

## Anthraquinones Tautomerism: VI.\* Substituted 1,4,5-Trihydroxyanthraquinones

V. Ya. Fain, B. E. Zaitsev, and M. A. Ryabov

Russian University of Peoples' Friendship, Moscow, 127349 Russia  
e-mail: vfain@mail.ru

Received January 9, 2006. Revised version October 20, 2006

**Abstract**—1,4,5-Trihydroxy-9,10-anthraquinone and its substituted derivatives exist in equilibrium of structures distinguished by quinoid tautomerism and rotational isomerism. Their electron absorption spectra contain  $\pi, \pi^*$ -bands corresponding to 9,10- and 1,10-, more seldom to 1,5- and 1,4-anthraquinoid structures. Of three isomeric 1,10-anthraquinones only 4,8,9-trihydroxy-1,10-anthraquinones were found. All tautomer may exist as conformers with contiguous CO and OH groups not bound by an intramolecular hydrogen bond. The considerable difference in color of structurally similar substituted compounds is due to tautomerism and conformer transformations.

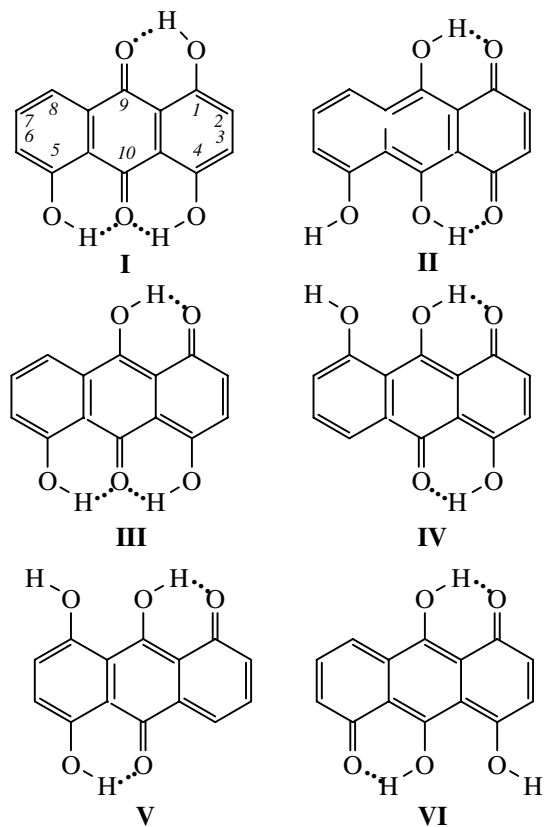
DOI: 10.1134/S1070428007050144

A compound commonly described as 1,4,5-trihydroxy-9,10-anthraquinone is among organic substances possessing very complex multiband  $\pi, \pi^*$ -absorption in the visible range of electronic spectrum. We reported in previous publications [1–3] that several  $\pi, \pi^*$ -bands in the spectra of hydroxyanthraquinones were due to their presence as several structures in equilibrium state originating from anthraquinoid tautomerism and rotational isomerism involving ruptures of intramolecular hydrogen bonds. The study of tautomerism becomes a most important problem in the anthraquinone chemistry. Undying interest in this class compounds is caused by their extensive application as natural and synthetic dyes, biologically active substances and drugs, analytical reagents and indicators, catalysts of important industrial processes, reagents for means of conservation and collection of information, and in many other instances [4].

It was shown for 1 hydroxy- [3] and 1,5 dihydroxy-anthraquinones [1] that introduction of R substituents into the anthraquinone skeleton frequently resulted in the shift of the tautomeric and conformational equilibria and in considerable changes in the color of compounds which could not be understandable based on the exclusively 9,10-quinoid structure of the anthraquinones. These observations inspired us to investigate the tautomerism and the rotational isomerism of substituted 1,4,5-trihydroxyanthraquinones, whose many representatives are present among widely spread natural substances used in pharmaceuticals

[4–6]. 1,4,5-Trihydroxyanthraquinone is also important as a model of tetracycline antibiotics [7].

