https://doi.org/10.1070/RCR5035

Hydrogen bonding-assisted transformations of cyclic chalcones: *E*/*Z*-isomerization, self-association and unusual tautomerism

Bagrat A. Shainyan,[a]* Mark V. Sigalov [b]

[a] *A.E.Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation*
[b] *Department of Chemistry, Ben-Gurion University of the Negev, 84104 Beer-Sheva, Israel*

Condensation of 1- or 2-indanones and 1,3-indandiones with aromatic or heteroaromatic carbaldehydes gives products that demonstrate various transformations and effects of general interest for organic chemistry. In the present review, phenomena such as tautomerism, *E*/*Z*-isomerization, π-conjugation, hydrogen bonding, and homo- and heteroassociation are considered. The relative stability of various isomers of cyclic chalcones is shown to be determined by the intramolecular hydrogen bonding in their molecules and the formation of associates. The same effects also result in the formation of unusual, otherwise unstable tautomers, such as 2*H*-indazoles. The hydrogen bonding-assisted keto-enol and *E*/*Z*-isomerization are analyzed. A novel, specific type of conjugation for the studied compounds was proposed and termed 'roundabout' conjugation.
The bibliography includes 101 references.

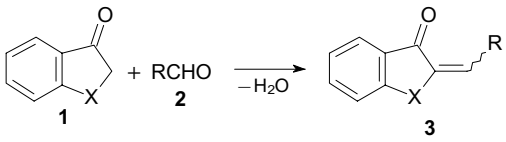
Contents

1. Introduction 1
2. Synthesis 2
2.1. Claisen – Schmidt and Michael reactions of 1,3-indandione 2
2.2. Claisen – Schmidt and Michael reactions of 1-indanone and its analogues 4
3. UV- and solvent-induced hydrogen bonding-assisted *E*/*Z*-isomerization in chalcone derivatives and their analogues 4
4. Effect of self- and heteroassociation 9
5. Unusual tautomerism of indazole derivatives 13
6. Conclusion 15
7. References 15

1. Introduction

Aldol condensation holds one of the central places in synthetic organic chemistry as an efficient way to form carbon – carbon bonds. The reactions of cyclic ketones **1** with aryl- and/or hetarylcarbaldehydes **2** (Scheme 1) are not just a special case of aldol condensation. These reactions are also an easy and convenient route to unsaturated ketones **3**, which are of interest for the investigation and better understanding of fundamental problems of organic chemistry, such as conjugation, tautomerism, *E*/*Z*-isomerization, hydrogen bonding, and intra- and intermolecular association.

Scheme 1



X = C=O (**a**), CH_2 (**b**); R = aryl, 2-pyrrolyl, 2(4)-imidazolyl, 2-pyrazolyl, 3-indazolyl, furyl, thienyl, pyridyl, *etc.*

From the synthetic point of view, the products of condensation **3**, as well as the products of their subsequent transformations, are promising photoswitches,[1] anion sensors,[2] semiconductors and photosemiconductors,[3] precursors for the synthesis of drugs[4] and dyes,[5] reagents for forensic expertise.[6]

With this in mind, the present review is devoted to the systematic analysis of the aforementioned problems, the special emphasis being placed on recent studies, and is addressed to a wide audience of organic chemists, both synthetics and theoreticians, engaged in the chemistry of N-heterocycles, structural chemistry, reactions of condensation of CH-acids, hydrogen bonding, and the processes of tautomerization and isomerization. The advantage of this review is the consideration of all processes and phenomena in interrelation and mutual influence, in contrast to their separate analysis, which is more common in the literature. The only report that discusses some of the issues that have arisen is our recent chapter in the book *A Closer Look at Hydrogen Bonds*.[7]

Currently, the chemistry of chalcones, including their cyclic analogues **3**, is an extensively growing area. Numerous representatives of this class of unsaturated compounds

B.A.Shainyan. Doctor of Science in Chemistry, Professor, Head of the Laboratory at the A.E.Favorsky Irkutsk Institute of Chemistry.
E-mail: bagrat@irioch.irk.ru
Current research interests: organofluorine chemistry, organosilicon chemistry, electronic effects, theoretical organic chemistry, stereochemistry.
M.V.Sigalov. Doctor of Science in Chemistry, Senior Researcher at the Ben-Gurion University of the Negev.
E-mail: msigalov@bgu.ac.il
Current research interests: chemistry of chalcones, heterocyclic compounds, hydrogen bonding, NMR.

Received 29 July 2021

© 2022 Uspekhi Khimii, ZIOC RAS, Russian Academy of Sciences and IOP Publishing Limited

have a vast field of applications in biology and medicine,[8–21] optics,[22,23] ionic liquids,[24,25] and as building blocks in the synthesis of heterocyclic compounds[26] and thermostable polymeric materials.[27–31] The methods of synthesis, structure, characteristic reactions, and physicochemical properties, including supramolecular structure of metal complexes, are summarized in a recent review.[32]

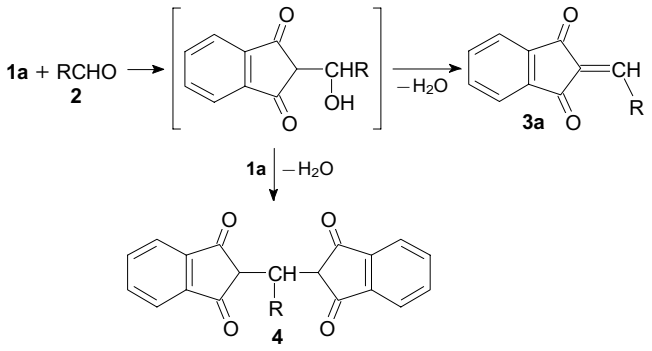
The aldol condensation of cyclic ketones with appropriate aldehydes, which is the main method for the synthesis of compounds **3**, proceeds in the presence of bases or Lewis acids and other miscellaneous catalysts.[32] It is well known that aldol condensation is a stereoselective process leading to products with the *E*-configuration of the double bond for unsymmetrical starting ketones.[33–35]

2. Synthesis

2.1. Claisen–Schmidt and Michael reactions of 1,3-indandione

1,3-Indandione **1a**, a strong CH-acid (pKa ≈ 7.3), easily reacts with aldehydes to give, after dehydration, the corresponding 2-(R-methylidene)-substituted condensation products **3a**. The reaction can also proceed with the formation of Michael products of condensation with two molecules of 1,3-indandione **4** (Scheme 2).

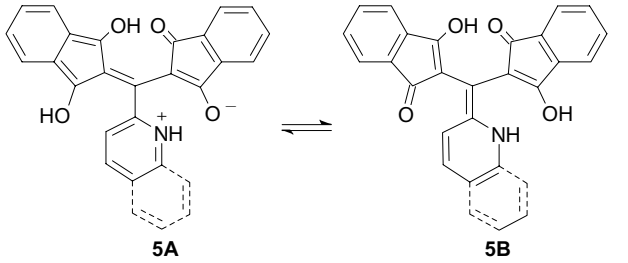
Scheme 2



The reaction course depends both on the structure of reactants and the reaction conditions. It is known that the reactions with aldehydes containing π-excess heterocyclic substituents, such as pyrrole, furan or thiophene, lead to the formation of methylidene-substituted compounds **3a**, while the formation of 1 : 2 condensation products **4** was not reported. Substituted benzaldehydes, depending on the conditions, form either compounds **3a** (under acid catalysis conditions)[36] or **4** (in ethanol or aqueous alkali).[37] However, 4-dimethylaminobenzaldehyde containing the most electron-donating substituent on the benzene ring, regardless of the reaction conditions, gives only product **3a**.[38]

In the case of π-deficient heterocyclic aldehydes, the situation is more complicated. Franz *et al.*[39] reported the synthesis and properties of a large series of various products of condensation of 1,3-indandione with different heteroaromatic aldehydes. For example, under basic catalysis conditions (ethanol solution in the presence of piperidine), 3-pyridinecarbaldehyde reacts with 1,3-indandione to give the product of 1 : 1 condensation **3a**, whereas 4-pyridinecarbaldehyde affords both **3a** and 1 : 2 condensation products **4**.[39] Under the same conditions, 2-pyridinecarbaldehyde also gives the 1 : 2 condensation product **4**. However, in dichloromethane, upon cooling and in the absence of a catalyst, 2-pyridinecarbaldehyde reacts with 1,3-indandione to afford another product, which was assigned the zwitterionic structure **5A** and which, in our opinion, could exist in equilibrium with tautomer **5B** without charge separation (Scheme 3).

