result, the acidity of the phenols is greater in water. The effect of strong intermolecular hydrogen bond between phenols and dioxane manifests itself above all in $pK'_{(OH)}$ values of the phenols with substituents acting as strong electron acceptors, *i.e.* those with low value of $pK'_{(OH)}$, since the strength of hydrogen bond depends also on the acidity of the proton donor. This explains also the magnitude of the reaction constant, which is somewhat smaller than in aqueous ethanol.

TABLE I
4-Substituted Phenols

Compound	Synthesis lit.	M.p., °C	Conc. · 10 ⁵ ^a mol/l	λ ^a nm	$pK'_{(4-OH)}$	σ_p^-
I	—	186	50	330	13.52	-0.660 ^b
II	—	— ^c	50	292	11.92	-0.170 ^b
III	—	— ^d	50	282	11.53	0.000 ^b
IV	—	43	50	295	10.91	0.226 ^b
XI	14	231.5—232.5	2	335	10.63	0.389
XVII	—	286—287	2	330	10.40 ^e	0.480
XXIII	15	194—196	4	350	10.38	0.487
XXV	16	199—200	3	372	10.38	0.487
XIX	17	277—278 ^f	3	314	10.15 ^g	0.578
XV	17	228.5—229	2	355	9.96	0.652
XIII	17	252—254	2	330	9.82	0.684
IX	18	135	10	295	9.53	0.821
VII	19, 20	108.5	4	305	9.41	0.874 ^b
XXI	21	221—223	4	375	9.01	1.024
V	22	115—116	5	280	8.95	1.126 ^b
VI	—	113.5	5	380	8.32	1.270 ^b

^a Wavelengths and concentrations used in determination of pK' values. ^b Taken from ref.¹³.

^c B.p. 70°C/17 Torr. ^d B.p. 76°C/13 Torr. ^e $pK'_{(NH)}$ 4.87. ^f Lit.²⁴ gives m.p. 266—267°C. For C₁₄H₁₂N₂O (224.3) calculated: 75.00% C, 5.37% H, 12.49% N; found: 74.91% C, 5.41% H, 12.37% N. ^g $pK'_{(NH)}$ 4.87.

The equation (1) and experimental dissociation constants for 4-substituted phenols IX, XI, XIII, XV, XVII, XIX, XXI, XXIII, and XXV were used to calculate substituent constants for relevant substituents. As it is seen in Table I all the studied substituents enhance the acidity of the phenol OH group. This can be attributed to the presence of electronegative atoms in heterocyclic ring. The greatest acidity is displayed by derivative XXI, containing three nitrogen heteroatoms. The acidity of this substance is comparable with that of derivative VI. The acidity of derivative XXV, having also three nitrogen atoms in the ring, is lower, due to the presence of another ring condensed with the benzo heterocycle which, by its electron-donor properties, exerts the opposite effect than the nitrogen heteroatoms which are electron acceptors. The value for benzoyl group is somewhat smaller than in derivative VII, the compound with similar structure. The derivatives with two heteroatoms are less acidic than derivative XXI. The 2-indolyl substituent, containing one heteroatom, increases the acidity of the phenol only very slightly and completes the sequence. Among the derivatives substituted with the groups with two heteroatoms the strongest electron-

TABLE II

2-Substituted Phenols and 2-Benzotriazolynaphthols

Compound	Synthesis lit.	M.p., °C	Conc. · 10 ⁵ , ^a mol/l	λ ^a nm	pK'(2-OH)	ΔpK' ^b
VIII	19, 20	— ^c	1.5	360	11.69	2.28
XIV	23	125.5	4	315	11.52	1.70
X	18	36.5	1.5	385	11.36	1.83
XII	14	176—177 ^d	4	350	11.21	0.58
XXIV	15	113—115	5	350	11.18	0.80
XX	17	169—170	5	320	11.03 ^e	0.88
XVIII	23	242.5—244.5	4	340	10.76 ^{f,g}	0.36
XXVI	16	141—142	5	350	10.65	0.27
XXII	21	125—127	4	325	10.50	1.49
XVI	23	131—131.5	4	380	10.38	0.42
XXVIII	21	144—145	5	355	9.17	—0.46
XXVII	21	204—205	4	375	9.63 ^h	—

^a Wavelengths and concentrations used in determination of pK values. ^b ΔpK' = pK'(2-OH) — pK'(4-OH). ^c B.p. 93—95°C/12 Torr. ^d Lit.²⁵ records m.p. 161—162°C and lit.²⁶ gives m.p. 175—176°C. For C₁₄H₁₁NO (209.2) calculated: 80.40% C, 5.30% H, 6.69% N; found: 80.62% C, 5.44% H, 6.57% N. ^e pK'(NH) 4.41. ^f The compound decomposes on the exposure to UV light. The spectrophotometric method is not therefore suitable for determination of pK'(OH). The value found potentiometrically^{27,28} (10.76) in the same medium markedly differs from the value determined by spectrophotometric method (11.87) and is regarded as more accurate. ^g pK'(NH) 4.52. ^h pK'(4-OH).