The 1,4,5-trihydroxyanthraquinone can exist in the form of 6 prototropic tautomers: a single one for each of 9,10- (I), 1,4- (II), and 1,5- (VI) anthraquinoid isomers, and three for 1,10-anthraquinone (III–V).



\* For communication V, see [1].

**Table 1.** Position of  $\pi, \pi^*$ -bands in electron absorption spectra of some 1,4,5-trihydroxy-9,10-anthraquinones and their tautomers

Substituents in 1,4,5-trihydroxyanthraquinone	Solvent	Assignment of $\pi, \pi^*$ -bands to tautomers and conformers, nm										References
		I			II	I	IV			VI		
		3 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	3 <sup>a</sup>	0 <sup>a</sup>	3 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	2 <sup>a</sup>	1 <sup>a</sup>	
H	Cyclohexane	462 sh	472	483		495 (483) <sup>b</sup>	505 sh	517	530 (523) <sup>b</sup>	562	(568) <sup>b</sup>	[11]
H	Methanol	457 sh				490		510 sh	525 sh			[12]
2-Methyl	Ethanol					490			530		580	[12]
2-Methyl	Ethanol		460 sh	479.5 sh		491		513	527			[5]
3-Methyl	Ethanol		465 sh	473 sh		494		515 sh	539 sh			[5]
6-Methyl	Ethanol-HCl		460			490 sh						[13]
7-Methyl	Methanol	460		476		489		507	522		567	[14]
3-(3-Oxopentyl)	Methanol		463	477		490		508	522			[15]
2,7-Dimethyl	Ethanol-dioxane, 10:1	457				487		507	520			[12]
2-Methyl-7-methoxy	Ethanol		460 sh	475 sh		489		511 sh	523			[5]
2-Methyl-7-methoxy	Chloroform					495						[16]
2-Methyl-7-methoxy	Chloroform		466	478		493		513	522			[17]
3-Methyl-6-methoxy	Ethanol								530			[18]
7-Methyl-2-methoxy	Ethanol		462.5		485	489.5		511	525			[19]
7-Methyl-2-methoxy	Ethanol	452			485	490		511	525			[17]
7-Methyl-3-methoxy	Methanol		458			486			519		560	[14]
2,3-Dimethyl-7-methoxy	Ethanol			480					527			[20]
7-Methyl-2,3-dimethoxy	Ethanol		463			487		507 sh	520			[21]
H	$-\Sigma\sigma^A$	1.47	1.60	1.73	1.82	1.86	1.94	2.06	2.20	2.52	2.65	

<sup>a</sup> Number of free hydroxy groups in conformers. <sup>b</sup> Data of PPP calculations.

Data on the position of experimentally measured  $\pi, \pi^*$ -band in the published spectra of some substituted 1,4,5-trihydroxy-anthraquinones are compiled in Table 1.

The numerous discrepancies cannot be understood based on the common conception of exclusively 9,10-anthraquinoid structures of these compounds. For instance, why the number of the  $\pi, \pi^*$ -bands in the different known spectra changes from 1 to 8? Why the longwave absorption band of 1,4,5-trihydroxy-6-methylanthraquinone in ethanol is observed at 490 nm, of its 7 methyl isomer in methanol at 567 nm, of 3-methyl isomer at 539 nm, and 2-methyl-substituted at 580 nm? The different positions of the methyl group in the anthraquinone core cannot produce these considerable shifts. Why the change of the solvent for 1,4,5-trihydroxy-2-methyl-7-methoxy-anthraquinone from ethanol to chloroform resulted in a significant blue shift from 523 to 495 nm? Or why are

so dissimilar the spectra of 1,4,5-trihydroxy-2-methyl-anthraquinone in ethanol measured by different authors? These data and analogous discrepancies become clear taking into account the tautomeric and conformational transformations of the compounds.