Scheme 3

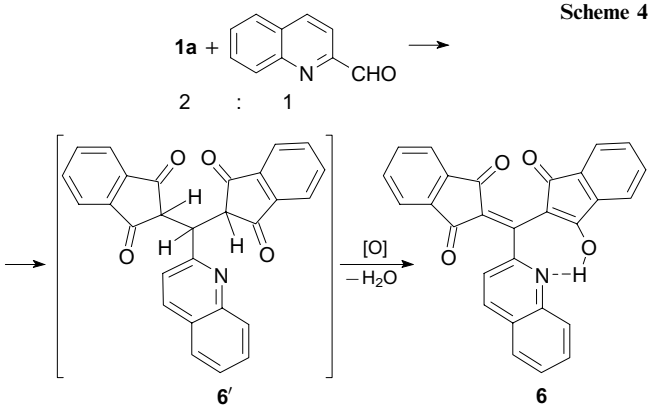


2-Quinolinecarbaldehyde reacts with **1a** in refluxing ethanol in the presence of piperidine as a base to give compound **5A** with the proposed zwitterionic structure similar to the reaction with pyridine. Aldehydes containing more electron-deficient heterocycles (*e.g.*, 3- or 4-pyridazine) give only 1 : 2 condensation products; the product derived from 3-pyridazinecarbaldehyde was also assigned the zwitterionic structure, whereas that based on 4-pyridazine-carbaldehyde underwent dehydration to yield the regular Michael adduct, the structure of which has been confirmed by NMR spectroscopy.[39]

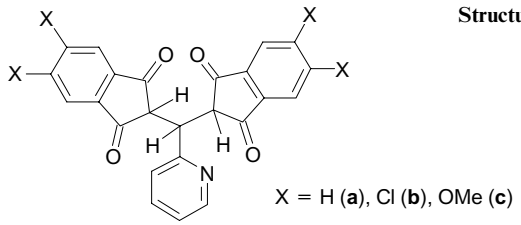
However, the proposed zwitterionic structures of the aforementioned condensation products seem to be erroneous. First, the formation of the depicted zwitterion must be energetically unfavourable as it is accompanied by partial loss of aromaticity of both the indandione and pyridine moieties. Second, and even more importantly, the structure was deduced only from the absence of certain signals in the NMR spectra. Recently, we have shown that, at least in one case, the piperidine-catalyzed reaction of 2-quinolinecarbaldehyde with 1,3-indandione in ethanol produces the product of spontaneous oxidation **6** of the unstable product **7** of dehydration of the Michael 1 : 2 adduct (Scheme 4).[40]

The unsaturated, fully conjugated structure of product **6** can already be determined by its colour (dark red crystals, λ_{max} = 490 nm),[40] which is sharply different from those of previously synthesized close analogues of its saturated precursor **6′**, namely, 2,2-(pyridin-2-ylmethylene)bis[1*H*-indene-1,3(2*H*)-dione] **7a** and 2,2-(pyridin-2-ylmethylene)-

Scheme 4



Structures 7

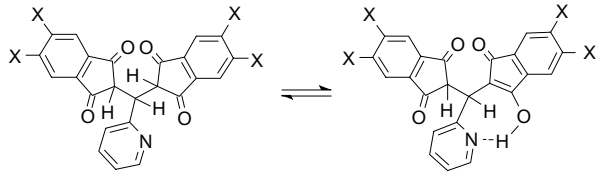


7a–c

bis[5,6-dichloro (or 5,6-dimethoxy)-1*H*-indene-1,3(2*H*)-dione] **7b**,**c**, which are colourless or light yellow.[41]

The unsubstituted compound **7a** exists in equilibrium with its enol form (Scheme 5), as proven by the temperature dependence of its dipole moment, for which the calculated values for the all-keto and enol forms differed significantly (1.44 and 6.13 D).[41] The measured dipole moment decreases with temperature, indicating a reduction in the fraction of the more stable H-bonded enol form. Its content must increase upon cooling, and indeed, the intensity of the corresponding signals in the NMR spectra increases so that no all-keto form can be detected in the spectrum at 200 K. Compound **7b** consists of only the keto-enol tautomer, whereas for tetramethoxy derivative **7c**, the equilibrium is completely shifted towards the all-keto form (see Scheme 5).

Scheme 5



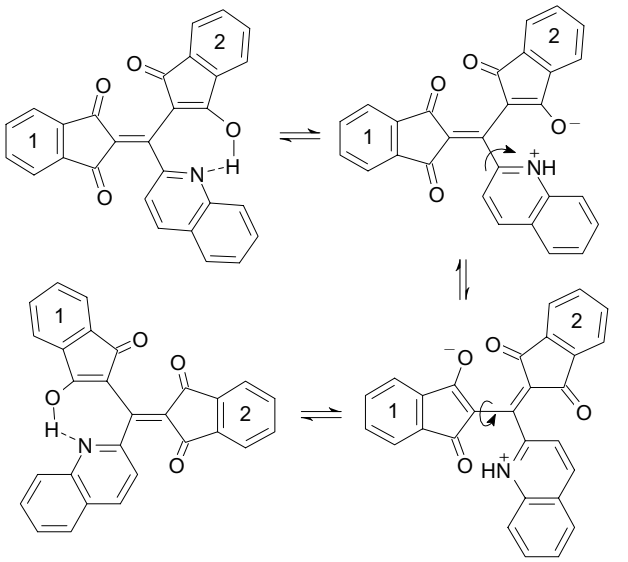
7a–c

Moreover, Franz *et al.*[39] did not observe the signals of labile OH and NH protons in the DMSO solution, in which they are usually clearly visible, and their conclusion on the zwitterionic structure was drawn only from the absence of the CH signals in the ^{1}H and ^{13}C NMR spectra. At the same time, the observed NMR spectra and the elemental analysis data are fully consistent with the structure of the oxidation product **6**.[40] Thus, the room-temperature ^{1}H NMR spectrum of **6**, apart from the signals of aromatic quinoline and indandione protons, shows a broad downfield enolic OH signal at ~16 ppm, which narrows at low temperature (220 K), reflecting the averaging of the signals of aromatic protons due to rotation of two indandione moieties and equilibration of the proton between the oxygen and nitrogen atoms (Scheme 6). The unexpected formation of the oxidation product raises the question of an oxidant. At first glance, it could be air oxygen, but the same product was obtained by carrying out the reaction in an argon atmosphere.[39,40]

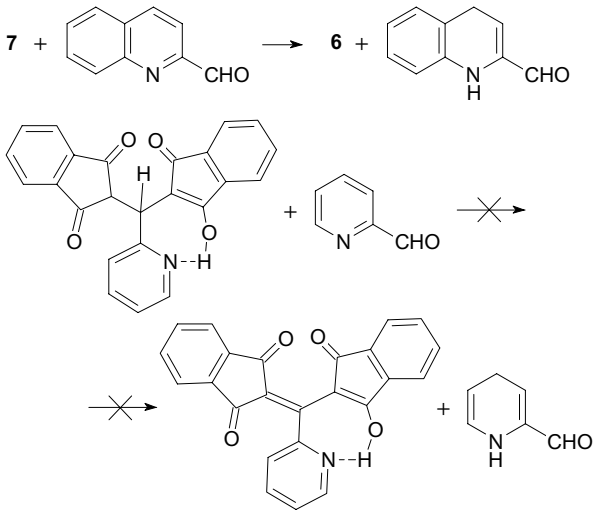
The only remaining possibility is that 2-quinolinecarbaldehyde acts as an oxidant being reduced to 1,4-dihydroquinoline-2-carbaldehyde (Scheme 7). The latter compound, as well as its ring-substituted derivatives, is stable, although capable of oxidation,[42] which makes this assumption reasonable.

Similar oxidation of the 2-pyridyl-substituted product of bis-condensation by 2-pyridinecarbaldehyde yielding

Scheme 6



Scheme 7

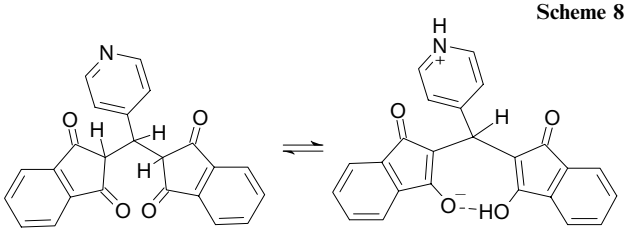


1,4-dihydropyridine-2-carbaldehyde is less likely for the following reasons. The latter product itself is unknown; the only known derivative is 4-oxo-1,4-dihydropyridine-2-carbaldehyde. The loss of aromaticity in the pyridine ring is much more unfavourable than in the case of the quinoline ring due to the retention of aromaticity in the carbocyclic ring in the latter. The additional energy gain results from a more branched conjugation system in quinoline derivative **6**.