acceptor is derivative *XIII*. This is obviously caused by the presence of the more electronegative oxygen together with nitrogen. Although sulphur atom is less electronegative than nitrogen atom, the $pK'_{(OH)}$ of derivative *XV* is smaller than that of derivatives *XVII*, *XXIII* and *XIX*. As to derivative *XVII* this fact can be accounted for by the presence of hydrogen atom at one of the heteroatoms. Derivative *XXIII*, on the other hand, differs substantially in structure from derivative *XV*. In structure *A* there is greater possibility of electron transfer through conjugated system than in structure *B* with the double bond. Derivative *XVII* should have been more acidic than derivative *XIX*, since inductive effect of the methyl group reduces electron-acceptor power of the substituent. In derivative *XIX*, however, there is apparent steric hindrance, since, as models showed, hydrogen atoms of the methyl groups interact with the hydrogen atom in position 3 of the phenol ring (structure *C*). In derivative *XVII*, contrarily to derivative *XIX*, intermolecular hydrogen bond can be further formed also with the NH group hydrogen. The relative influence of these effects on the acidity of compound *XIX* cannot be evaluated quantitatively. As compound *XVI* is less acidic than substance *XIX*, this indicates, however, the strong intermolecular hydrogen bond of the type $NH \cdots O$ in derivative *XVII* in 50% aqueous dioxane.

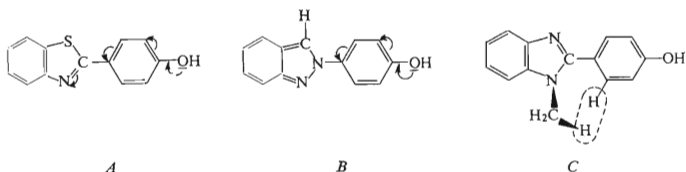
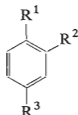
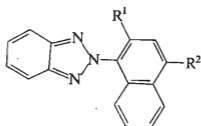


Table II shows that 2-substituted phenols have greater pK' values than corresponding 4-substituted derivatives. The dissociation constants of 2-substituted derivatives, besides the effects which play a role also in the case of 4-substituted derivatives (intermolecular hydrogen bonding, inductive and resonance effects), are influenced also by other factors, such as steric and field effects and intramolecular hydrogen bond³⁰. Taft³¹ succeeded in quantitative estimation of each of these effects separately in the case of 2-substituted derivatives in which intramolecular hydrogen bond does not occur. Even though Taft constants can be successfully employed in some correlation with experimental data, they have not been generally accepted³². The behaviour of the derivatives with intramolecular hydrogen bond cannot be described in terms of the so far known rules on structure effects on the reactivity and physico-chemical properties. In the case of the studied 2-substituted phenols and the naphthol *XXVIII* the effect of substituents on dissociation constants is quite complex because of occurrence of various steric and "field" effects.

As IR spectra show, compound *XII* cannot form intramolecular hydrogen bond³³. Its decreased acidity relative to 4-substituted derivative *XI* is therefore obviously due to secondary steric effect of hydrogens in positions 1 and 3 of the indole ring on the phenolic hydrogen. This interaction results in deviation from coplanarity of the molecule and the reduction of the conjugation of the benzoheterocyclic substituent with phenol. The decreased acidity of the other 2-substituted phenols is mainly due to intramolecular hydrogen bond, occurring in all these derivatives



	R ¹	R ²	R ³	X	Y
VII,		{ H	OH	—	—
VIII,	CH ₃ CO	{ OH	H	—	—
IX,		{ H	OH	—	—
X,	C ₆ H ₅ CO	{ OH	H	—	—
XI,		{ H	OH	CH	NH
XII,		{ OH	H	CH	NH
XIII,		{ H	OH	N	O
XIV,		{ OH	H	N	O
XV,		{ H	OH	N	S
XVI,		{ OH	H	N	S
XVII,		{ H	OH	N	NH
XVIII,		{ OH	H	N	NH
XIX,		{ H	OH	N	N—CH ₃
XX,		{ OH	H	N	N—CH ₃
XXI,		{ H	OH	—	N
XXII,		{ OH	H	—	N
XXIII,		{ H	OH	—	CH
XXIV,		{ OH	H	—	CH
XXV,		{ H	OH	—	—
XXVI,		{ OH	H	—	—



XXVII, R¹ = H; R² = OH
 XXVIII, R¹ = OH; R² = H

in nonpolar medium, as shown by IR spectra³³. Proving that steric effects in all the 2-substituted derivatives with heterocyclic groups are similar in magnitude, the relative strength of intramolecular hydrogen bond can be estimated from the difference between $pK'_{(OH)}$ values of 2- and 4-substituted phenols.