As show quantum-chemical calculations the spectrum of each tautomer contains a single  $\pi, \pi^*$ -band, and the presence of several  $\pi, \pi^*$ -bands in the experimental spectra indicates the existence of tautomeric and/or conformational equilibria. A criterion of correct assignment of the experimental  $\pi, \pi^*$ -bands to individual tautomers is not the most close coincidence with the calculated value but their linear correlation [8].  $\pi$ -Electronic PPP method in Dewar version [9] applying variable  $\beta$ -approximation [10] is still the only semiempirical quantum-chemical procedure that has been proved by many examples to be capable of adequate simulating the results

of the structural transformations in hydroxyanthraquinones.

The assignment of  $\pi, \pi^*$ -bands to tautomer compounds by means of linear correlation between the experimental  $\lambda_{\max}$  and the values obtained by quantum-chemical calculations [22] does not always result in their exhaustive identification [23]. Only three among the known experimental  $\pi, \pi^*$ -bands of 1,4,5-trihydroxy-2-methylanthraquinone correspond to the values calculated by PPP method for 9,10-, 1,10-, and 1,5-quinoid forms [equation (1)].

$$\lambda_{\max}(\text{nm}) = (1.048 \pm 0.039)\lambda_{\text{calc}} - (16 \pm 20), \quad (1)$$

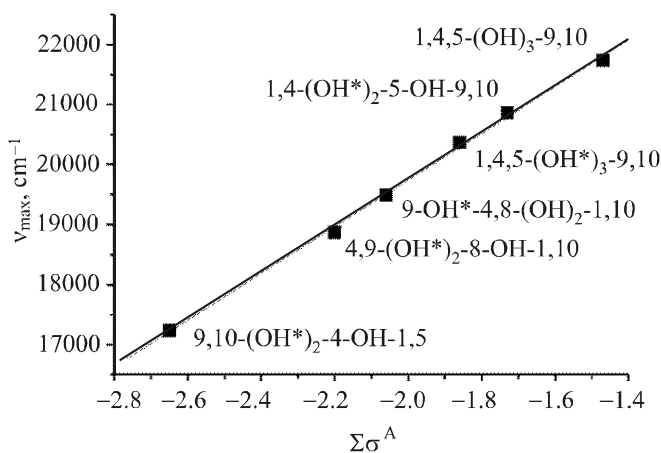
Number of tautomers  $N$  3, correlation coefficient  $r$  0.9993, standard deviation  $s$  2.4 nm.

The total assignment of bands was reached by correlation of  $\nu_{\max}$  with sums of  $\sigma^A$ -constants of free (OH) and involved into intramolecular hydrogen bonds (OH\*) hydroxy groups calculated for all possible tautomers [2] [for instance, Fig. 1, equation (2)].  $\pi, \pi^*$ -Bands with no analogs in spectra calculated by PPP method correspond to conformers of 9,10- and 1,10-anthraquinoid tautomers.

$$\nu_{\max} = k\Sigma\sigma^A + \nu_0 \text{ cm}^{-1}, \quad (2)$$

where  $k$  is the response of  $\nu_{\max}$  values to tautomeric and conformational transformations,  $\nu_0 = \nu_{\max}$  at  $\Sigma\sigma^A = 0$ .

For 1,4,5-trihydroxyanthraquinone in cyclohexane this relation is described by equation (3).



**Fig. 1.** Correlation of experimental  $\nu_{\max}$  values of 1,4,5-trihydroxy-2-methyl-9,10-anthraquinone in ethanol with sums of  $\sigma^A$ -constants of hydroxy groups free and involved in intramolecular hydrogen bonds.

$$\nu_{\max}(\text{cm}^{-1}) = (3743.6 \pm 72.9)\Sigma\sigma^A + (27140 \pm 142); \quad (3)$$