In this regard, it is worth considering the behaviour of the 1 : 2 condensation product of 4-pyridinecarbaldehyde, since its structure depends on the solvent. The ^{1}H NMR spectrum in CD_2Cl_2 confirms the all-keto structure of the reaction product,[41] whereas in DMSO-d_6 solution, it exists as a zwitterionic enol tautomer containing a strong intramolecular hydrogen bond and a protonated pyridine moiety (Scheme 8).[39,41]

Its close analogue, the product of the reaction with 4-quinolinecarbaldehyde, exists in a similar zwitterionic form both in the solid state (according to X-ray analysis) and in DMSO-d_6 solution (according to NMR data).[39]

Scheme 8

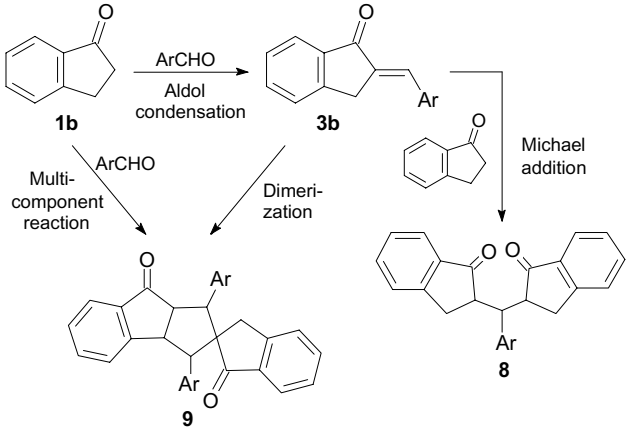


2.2. Claisen–Schmidt and Michael reactions of 1-indanone and its analogues

Although 1-indanone **1b** is less acidic than 1,3-indandione **1a**, it also readily reacts with aldehydes to give the condensation products, which can exist either in the *E*- or *Z*-configuration about the exocyclic double bond. This process can proceed in the presence of bases or Lewis acids as well as other catalysts.[32] Aldol condensation is a stereoselective process leading to products with the *E*-configuration of the double bond.[33–35]

The aldol condensation products **3b** are able to react with the second molecule of **1b**, thereby giving the regular Michael adducts bis(indane-1,5-diketones) **8** and dimerizing to form spiropolycyclic 1,5-diketones **9** (Scheme 9). In some cases, the formation of spirocycles **9** occurs in one step with simultaneous participation of two molecules of each reagent, and this reaction is called a multicomponent reaction.[43,44]

Scheme 9



The main factors that direct the reaction towards the desired products are the solvent, the temperature, and the catalyst used. Thus, Lantaño *et al.*[43] reported a detailed study of the reaction of 1-indanone **1b**, its 5,6-dimethoxy-substituted derivative **10** and 1-tetralone **11** with benzaldehyde, *p*-methoxybenzaldehyde, and 3- and 4-pyridine aldehydes under various reaction conditions. The authors showed that reactions with benzaldehydes proceed under more severe conditions than with pyridine aldehydes. Thus, aldol condensation and the subsequent Michael addition affording 1,5-diketone **8** occur at room temperature for benzaldehyde and 4-methoxybenzaldehyde, while similar reactions with pyridine aldehydes take place upon cooling to 0 °C. Dimerization of arylidene-1-indanone to give spiropolycyclic compound **9** requires reflux for benzaldehydes and room temperature for π-deficient pyridine aldehydes. The highest yields of all products were achieved using a mixture of NaOH–EtOH–H_2O as the reaction medium. 1-Tetralone was less active in these reactions, and regardless of the temperature and reagent ratio, only arylidene-1-tetralone was formed. This fact was explained by the noncoplanarity of the enone part of the 1-tetralone molecule, which reduces the electrophilicity of the C-β atom.[43]

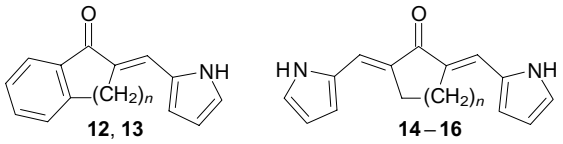
A careful and detailed study of the dimerization reaction was undertaken by Camps *et al.*[44] Using 1-indanone **1b** and its 5,6-dimethoxy derivative **10** and a large number of aldehydes, including 2-, 3-, and 4-pyridinaldehydes as π-deficient aldehydes and 2-phenyl-, 2-furyl-, 2-thienyl- and 2-(*N*-methyl)pyrrolylaldehyde as π-excessive ones, it was shown that electron-donating substituents in both indanone and the aldehyde slow down the reaction. The proposed mechanism of dimerization was based on DFT calculations and included deprotonation of the CH_2 group in the indanone moiety of compound **3b**, the Michael addition of the formed carbanion to the second molecule of **3b** and intramolecular Michael addition in the intermediate.

3. UV- and solvent-induced hydrogen bonding-assisted *E*/*Z*-isomerization in chalcone derivatives and their analogues

The present section is devoted to photoinduced (photoswitchable) hydrogen bonds and their influence on the structure and properties of organic compounds, in particular, their tendency towards *E*/*Z*-isomerization. The focus will be on cyclic chalcones, but some of the most interesting examples of other types of compounds as well as the solvent effect on *E*/*Z*-isomerization will also be considered.

Aldol condensation is a stereoselective process resulting in the formation of products generally containing a double bond in the *E*-configuration.[21–23] The lower stability of the *Z*-isomers was explained by the strong steric repulsion of the aryl group and carbonyl oxygen.[45] An easy $E \rightarrow Z$ isomerization of 2-arylidene cycloalkanones by the action of not only strong UV irradiation but even scattered daylight was demonstrated; the exceptions were 4-Me_2N-arylidene alkanones, which did not undergo isomerization under such conditions.[46] In the first papers on the photoinduced *E*/*Z*-isomerization of 2-arylidene-1-indanones and 1-tetralones, the ^{1}H NMR spectrum of the *Z*-isomer obtained by UV irradiation of the solution of its *E*-counterpart showed a downfield chemical shift of arylidene *ortho*-protons signal.[47,48] This was explained by the anisotropic effect of the carbonyl group; no conclusion on the existence of the C–H···O hydrogen bond was made. It is reasonable to assume that such a hydrogen bond, even if it is formed, is rather weak and cannot outweigh the steric repulsion between the phenyl and carbonyl groups. Stronger hydrogen bonds must be formed by stronger proton donors, such as OH or NH groups, properly oriented with respect to the carbonyl oxygen atom. Based on the expected geometry of the new hydrogen bond formed after $E \rightarrow Z$ isomerization, the most suitable are chalcones with five-membered heterocycles, such as with Ar = 2-pyrrolyl and its diazolyl analogues. Strange as it is, these chalcone-type compounds are almost unknown. To the best of our knowledge, there are only two papers that reported 2-pyrrolylidene-1-tetralone[18] and bis(2-pyrrolylidene)-substituted cyclopentanone and cyclohexanone,[49] and no structural information was given for any of them. Recently, we have synthesized the 2-pyrrolylidene deriva-

Structures 12 – 16

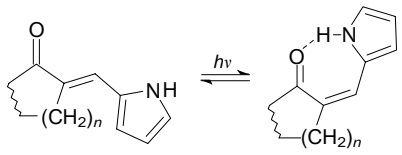


n = 1 (**12**, **14**), 2 (**13**, **15**), 3 (**16**)

tives of 1-indanone and 1-tetralone **12**, **13** and bis-(2-pyrrolylidene) cycloalkanones **14** – **16**.[50]

Compounds **12** and **13** were isolated as *E*-isomers, and compounds **14** and **15** were isolated as *E*,*E*-isomers (the case of **16** was more complicated). UV irradiation of solutions of the *E*- and *E*,*E*-isomers results in the formation of the *Z*-isomers for **12**, **13** and *Z*,*E*- and *Z*,*Z*-isomers for **14**, **15** (Scheme 10, the last compound was formed as a minor component in the mixture).

Scheme 10



The main spectral features allowing the assignment of *E*- and *Z*-moieties of compounds **12** – **15** are a downfield shift of the NH proton by 3.0 – 3.5 ppm, indicating the existence of a strong intramolecular hydrogen bond, and a high-field shift of ~1 ppm of the olefin proton due to its removal from the anisotropic effect of the carbonyl group in the *Z*-isomers.

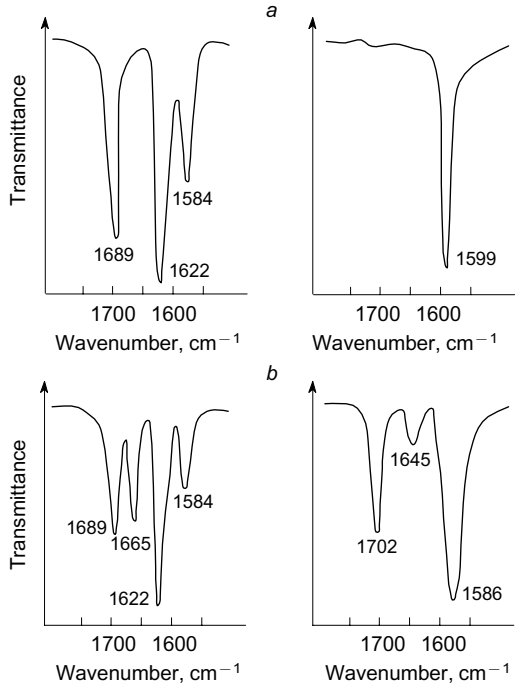


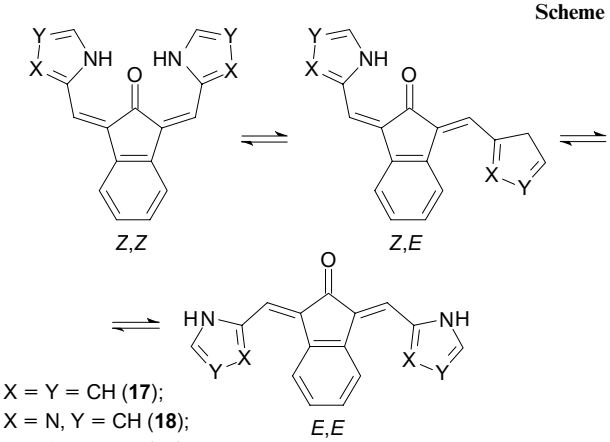
Figure 1. IR spectra of the solutions of compounds **12** (left) and **15** (right) in CH_2Cl_2 in the region 1800 – 1500 cm^{-1} before (*a*) and after UV irradiation (*b*). The figure was prepared by the authors using the data from the study.[51]