The intramolecular hydrogen bond in 2-substituted derivatives is in 50% aqueous dioxane affected both by the proton donor (water) and by the proton acceptor (dioxane). Both form intermolecular hydrogen bond with phenol OH proton or with proton-acceptor heteroatom. From the results given in Table II it seems likely that $OH \cdots N$ bond or the proton donor completes more effectively with intramolecular hydrogen bond. Comparison of the differences in $pK'_{(OH)}$ values of derivatives *XIV*, *XVI*, *XVII*, *XVIII* and *XX* reveals that the strongest intramolecular hydrogen bond occurs in 2-(2-benzoxazolyl)phenol. This compound, besides nitrogen, contains in the heterocycle the most electronegative atom and, therefore, the basicity of the nitrogen is most decreased. The weakening of the intramolecular hydrogen bond by the proton donor is thus smallest. The strength of the hydrogen bond decreases further in the order 2-(2-benzthiazolyl)phenol, 2-(2-benzimidazolyl)phenol. This decrease is reverse to the basicity of the heterocyclic rings, since oxazols are 10^6 times less basic than imidazols and 10^2 times less basic as thiazols³⁴. The $pK'_{(OH)}$ of compound *XX* is mainly influenced by steric effect of N-methyl group, similarly as the value of compound *XIX* (structure *C*).

The UV absorption spectra show³³ that the molecule of compound *XX* is non-coplanar in hydroxylic solvents, while in nonhydroxylic solvents it is co-planar and has strong intramolecular hydrogen bond. In the 50% aqueous dioxane medium this bond is completely broken. As follows from the $pK'_{(NH)}$ values of 4-substituted derivatives with benzimidazolyl group, the methyl group on the nitrogen of the heterocycle increases by its inductive effect the basicity of benzimidazolyl group, as expected. On the other hand, 2-substituted derivatives are weaker bases, relative to the 4-substituted ones. This in the case of 2-(2-benzimidazolyl)phenol is likely due to intramolecular hydrogen bond and in the case of 2-(N-methyl-2-benzimidazolyl)phenol due to the steric effect. The basicity of N-methyl-2-benzimidazolyl group in the 2-substituted phenol is strong enough to enable the formation of intermolecular hydrogen bond of the type $N \cdots H-O$ with the proton donor in this medium. Together with the steric effect this could be the main factor which is responsible for the distortion of coplanarity of the molecule and thus also the splitting of the intramolecular hydrogen bond. At the same time the non-coplanarity of compound *XX* decreases the basicity of N-methyl-2-benzimidazolyl substituent more than the intramolecular hydrogen bond in compound *XVIII* reduces the basicity of the 2-benzimidazolyl group.

Compounds *XXII*, *XXIV*, and *XXVI* with similar structure of heterocyclic substituent has the representative with comparatively strongest hydrogen bond in 2-(2-benzotriazolyl)phenol, whose nitrogen heteroatoms capable of forming intramolecular bond are least basic. The significant electronic effect of 2-benzotriazolyl group

(Table I) increases further the acidity of the phenol and obviously also contributes to the comparatively strong intramolecular hydrogen bond in 2-(2-benzotriazolyl)-phenol. In compound *XXVI*, with much smaller electronic effect of the heterocyclic substituent and with the increased basicity of nitrogen heteroatoms, due to the presence of another condensed ring, the intramolecular hydrogen bond is weak. The hydrogen bond is also weaker in 2-(2-indazolyl)phenol, since 2-indazolyl group is more basic than 2-benzotriazolyl group.

In all the 2-substituted phenols containing heterocyclic substituent and intramolecular hydrogen bond, this bond is cleaved on going from aprotic solvents to protic ones, the main centre of the cleavage being the proton acceptor in this bond. In protic solvents an increased basicity of the proton acceptor does not lead to strengthening of the intramolecular hydrogen bond, but, as the result of the attack by proton donor, to the more extensive cleavage. The greatest difference between $pK'_{(OH)}$ of 2- and 4-substituted phenols is observed with the derivatives containing acetyl and benzoyl groups. The oxygen of the 2-substituted derivatives of these compounds acts in the intramolecular hydrogen bond as proton acceptor. The greatest difference in pK' values can be ascribed to the low basicity of the proton acceptor in the intramolecular hydrogen bond, which aids in its stabilization. Steric effects may also play an important role, however, since these 2-substituted derivatives differ from the 2-substituted phenols with heterocyclic substituents.