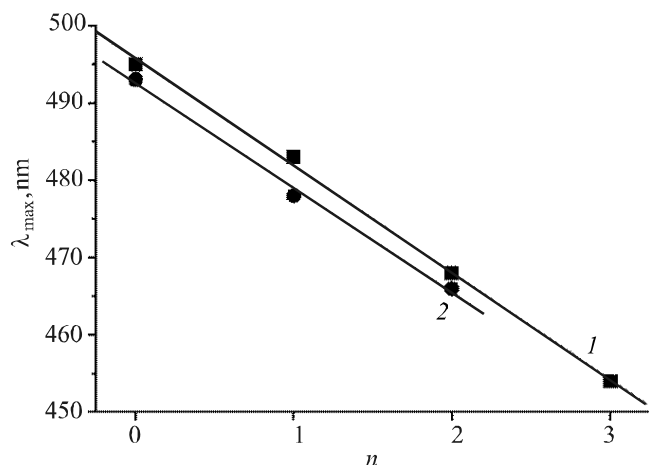
$N$  8,  $r$  0.9989,  $s$  65  $\text{cm}^{-1}$ .

Here only 9,10-1,10-1,5-, but not 1,10-1,4-anthraquinoid tautomerism was found; therewith 9,10- and 1,10-quinoid tautomers were capable to form conformer, where one, two, or all three intramolecular hydrogen bonds are ruptured, and the 1,5-anthraquinone was found only as a conformer with two free OH groups in positions 4 and 10 [2].

The correlation parameters of equation (2) for some substituted 1,4,5-trihydroxyanthraquinone are given in Table 2.

**Table 2.** Correlation parameters of equation (3)

Substituents in 1,4,5-trihydroxyanthraquinone	Solvent	$N$	$r$	$s, \text{cm}^{-1}$	$k$	$\nu_0, \text{cm}^{-1}$
H	Methanol	4	0.99987	24	$3880 \pm 44$	$27600 \pm 85$
2-Methyl	Ethanol	6	0.9990	80	$3890 \pm 87$	$27500 \pm 177$
3-Methyl	Ethanol	5	0.995	145	$5000 \pm 299$	$29600 \pm 570$
7-Methyl	Methanol	6	0.9989	78	$3550 \pm 85$	$27000 \pm 172$
2,7-Dimethyl	Ethanol-dioxane, 10:1	4	0.9995	45	$3650 \pm 81$	$27300 \pm 156$
3-(3-Oxopentyl)	Methanol	5	0.9981	69	$4000 \pm 143$	$28000 \pm 272$
2-Methyl-7-methoxy	Ethanol	5	0.997	94	$4400 \pm 193$	$28700 \pm 368$
7-Methyl-2-methoxy	Ethanol	6	0.9994	45	$4300 \pm 74$	$28500 \pm 137$
7-Methyl-3-methoxy	Methanol	4	0.9993	81	$4300 \pm 117$	$28600 \pm 242$
7-Methyl-2,3-dimethoxy	Ethanol	4	0.9996	38	$4000 \pm 84$	$28000 \pm 163$



**Fig. 2.** Values of  $\lambda_{\max}$  of conformers of 1,4,5-trihydroxy-9,10-anthraquinone (1) in cyclohexane and 1,4,5-trihydroxy-2-methyl-7-methoxy-9,10-anthraquinone (2) in chloroform as a function of a number of ruptured intramolecular hydrogen bonds  $n$ .

The results of the correlation analysis by equation (2) require assignment of the band at 460 nm for different substituted 1,4,5-trihydroxyanthraquinones to different conformers, containing two or three free hydroxy groups in 9,10-quinoid tautomer (Table 1). This condition follows from the fact that a number of  $\pi, \pi^*$ -bands appears as shoulders whose position is estimated with a rather large uncertainty. The refinement of the corresponding  $\nu_{\max}$  values allows a refined assignment to the given conformers.