UV-induced *E*/*Z*-isomerization also causes clearly visible changes in the IR spectra, as shown in Fig. 1 for compounds **12** and **15**. After UV irradiation of **12**, along with the bands belonging to the *E*-isomer, an intense band at 1665 cm^{-1} appears with a frequency lower than that of $\nu(C{=}O)_{ass}$ in the spectrum of the solid compound (1674 cm^{-1}), indicating the formation of the H-bonded *Z*-isomer.[51] For compound **15**, the formation of the *Z*,*E*-isomer after UV irradiation is proved by a small low-frequency shift of the $\nu(C{=}O)$ band from 1599 to 1586 cm^{-1} and the appearance of the $\nu(C{=}O)_{free}$ band at 1702 cm^{-1} (see Fig. 1). A low-intensity band at 1645 cm^{-1} belongs to the intramolecularly H-bonded structural motif.[51]

Keeping the irradiated solutions in the dark leads to a quantitative recovery of the starting *E*- or *E*,*E*-isomers (*vide infra*).

In a series of bis(azolylmethylidene)-2-indanone derivatives **17** – **19**, a great variety of isomeric forms with respect to the exocyclic double bond(s) as well as their tautomers and rotamers differing by the position of the NH group in the ring was demonstrated (Scheme 11).[51]

Scheme 11



X = Y = CH (**17**);
X = N, Y = CH (**18**);
X = CH, Y = N (**19**)

The stability of *Z*,*Z*-, *Z*,*E*- and *E*,*E*-isomers strongly depends on the type of heterocycle and the solvent. The increase in the number of nitrogen atoms when moving from **17** to **19** results in a higher stability of the *Z*,*E*- and *E*,*E*-isomers. The existence and relative content of specific isomers of compounds **17** – **19** were studied by ^{1}H NMR and IR spectroscopy in various media.[51] Bis-pyrrolylidene derivative **17** exists exclusively in the *Z*,*Z*-form, both in nonpolar and highly polar solvents, due to the presence of two strong intramolecular hydrogen bonds N – H···O and the absence of factors stabilizing other isomers. In a basic medium (DMSO), the formation of an intermolecular hydrogen bond of the pyrrolic NH proton with the solvent molecule does not outweigh the strength of the intramolecular hydrogen bond. In the case of compounds **18** and **19**, the additional stabilization arises from the formation of an intramolecular C – H···N hydrogen bond between the pyridinic nitrogen of azole rings and one or two aromatic protons; in polar basic media, the formation of a stabilizing intermolecular hydrogen bond with the solvent molecule acts in the same direction. In polar media, the behaviour of compound **18** strongly differs from that of **17**. The ^{1}H NMR spectrum of **18** in DMSO proves the presence of two species in the ratio of 2.5 : 1, the major isomer being *Z*,*Z*-**18**. On

Table 1. The relative energies (kcal mol^{-1}) of the isomers of compounds **18** and **19** and their solvate complexes with DMSO in the gas phase and in solution.[51]

Isomer	Isolated molecules	PCM	DMSO-PCM	2DMSO-PCM
18-*Z*,*Z*	0.0	0.0	5.6	2.3
18-*Z*,*E*	4.4	2.6	0.0	0.6
18-*E*,*E*	10.5	6.2	7.3	0.0
19-*Z*,*Z*	0.0	0.0	3.3	5.1
19-*Z*,*E*	5.3	2.4	0.0	1.9
19-*E*,*E*	13.2	6.0	4.0	0.0

standing, the ratio inverts, and the major isomer becomes *Z*,*E*-**18** with a C–H···N hydrogen bond between the *o*-proton of the aromatic ring and the imidazole nitrogen atom. The ^{1}H NMR spectrum of **19** in $CDCl_3$ is similar to that of **18** in DMSO and proves the presence of *Z*,*Z*-**18** and *Z*,*E*-**18** in the ratio of 3 : 1. In more polar CD_2Cl_2, the latter isomer predominates.

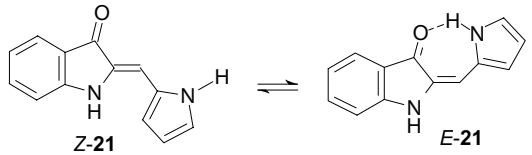
The order of the theoretically calculated relative stability (kcal mol^{-1}) of the isomers of pyrrolyl derivative **17** remains the same (*Z*,*Z* < *Z*,*E* < *E*,*E*) for the isolated molecules in gas phase and in a polar solvent (PCM, polarizable continuum model) as well as for their complexes with DMSO. However, for the isomeric imidazolyl derivatives **18** and **19**, it is dramatically changed (Table 1).[51]

For the isolated molecules in both the gas phase and in solution, the most stable isomer is *Z*,*Z*; for the 1 : 1 complexes with DMSO, it is *Z*,*E*; and for the 1 : 2 complexes, it is *E*,*E*.

(2*E*,6*E*)-2,6-Bis((1*H*-pyrrol-2-yl)methylene)cyclohexan-1-one **20** was obtained *via* a slightly modified procedure described in our work [50] by *Claisen–Schmidt* condensation (see Scheme 2) and studied both experimentally and theoretically.[52] It was observed that the *E*,*Z*-isomer formed almost quantitatively under UV irradiation (Scheme 12) and did not undergo photopolymerization. However, in the presence of triethanolamine, which forms a hydrogen-bonded complex with the **20**-*E*,*E*-isomer and thereby prevents $E \rightarrow Z$ isomerization, the carbonyl oxygen becomes able to abstract a proton from triethanolamine, allowing polymerization accompanied by the bleaching of the solution to occur.

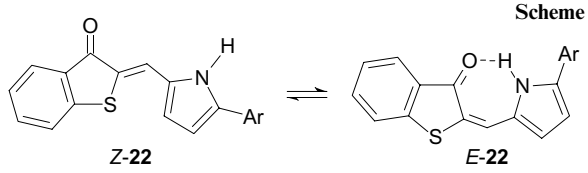
Close structural analogues of compounds **3** (see Scheme 1) with X = NH or S — hemi-indigo (hemi-thioindigo) derivatives, having intramolecular hydrogen bonds in one of the two isomers (*E* or *Z*), have attracted great attention in recent years as photoswitches applicable for practical use.[53–57] Thus, 2-(1*H*-pyrrol-2-yl-methylene)-1,2-dihydro-3*H*-indol-3-ones **21** was found to undergo *E*/*Z*-isomerization, the equilibrium being shifted to the *E*-isomer stabilized by the intramolecular N–H···O hydrogen bond (Scheme 13).[53–55] Theoretically calculated electronic spectra showed a 40–50 nm bathochromic shift of the absorption maximum of the *E*-isomer with respect to that of the *Z*-isomer,[56] which is in excellent agreement with the experimental value (524 *vs* 470 nm in benzene),[55] due to the extended π-system of conjugation (see also Scheme 18 below).

Scheme 13



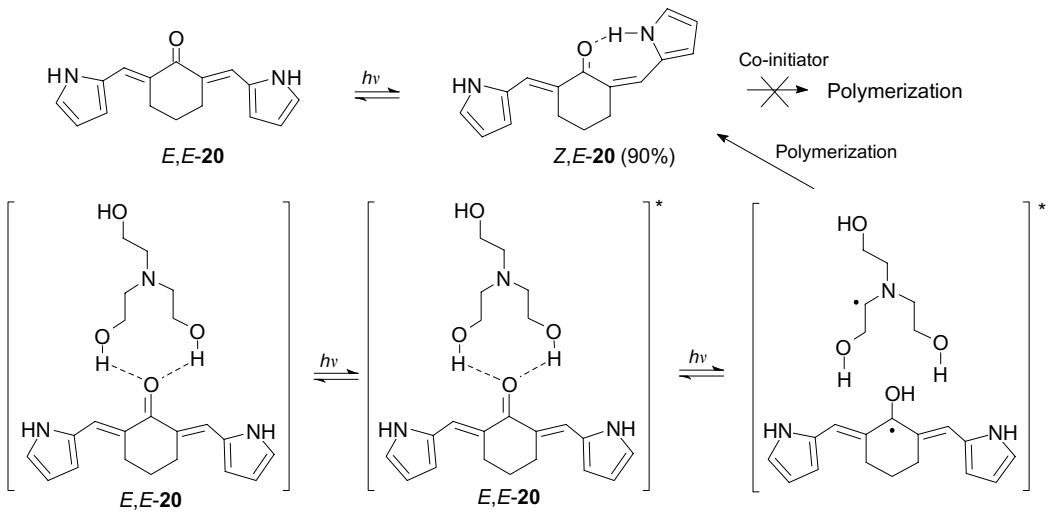
The 2-pyrrolyl hemi-thioindigo derivatives **22** (Scheme 14), very close analogues of compounds **21** bearing aryl or 2-pyrrolyl moieties at the exocyclic double bond, have also been recently studied as photoswitches stabilized in the *E*-configuration by the N–H···O intramolecular hydrogen bond.[57, 58]

Scheme 14



The ease of *E*/*Z*-isomerization (and, hence, the efficiency of photoswitching) strongly depends on the relative positions of the absorption band maxima between the two isomers — the larger the difference, the stronger the equilibrium is shifted towards the *E*-isomer.[57] In turn, the

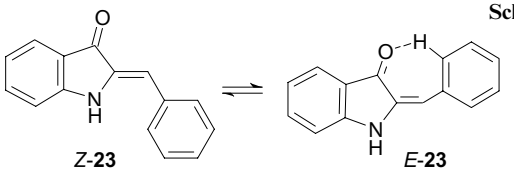
Scheme 12



wavelength gap between the two isomers depends on the substituent in the benzene ring and is maximal (>70 nm) for electron-donating groups and/or in the presence of the second aryl group in the pyrrole ring.