Naphthol derivatives *XXVII* and *XXVIII* do not follow the trend observed with phenol derivatives, because of the greater acidity of 1,2-substituted derivative *XXVIII*, relative to 1,4-substituted naphthol *XXVII*. The structure of naphthalene rings is the main reason of the increase in the basicity of the proton acceptor in the intramolecular hydrogen bond in compound *XXVIII* and thus the formation of comparatively strong intermolecular hydrogen bond of the type $N...H-O$ with water. This fact, along with steric effect³³, accounts for the complete cleavage of the intramolecular hydrogen bond in compound *XXVIII* and non-coplanarity of its molecule. The greater acidity of compound *XXVIII* relative to compound *XXVII* is caused by the structure of naphthalene ring.

We thank Drs T. Sticzay and N. Šubertová for UV spectra measurements.

REFERENCES

1. Chaudet J. H., Newland C. C., Patton H. V., Tamblyn J. W.: *SPE Trans.* 1, 26 (1960).
2. Hrdlovič P.: *Thesis*. Slovak Academy of Sciences, Bratislava 1967.
3. Merrill J. R., Bennett R. G.: *J. Chem. Phys.* 43, 1410 (1965).
4. Heller H. J.: *European Polymer J.*, Suppl. 1969, 105.
5. Pimental G. C., McClellan A. L.: *The Hydrogen Bond*, p. 181. W. H. Freeman, San Francisco and London 1960.
6. Sadekov I. D., Mirkin V. I., Luckij A. E.: *Uspechi chimii* 39, 381 (1970).
7. Hermans J. J., Leach S. J., Sheraga H. A.: *J. Am. Chem. Soc.* 85, 1390 (1963).

8. Karvaš M., Hrdlovič P., Durmis J., Holčík J.: Chem. průmysl 19, 109 (1969).
9. Runge F., Blanke H. J.: J. Prakt. Chem. [4], 1, 110 (1954).
10. Hrdlovič P., Belluš D.: Chem. zvesti 21, 410 (1967).
11. Albert A., Serjeant E. P.: *Ionization Constants of Acids and Bases* (Russian transl.), p. 64. Izd. Chimija, Moscow—Leningrad 1964.
12. Cohen L. A., Jones W. M.: J. Am. Chem. Soc. 85, 3397 (1963).
13. Jaffé H. H.: Chem. Rev. 53, 191 (1953).
14. Shriner R. L., Ashley W. C., Welch E.: Org. Syn. 22, 98 (1942).
15. Karvaš M., Ježo I., Durmis J., Balogh A.: Chem. zvesti 25, 445 (1971).
16. Chmátal V., Poskočil J., Allan Z. J.: Chem. listy 52, 1156 (1958).
17. Hein D. W., Alheim R. J., Lea Witt J. J.: J. Am. Chem. Soc. 79, 427 (1957).
18. Cullinaue N. M., Edwards B. F. R.: J. Appl. Chem. 9, 133 (1959).
19. Freudenberg K., Orlhner L.: Ber. 55, 1749 (1922).
20. Rosenmund K. W., Schnurr W.: Ann. 464, 88 (1928).
21. Karvaš M., Holčík J.: Chem. průmysl 17, 543 (1967).
22. Reimer K. L., Tieman F.: Ber. 9, 824 (1876).
23. Hardy W. B., Forster W. S., Hosler J. F. (American Cyanamid Company): US-Pat 3 049 509 (1962).
24. Mangini A., Montanari F.: Boll. Sci. Fac. Chim. Ind. Bologna 14, 36 (1956).
25. Calvaire A., Pallaund P.: Compt. Rend. 250, 3194 (1960).
26. McLoughlin B. J., Smith L. H. (Imperial Chemical Industries): Belg. Pat. 550 800 (1965).
27. Jonston W. D., Freiser H.: Anal. Chim. Acta 11, 301 (1954).
28. Lundgren H. P., Binkley C. H.: J. Polymer Sci. 14, 139 (1954).
29. Dearden J. C.: Rev. Univ. Ind. de Santander 7, (1/2) 21 (1965).
30. Ingold C. K.: *Otázka struktury a mechanismu v organické chemii*, p. 669. Published by Nakladatelství ČSAV, Prague 1957.
31. Taft R. W., jr: J. Am. Chem. Soc. 74, 3120 (1952).
32. Exner O.: Chem. listy 53, 1316 (1959).
33. Durmis J., Karvaš M., Maňásek Z.: Unpublished results.
34. Haake P., Bausher L. P.: J. Phys. Chem. 72, 2213 (1968).

Translated by J. Hettflejš.