The comparison of  $k$  values permits quantitative estimation of the substituents effect on the response of the substituted 1,4,5-trihydroxyanthraquinones to tautomeric and conformational transformations. Thus the data in Table 2 show that the introduction of a methyl group in the position 3 increases this response, into position 7, decreases, and in position 2, virtually does not affect. The presented assignments are confirmed by a number of independent correlations, for instance, between the experimental values of  $\lambda_{\max}$  for 1,4,5-tri- and 1,4-dihydroxyanthraquinones [equation (4)], by proportional response of tautomers of 1,4,5-trihydroxyanthraquinone to the introduction of a methyl group into the position 7 [equation (5)] on to the change in the position of a methyl [equation (6)] or a methoxy group on the anthraquinone framework [equation (7)].

$$\lambda_{\max}(1,4,5) (\text{nm}) = (1.101 \pm 0.029)\lambda_{\max}(1,4) - (42.0 \pm 14.4);$$

$$N 6, r 0.9986, s 1.4 \text{ nm.} \quad (4)$$

$$\lambda_{\max}(7\text{-Me}) (\text{nm}) = (0.907 \pm 0.017)\lambda_{\max}(1,4,5) + (45.2 \pm 8.2);$$

$$N 4, r 0.9997, s 0.8 \text{ nm.} \quad (5)$$

$$\lambda_{\max}(2\text{-Me}) (\text{nm}) = (1.129 \pm 0.018)\lambda_{\max}(7\text{-Me})$$

$$- (60.6 \pm 9.3);$$

$$N 6, r 0.9995, s 1.5 \text{ nm.} \quad (6)$$

$$\lambda_{\max}(7\text{-Me-3-MeO}) (\text{nm})$$

$$= (0.974 \pm 0.030)\lambda_{\max}(7\text{-Me-2-MeO}) + (8.6 \pm 14.9);$$

$$N 3, r 0.9995, s 1.3 \text{ nm.} \quad (7)$$

The slopes in these equations reflect the relative sensitivity of  $\lambda_{\max}$  values for the two compared compounds with respect to the tautomeric and conformational transformations. For instance, equation (6) suggests that  $\lambda_{\max}$  of the 1,4,5 trihydroxy-2-methylantraquinone is more sensitive nearly by 13% than  $\lambda_{\max}$  of its 7 methyl isomer.

Equations (4–7) follow from the general law which states that  $\lambda_{\max}$  values change proportionally to the changes in the structure of the compounds [8]. The existence of this general law is confirmed by new examples. For instance,  $\lambda_{\max}$  of conformers of 1,4,5-trihydroxy-9,10- and 1,4,5-trihydroxy-2-methyl-7-methoxy-9,10-anthraquinones depends linearly on the number  $n$  of intramolecular hydrogen bonds ruptured as a result of the conformational transformations [Fig. 2, equations (8, 9)].

$$\lambda_{\max}(1,4,5) (\text{nm}) = (495.7 \pm 0.8) - (13.80 \pm 0.42)n;$$

$$N 4, r 0.9991, s 0.9 \text{ nm.} \quad (8)$$

$$\lambda_{\max}(2\text{-Me-7-MeO}) (\text{nm}) = (492.5 \pm 1.1)$$

$$- (13.50 \pm 0.87)n;$$

$$N 3, r 0.998, s 1.2 \text{ nm.} \quad (9)$$

Equation (9) permitted the calculation of the position of  $\pi, \pi^*$ -band in the spectrum of yet unknown conformer with three hydroxy groups free of intramolecular hydrogen bonds (452 nm) that might simplify its identification at future measurements. As seen from Table 1, the position of this  $\pi, \pi^*$ -band coincides with that found for isomeric 1,4,5-trihydroxy-7-methyl-2-methoxy-9,10-anthraquinone.

Another example: Dependence of  $\lambda_{\max}$  on the number  $m$  of prototropic migrations of hydrogens in the intramolecular hydrogen bonds  $\text{O-H}\cdots\text{O}=\text{C}$  (for 1,10- and 1,5-anthraquinones  $m = 1$  and 2 respectively) [equations (10, 11)].

$$\lambda_{\max}(1,4,5) (\text{nm}) = (33.000 \pm 0.577)m + (496.3 \pm 0.7);$$

$$N 3, r 0.99985, s 0.8 \text{ nm.} \quad (10)$$

$$\lambda_{\max}(7\text{-Me-3-MeO}) (\text{nm}) = (37.000 \pm 2.309)m + (484.7 \pm 3.0);$$

$$N 3, r 0.998, s 3 \text{ nm.} \quad (11)$$

Equations (10, 11) also confirm the validity of the performed assignments.