For hemi-indigo derivative **23** differing from compound **21** by the substituent at the terminal carbon of the exocyclic C=C bond, fluorescence (spin-allowed transition from the excited to ground state) was studied by femtosecond absorption spectroscopy in dioxane and methanol.[59] Distinct from the related pyrrolyl derivative **21** in Scheme 13, only a weak C–H···O intramolecular hydrogen bond is possible in the *E*-isomer of compound **23** (Scheme 15).

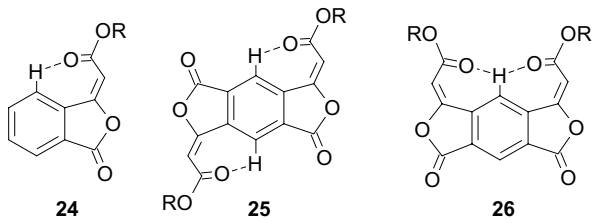
Scheme 15



In methanol, this weak H-bond is broken due to solute–solvent interactions so that fluorescence in methanol is pale and photoisomerization is ineffective, whereas in dioxane, it is bright.[59]

In an earlier work,[60] the existence of the intermolecular C_{Ar}–H···O=C hydrogen bond for a series of isobenzofuranone derivatives **24**–**26** was confirmed by X-ray analysis, NMR spectroscopy and theoretical calculations. The energy of the H-bond in **24**–**26** was estimated to be ~4 kcal mol^{-1}.

Structures 24–26

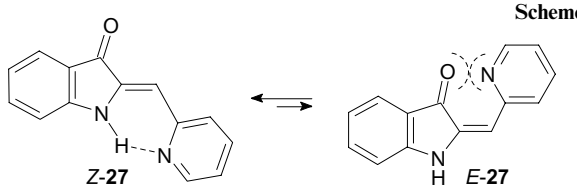


Later, the NMR, geometric and topological characteristics of the derivatives of compound **24** substituted in the benzene ring were calculated, and their ^{1}H and ^{13}C NMR spectra were measured.[61]

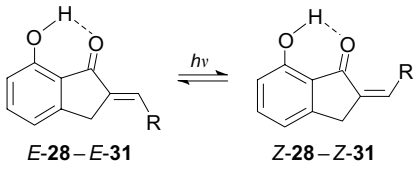
Unlike in the above 2-pyrrolyl derivatives, in the 2-pyridylmethylidene-3-indolinone **27**, the equilibrium between the *E*- and *Z*-isomers is strongly shifted towards the latter form, both because of the presence of the N–H···N intramolecular hydrogen bond in it and due to repulsive interaction of the oxygen and nitrogen lone electron pairs destabilizing the *E*-isomer (Scheme 16).[62]

Recently, we described a rare case of photoinduced bifurcated hydrogen bond formation.[63] The studied compounds included 7-hydroxy-2,3-dihydro-1*H*-inden-1-ones

Scheme 16



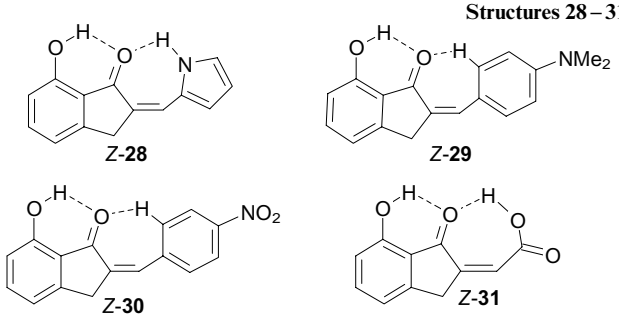
Scheme 17



28–**31** having different substituents R at the exocyclic double bond (Scheme 17). The 7-hydroxy group forms an intramolecular O–H···O hydrogen bond with the indanone carbonyl group, whereas the R group is capable of UV-induced *E*,*Z*-isomerization.

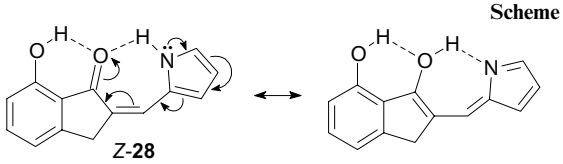
After UV irradiation, in the *Z*-configuration, isomers *Z*-**28**–*Z*-**31** form different types of bifurcated hydrogen bonds: O–H···O···H–N (compound *Z*-**28**), O–H···O···H–C (*Z*-**29**, *Z*-**30**), and O–H···O···H–O (*Z*-**31**).

Structures 28–31



The analysis of the hydrogen bond lengths of the *Z*- and *E*-isomers of compounds **28**–**31** revealed an interesting and unprecedented shortening of the intramolecular O–H···O=C hydrogen bonds in going from the *E*-isomers, in which it is two-centered, to the *Z*-isomers, in which it becomes bifurcated.[63] According to the existing notions, dissipation of the hydrogen bond accepting ability of the carbonyl group to two hydrogen bond donating centers in the *Z*-isomers must weaken, thus resulting in the elongation of the already existing hydrogen bond involving the phenolic hydroxy group.[64] Instead, according to MP2 calculations, it is shortened by 0.021–0.065 Å and strengthened by 0.5–0.7 kcal mol^{-1}. Theoretical results were confirmed by the NMR experiment: in the ^{1}H NMR spectrum of the *E*-isomer of compound **24**, the signals of the NH and phenolic OH groups appear at 8.68 and 9.40 ppm, whereas in that of the *Z* isomer, both signals are shifted downfield to 13.10 and 9.67 ppm, respectively.[63] The downfield shift of the phenolic hydroxyl from 9.40 to 9.67 ppm by 0.27 ppm unequivocally proves the strengthening of the O–H···O=C hydrogen bond upon bifurcation. A similar behaviour was observed for the OH signal in the spectra of the aryl derivatives **29**, **30**. This unusual behaviour was explained by the effect which we referred to as the 'roundabout conjugation' and which can be illustrated by Scheme 19.

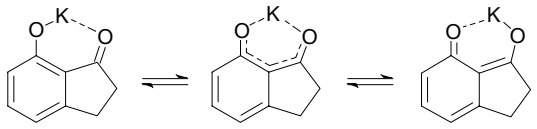
Scheme 19



The depicted conjugation must result in some equalization of the C–C and C=C bond lengths in the –CH=C–C=O motif, and indeed, the difference in the bond lengths reduces in going from *E*- to *Z*-isomers, with the maximum (0.03 Å) for compound **28** and the minimum (~0.0 Å) for compound **30** having a very weak O···H–C_{Ar} hydrogen bond.[63]

The concept of 'roundabout conjugation' was also supported by an interesting synthetic observation:[63] during the synthesis of compounds **28**–**31**, it was shown that the starting 7-hydroxy-1-indanone does not enter the *Claisen–Schmidt* condensation with aldehydes in the presence of KOH but, instead, gives a salt, potassium 3-oxo-2,3-dihydro-1*H*-inden-4-olate **32** (Scheme 20).[65] The phenolate form is evidently more aromatic and must predominate over the quinoid form; indeed, both the calculations and the X-ray diffraction study revealed the chelate structure of salt **32** with a somewhat shorter ArO···K bond.[65]

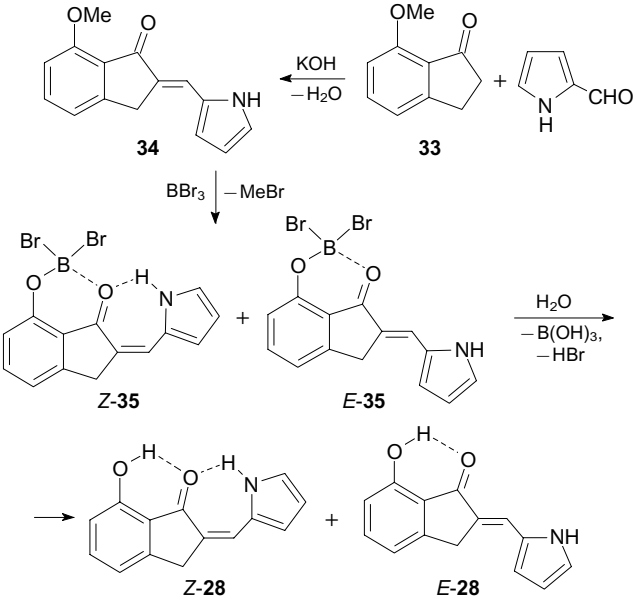
Scheme 20



32

For compounds **29**–**31**, the inertness of 7-hydroxy-1-indanone under alkaline conditions was circumvented by using acidic catalysis, but in view of the sensitivity of the pyrrolic fragment to acids, the method turned out to be impractical for the synthesis of **28**, resulting in strong resinification and only 5–8% yield of the target product.[65] Therefore, compound **28** was obtained from the *O*-protected reagent 7-methoxy-1-indan-one **33** by its condensation with 1*H*-pyrrole-2-carbaldehyde under basic conditions with subsequent deprotection of intermediate **34** with BBr_3 for the removal of the protecting methyl group (Scheme 21).[63] Compound **28** isolated by this procedure represented a mixture of the *Z*- and *E*-isomers in the 5 : 1 ratio, distinct from its analogues **29**–**31**, which are formed exclusively as the *E*-isomers.[63] The observed difference in the isomeric composition was assigned to the different stability of the isomeric reactive complexes **35** with BBr_3 at the demethylation stage.

Scheme 21

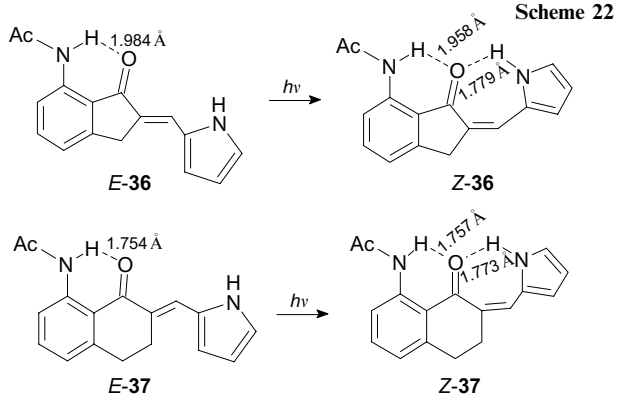


34 **33** ***Z*-35** ***E*-35** ***Z*-28** ***E*-28**

According to calculations, *Z*-**35** is more stable than *E*-**35**, and the extent of roundabout conjugation is also higher for the *Z*-isomer. Both of these factors are responsible for the predominance of *Z*-**35**, which is retained at the stage of hydrolytic decomposition of the complex.

In this regard, an intriguing question arises: is it a common rule that two components of a bifurcated hydrogen bond would demonstrate such a synergistic effect, that is, strengthen each other? Considering the dimers formed by *E*-isomers of compound **30**, it was concluded that either strengthening or conventional weakening may occur depending on the structure of the dimer (see Section 4).[66] Moreover, when studying the *E*/*Z*-isomerization in *peri*-acetamido-substituted analogues of compound **28**, *N*-[3-oxo-2-(1*H*-pyrrol-2-ylmethylene)-2,3-dihydro-1*H*-inden-4-yl]acetamide **36** and *N*-[8-oxo-7-(1*H*-pyrrol-2-ylmethylene)-5,6,7,8-tetrahydronaphthalen-1-yl]acetamide **37**, we found that the *Z*-isomer of compound **36** does show the same changes in the lengths of the intramolecular components of the bifurcated hydrogen bond as in **28**, whereas its homolog **37**, having a stronger intermolecular AcNH···O=C hydrogen bond, does not (Scheme 22).[67] This allowed us to conclude that the strengthening of one component of the bifurcated H-bond upon the formation of another component is more probable for weaker hydrogen bonds than for stronger ones.

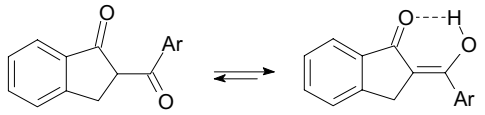
Scheme 22



***E*-36** ***Z*-36** ***E*-37** ***Z*-37**

Hydrogen-bond-assisted *E*/*Z*-isomerization can not only stabilize the corresponding isomer but also lead to otherwise unstable structures. Thus, in a very recent work,[68] investigation of hydroxy-substituted cyclic chalcone derivatives **38** showed the formation and even predominance of the enol tautomer (Scheme 23). Integration of the corresponding signals in the ^{1}H NMR spectrum in $CDCl_3$ solution gave a ratio of 34 : 66 in favour of the enol tautomer.

Scheme 23



keto-**38** (34%) enol-**38** (66%)

Ar = C_6H_4-4-NMe_2

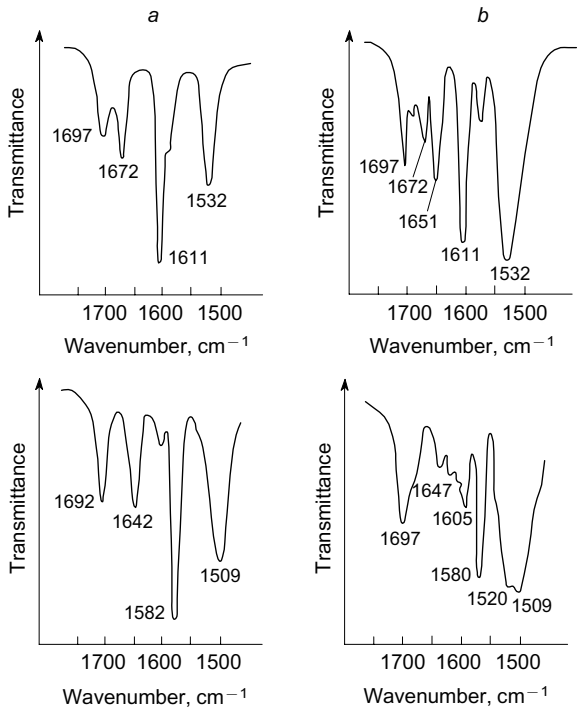


Figure 2. FT-IR spectra of compounds **36** (top) and **37** (bottom) in CH_2Cl_2 before (*a*) and after 10 min of UV irradiation (*b*). The figures were prepared by the authors using the data from the study.[67]

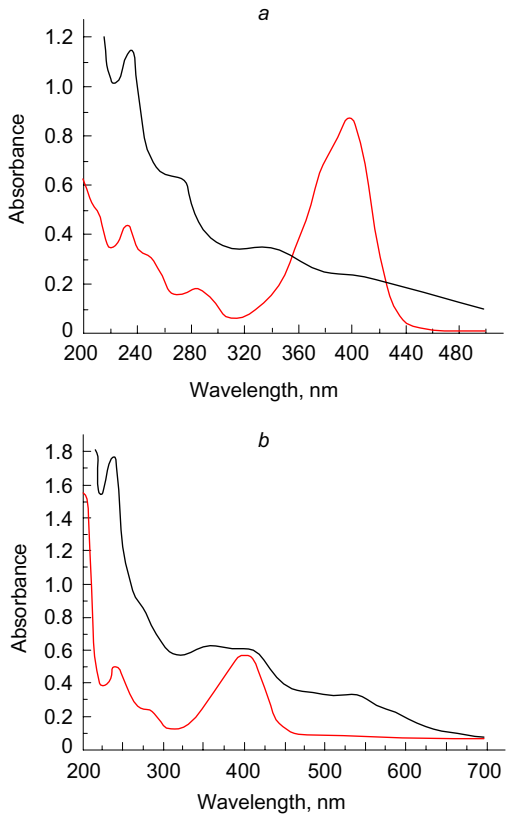


Figure 3. UV-VIS spectra of compounds **36** (*a*) and **37** (*b*) in MeCN before (red) and after UV irradiation (black). The figure was prepared by the authors using the data from the study.[67]

The formation of the *Z*-isomer of compound **36** is also proved by the decrease in the intensity of the ν(C=O) band at 1672 cm^{-1} and the appearance of a new band at 1651 cm^{-1} in the IR spectrum after UV irradiation. The measured difference $\Delta\nu$(C=O) of 21 cm^{-1} between *E*-**36** and *Z*-**36** isomers nicely coincides with the calculated value of 19 cm^{-1} (Fig. 2).

Changes in the IR spectra of compound **37** observed upon UV irradiation of its solution (Fig. 3) are similar to those observed for compound **36**. The more pronounced decrease in the frequency of the *Z*-isomer *vs* *E* in **37** compared to that in **36** is consistent with the stronger NH···O=C H-bond in the former.[67]

The UV-VIS spectra of compounds **36** and **37** before and after 40 min of UV irradiation are shown in Fig. 3. The intensity of the longwave bands of the *E*-isomers decreases after irradiation, and the solutions turn reddish-brown (**36**) or red (**37**). After staying for a day, the solutions turn pale yellow, and the spectra become identical to those of the starting solutions, indicating the reversibility of the *E*/*Z*-isomerization.