Regular character of the found relationships, very high  $r$  values and low  $s$  undoubtedly show their reliability even at the minimum number of points.

The data in Table 1 show that introduction of substituents into the  $\beta$ -position of the anthraquinone skeleton quite weakly affects, as is expected, the  $\lambda_{\max}$  values of identical tautomers, but can shift the tautomeric and conformational equilibria. The considerable color difference in the structurally similar compounds is due to just these transformations.

The conformers are classed in Table 1 according to the number of the free hydroxy groups. Inasmuch as in the tautomeric quinoid structures some hydroxy groups are not adjacent to carbonyls and consequently cannot form intramolecular hydrogen bonds the number of free OH groups and ruptured intramolecular hydrogen bonds do not coincide.

Thus the multiband  $\pi, \pi^*$ -absorbance of 1,4,5-trihydroxyanthraquinone and its substituted derivatives is due to the presence of various tautomers and conformers existing in a dynamic equilibrium. The number of these states and their structure are likely to depend on the method of preparation and the conditions of the spectrum registering.

The data obtained revealed a number of non-obvious structural features of compounds under investigation. Their most characteristic forms are 9,10- and 1,10-quinoid tautomers.  $\pi, \pi^*$ -Bands corresponding to 1,4 quinoid structures were identified only in 7-methyl-2-methoxy-substituted compound. The existence of the states with 1,5-quinoid structures **VI** is rather unexpected.

Among three possible 1,10-quinoid structures only structure **IV** was found. They were distinguished only on combining correlations with the values calculated by quantum-chemical methods and with sums of  $\sigma^A$ -constants of free and bound hydroxy groups. Tautomer **III** differs from **IV** and **V** by the  $\lambda_{\text{calc}}$  value (513 versus 523 nm). In the case of 1,4,5 trihydroxy-2-methyl-, -7-methyl-, and -7-methyl-3-methoxyanthraquinones whose three tautomeric structures were identified the experimental  $\lambda_{\max}$  values were in linear relation with  $\lambda_{\text{calc}}$  values at the use of 523 nm figure ( $r$  0.9990–0.9996) but not 513 nm. Obviously, the other conditions being the same, the formation of the most stable tautomer is the most likely. The stability of substances in solutions is governed by solvation factors  $M$ . Of two tautomers **IV** and **V** with

identical  $\lambda_{\text{calc}}$  values the  $M$  corresponding to **IV** is larger (4.166 versus 4.085 [23]), therefore the formation of structure **IV** is more likely than structure **V**. On the other hand the  $\Sigma\sigma^A$  values for compounds **III–V** are identical, but the correlation with  $\Sigma\sigma^A$  makes it possible to distinguish conformers **IV** from conformers of other tautomers. The lack in the absorption spectra of the  $\pi, \pi^*$ -bands belonging to the 1,10-quinoid structure with three hydroxy groups involved in intramolecular hydrogen bonds confirms the existence of tautomer **IV** and not **III**.

On the contrary, for 9,10-anthraquinones **I** the structures with three bound hydroxy groups are characteristic (Table 1). This statement is in agreement with a possibility of two intramolecular hydrogen bonds formation involving one carbonyl and two hydroxy groups. It is a common belief that the contiguous carbonyl and hydroxy group always form an intramolecular hydrogen bond. The data in Table 1 show that it is not an obligatory case: The conformer with the ruptured intramolecular hydrogen bonds are fairly frequent.

The results of this study are well consistent with the previously reported [1–3]. The concepts of tautomeric and conformational equilibria provided a possibility for the first time to understand the great number of  $\pi, \pi^*$ -bands and their positions in the numerous absorption spectra of hydroxy-substituted anthraquinones, thus supporting the reliability of the developed concepts.

## REFERENCES

1. Fain, V.Ya., Zaitsev, B.E., and Ryabov, M.A., *Zh. Org. Khim.*, 2006, vol. 42, p. 1674.
2. Fain, V.Ya., Zaitsev, B.E., and Ryabov, M., *Zh. Org. Khim.*, 2006, vol. 42, p. 1479.
3. Fain, V.Ya., Zaitsev, B.E., and Ryabov, M.A., *Zh. Org. Khim.*, 2006, vol. 42, p. 1484.
4. Fain, V.Ya., *9,10-Antrakhinony i ikh primeneniye* (9,10-Anthraquinone and Its Application), Moscow: Izd. Tsentra fotokhimii RAN, 1999, 92 p.
5. Thomson, R.H., *Naturally Occurring Quinones. II*, New York: Academic Press, 1971, 734 p.; *III*, New York: Chapman and Hall, 1987, p. 350.
6. Muzychkina, R.A., *Prirodnye antrakhinony. Biologicheskie svoystva i fiziko-khimicheskie kharakteristiki* (Natural Anthraquinones. Biological Properties and Physicochemical Characteristics), Tolstikov, G.A., Ed., Moscow: Fазis, 1998, 864 p.
7. Ollis, W.D. and Sutherland, I.O., *Recent Developments in the Chemistry of Natural Phenolic Compounds*, Ollis, W.D., Ed., New York: Pergamon, Press, 1961.
8. Fain, V.Ya., *Korrelyatsionnyi analiz elektronnykh spektrov*



- pogloshcheniya* (Correlation Analysis of Electronic Absorption Spectra), Moscow: Kompaniya Sputnik+, 2002, 157 p.
- Dewar, M. J. S., *The Molecular Orbital Theory of Organic Chemistry*, New York: McGraw-Hill, 1969.
  - Nishimoto, K. and Forster, L.S. *Theor. Chim. Acta*, 1966, vol. 4, p. 155.
  - Brockmann, H., Boldt, P., and Niemeyer, J., *Chem. Ber.*, 1963, vol. 96, 1356. Brockmann, H. and Brockmann, H., Jr. *Chem. Ber.*, 1963, vol. 96, p. 1771.
  - Fain, V.Ya., *Tablitsy elektronnykh spektrov pogloshcheniya antrakinona i ego proizvodnykh* (Table of Electronic Absorption Spectra of Anthraquinone and Its Derivatives), Leningrad: Khimiya, 1970, 168 p.
  - Graves, G.D. and Adams, R., *J. Am. Chem. Soc.*, 1923, vol. 45, p. 2439.
  - Yagi, A., Makino, K., and Nishioka, I., *Chem. Pharm. Bull. Tokyo*, 1977, vol. 25, p. 1764.
  - Krohn, K. and Behnke, B., *Chem. Ber.*, 1980, vol. 113, p. 2994.
  - Chandrasenan, K., Neelakantan, S., and Seshadri, T.R., *Proc. Indian. Acad. Sci.*, 1960, vol. 51A, p. 296.
  - Manojlovic, N.T., Solujic, S., Sukdolak, S., and Krstic, L.J., *J. Serb. Chem. Soc.*, 2000, vol. 65, p. 555.
  - Gopolakrishnan, S., Neelakantan, S., and Raman, P.V., *J. Indian Chem. Soc.*, 1990, vol. 67, p. 390.
  - Stensio, K.E. and Wachtmeister, C.A., *Acta Chem. Scand.*, 1969, vol. 23, p. 144.
  - Rao, G.S.R., Hanumaia, T., and Rao, K.V.J., *Indian J. Chem.*, 1980, vol. 19V, p. 97.
  - Birkinshaw, J.H. and Gourlay, R., *Biochim. J.*, 1961, vol. 80, p. 387.
  - Fain, V.Ya., Zaitsev, B.E., and Ryabov, M.A., *Zh. Org. Khim.*, 2005, vol. 41, p. 43.
  - Fain, V.Ya., Zaitsev, B.E., and Ryabov, M.A., *Zh. Org. Khim.*, 2005, vol. 41, p. 722.