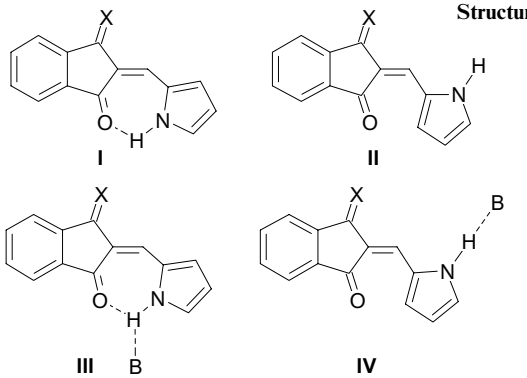
The length of the C=O···H−O hydrogen bond as measured in the crystal, in which the enol form is the only structure, is ~1.8 Å. The keto-enol equilibrium is solvent- and temperature-dependent. The keto form amounts to 6, 13 and 49% in acetone, MeOH and DMSO, respectively, and with increasing temperature, its content increases due to the larger number of degrees of freedom.[68]

4. Effect of self- and heteroassociation

The predominance of one form in an equilibrium mixture of several isomers, conformers, or tautomers is usually analyzed theoretically by comparing their relative total or free energies. More rarely, different models of solvation, specific or nonspecific, are used that can change or even invert the ratio of the equilibrating species of different polarity in polar, strongly acidic or strongly basic solvents. Strange as it might seem, there are almost no examples of the effect of self-association on the relative stability of the equilibrating species, although most compounds exist in solution in the form of associated rather than monomeric molecules.

Depending on the basicity and polarity of the solvent, the formation of its H-bonded complexes with the solute may successfully compete with self-association. Thus, 2-(pyrrol-2-ylmethylene)-1,3-indandione **39** and 2-(pyrrol-2-ylmethylene)-3-dicyanomethylidene-1-indanone **40** form strong intramolecular hydrogen bonds in the properly oriented 'inward' rotamer (**I**) and have a free NH group in

Structures 39, 40



X = O (**39**), $C(CN)_2$ (**40**); B is acetone, DMSO, pyridine

the 'outward' rotamer (**II**).[69] The energy difference (B3LYP/6-311G**) between the 'inward' and 'outward' rotamers is 8.09 (X = O) and 7.42 kcal mol^{-1} (X = C(CN)$_2$), respectively, in favour of the former. Strong bases, such as acetone, DMSO or pyridine, form intermolecular H-bonded associates with both rotamers having a bifurcated (**III**) or a two-centered H-bond (**IV**).

The intramolecular component of the bifurcated H-bond in the 'inward' rotamer **III** remains much stronger than the intermolecular H-bond with the external base, but in the 'outward' rotamer, the intermolecular H-bond becomes comparable in length, so the energy difference ΔE between the solvated rotamers **III** and **IV** decreases to 3.05, 2.93 and 2.05 kcal mol^{-1} for the solvates of compound **39** with acetone, DMSO and pyridine and down to 0.71, 0.71 and 0.11 kcal mol^{-1} for compound **40** in the same order of solvents (though still in favour of the 'inward' rotamer). The presence of two solvate complexes of compounds **39** and **40** in solution was confirmed by the appearance of two downfield NH signals in the range of 11.2–13.5 ppm in these solvents. IR analysis showed that the $\nu_{C=O}$ bands for **39** and **40** have the same frequencies in the crystal and in CCl_4 solution, which implies that they do not form self-associates either in the crystal or in the solution.[69]

The *E*-configuration of compounds **12** and **13** was confirmed by an X-ray study.[50] In the crystal, dimers are formed due to intermolecular hydrogen bonds NH···O=C of the same length (Fig. 4).

The dimeric structures are also preserved in solution. The formation of H-bonded associates of compound **12** in $CDCl_3$ solution, which is similar to its dimer in the crystal, has been proven by a high-field shift of the NH and vinylic CH signals by 0.50 and 0.11 ppm, respectively, in the ^{1}H NMR spectrum upon dilution (Fig. 5). Taking into account that for the monomers, the signal of the H-nonbonded NH group must appear in a higher field, the observed changes unequivocally prove the dissociation of the dimers leading to the fast averaging of the signals of dimers and monomers in equilibrium on the NMR timescale.

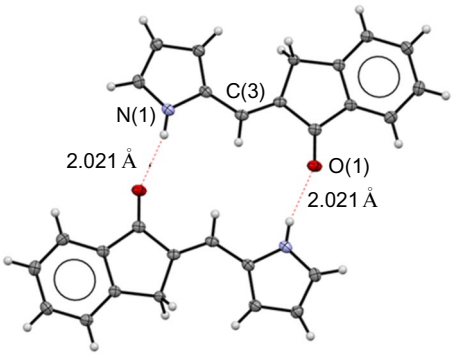
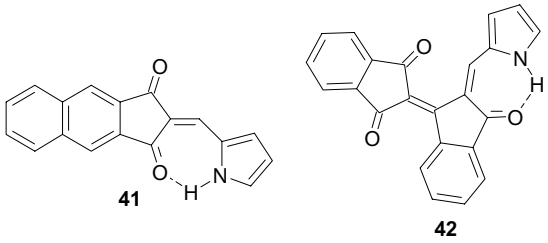


Figure 4. Molecular structure of the cyclic dimer of compound **12**. A similar structure was determined for compound **13**, with NH···O=C bond lengths of 1.971 Å. The figure was prepared by the authors using the data from the study.[50]

Structures 41, 42



The ability of pyrrolyl derivatives **39** and **40** and their analogues **41** and **42** to form intra- and intermolecular hydrogen bonds with various acceptors makes them potential sensors for anions.[70] Pyrrole-based anion receptors attract great interest; most of the known anion receptors have pyrrolyl groups in their molecules.[71–78]

The anion-sensing properties towards most anions are determined by hydrogen bonding or, in the case of strongly basic anions such as fluoride, by the ability to deprotonate the NH pyrrolic group. The push-pull compounds **39**–**42** containing a pyrrole ring as a donor and the 1,3-indandione-derived moieties as an acceptor unit are characterized

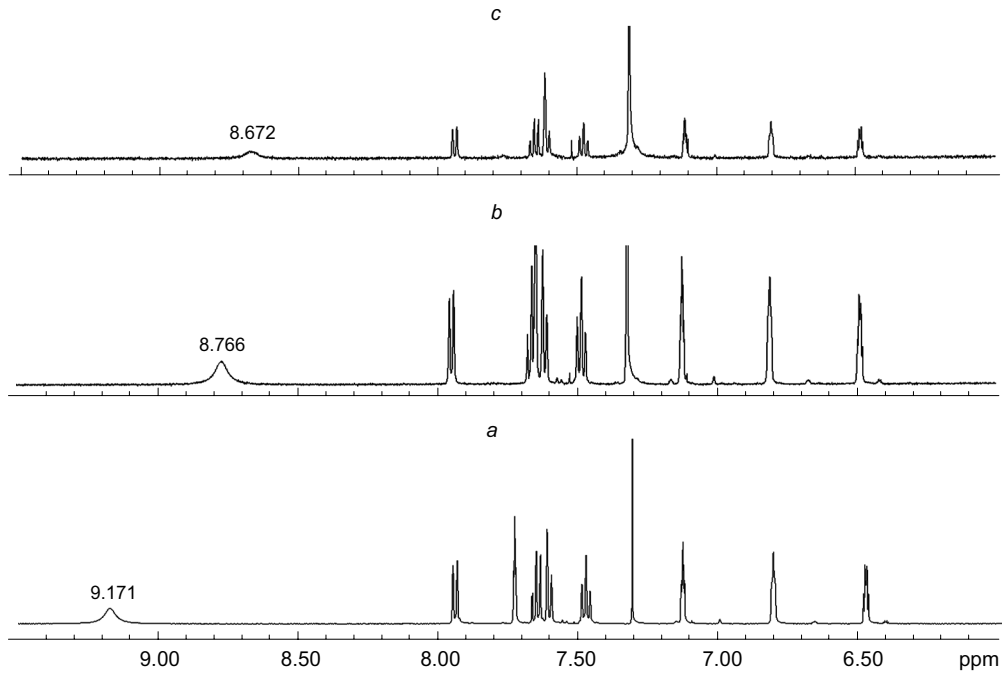


Figure 5. 1H NMR spectra of compound **12** in $CDCl_3$: saturated solution (*a*), 3-fold dilution (*b*), 10-fold dilution (*c*). The figure is reproduced from Sigalov *et al.*[50] with the permission of the American Chemical Society.

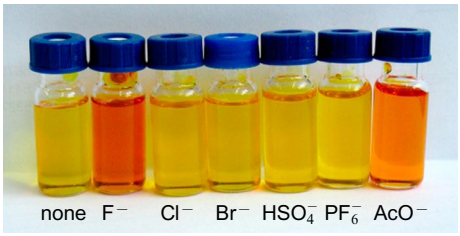


Figure 6. Solutions of compound **41** in DMSO in the presence of 10 equiv. of various anions. The figure is reproduced from Sigalov *et al.*[70] with the permission of the American Chemical Society.

by the presence of strong intramolecular hydrogen bonds in their molecules.[70] In the presence of fluoride and acetate anions, their solutions change colour (Fig. 6).

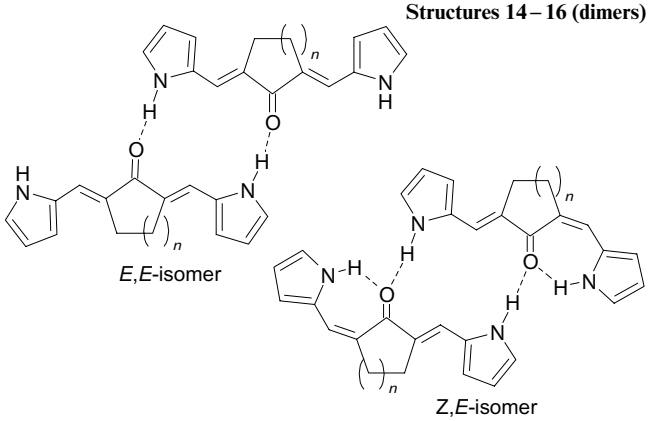
NMR and UV spectroscopic studies, as well as theoretical calculations including the atoms-in-molecules (AIM) analysis showed that compounds **39**–**42** undergo solvent-assisted rupture of the intramolecular hydrogen bond followed by the formation of a strong intermolecular hydrogen bond with acetate and fluoride anions; in the last case, the proton is abstracted from the pyrrole ring to give bifluoride anion HF_2^-. Therefore, the studied compounds can be considered as fluoride and acetate sensors. Their insensitivity to other anions (see Fig. 6) is due to the low stability of the corresponding H-bonded solute–solvent complexes.

Although the solvation of compounds **39** and **40** only reduces the relative stability of the isolated isomers, a stability inversion can also be observed. Thus, the relative stability of compounds **14**–**16** expectedly increases in the order *E*,*E* < *E*,*Z* < *Z*,*Z*, as determined by the number of intramolecular hydrogen bonds. However, the condensation products have the *E*,*E*-configuration and isomerize into the *E*,*Z*- and *Z*,*Z*-isomers only under the action of UV irradiation. This apparent contradiction between the experiment and theory was explained by the association of the monomeric species containing strong basic and acidic centers in the molecule, as in their analogues containing one 2-pyrrolylmethylidene moiety. Calculations of dimers of different isomers in the gas phase and in a polar medium (DMSO) confirmed this conclusion.[50]

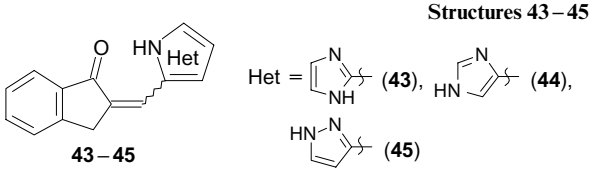
A similar situation occurred for the *Z*- and *E*-isomers of 2-(1*H*-diazol-2-ylmethylene)indane-1-ones **43**–**45**.[79]

Depending on the diazolyl moiety, the NH···O H-bonded *Z*-isomers are 1.6–3.2 kcal mol^{-1} lower in energy than the corresponding most stable rotamers and

Structures 14–16 (dimers)

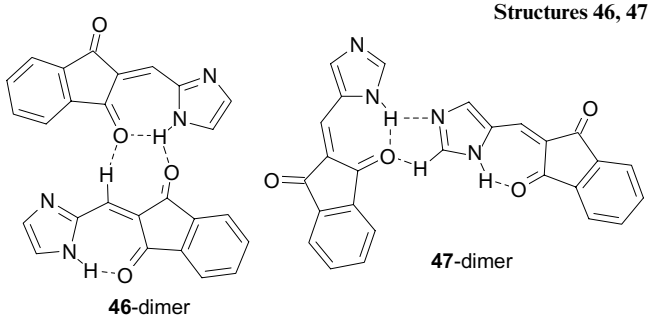


Structures 43–45



tautomers of the *E*-isomers. Similar to the above, the apparent inconsistency with the formation of *E*-isomers in the synthesis is explained by the formation of more stable associates (*E*,*E*-dimers) from less stable monomers. The possibility of the formation of such dimers has been proven by X-ray diffraction analysis of 2-(1*H*-diazol-2-ylmethylene)-1*H*-indene-1,3(2*H*)-diones **46** and **47** as close analogues of compounds **43** and **44**. The calculated geometries are in excellent agreement with those determined by X-ray study. Note that the dimers are produced in different ways, with the formation of intermolecular hydrogen bonds N–H···O or N–H···$N_{pyridinic}$.

Structures 46, 47

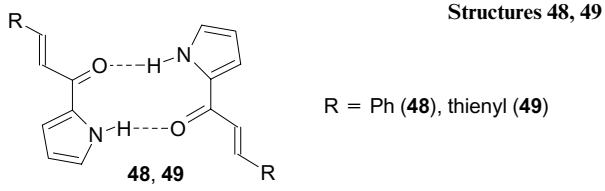


The IR analysis of solid samples and various solutions made it possible to draw a conclusion about the supramolecular structure of the studied compounds **43**–**47**. In the solid state, compounds **43**–**45** form associates with monomeric units linked by N–H···N hydrogen bonds. In CCl_4, $CHCl_3$ and CH_2Cl_2 solutions, compounds **46** and **47** exist in equilibrium between monomers and dimers having NH···O=C bifurcated hydrogen bonds, as well as higher associates.

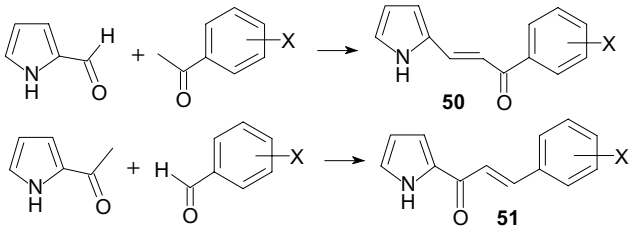
To assess the strength of self-associates of (*E*)-1-(1*H*-pyrrol-2-yl)-3-(thiophen-2-yl)prop-2-en-1-one **48** and (*E*)-3-phenyl-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one **49**, the solubility in different media and melting points were compared to those for *trans*-chalcone Ph–C(O)–CH=CH–Ph. The structures of symmetrical dimers **48** and **49** closed by the intermolecular H-bonds N–H···O=C were confirmed by X-ray structural analysis.[80]

A higher melting point for compound **49** allowed the authors to assume the presence of another type of intermolecular interaction in this compound, which was shown to be t-stacked interactions, including the π-system of the thienyl ring.[80]

Structures 48, 49



Scheme 24

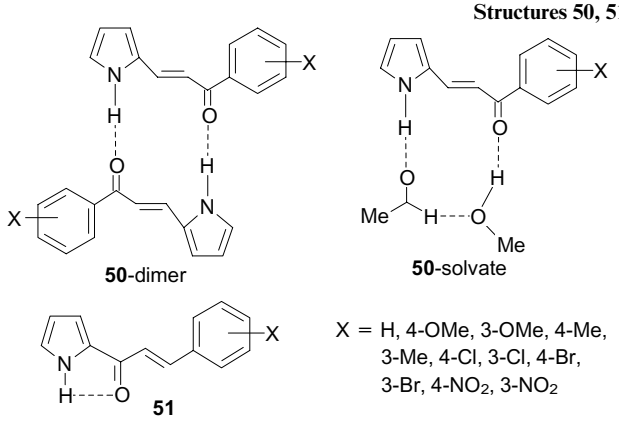


X = H, 4-OMe, 3-OMe, 4-Me, 3-Me, 4-Cl, 3-Cl, 4-Br, 3-Br, 4-NO_2, 3-NO_2

Interestingly, pyrrolyl analogues of chalcones were synthesized by the reaction of pyrrole-2-carbaldehyde with substituted acetophenones and, *vice versa*, of substituted benzaldehydes with 2-acetylpyrrole (Scheme 24).[81] Products **50** and **51** differ in the position of the carbonyl group.

The structures of the products, as depicted in the original paper, suggested the *trans*-arrangement of the double bond, although no $J_{H\alpha H\beta}$ constants were reported. The formation of dimers of **50**, or their solvates with MeOH, and intramolecular H-bonding in **51** was proposed.

Structures 50, 51



X = H, 4-OMe, 3-OMe, 4-Me, 3-Me, 4-Cl, 3-Cl, 4-Br, 3-Br, 4-NO_2, 3-NO_2

The formation of H-bonds was confirmed by studying the solvent effect on the chemical shifts X = H using acetone, MeCN, methanol, $CDCl_3$ and DMSO. The effect was more pronounced in **50** than in **51**. The formation of **50**-dimer could be unfavourable in methanol because of the formation of the stronger H-bonded **50**-solvate (see Scheme 24). In compound **51**, the intramolecular hydrogen bond is possible, so the solvent effect can be less than in **50**.[81]

3-(1*H*-Pyrrol-2-yl)-1-(thiophen-2-yl)propan-2-one **52**, which is very similar to compound **50**, was synthesized as in Scheme 24 by the reaction of pyrrole-2-carbaldehyde and 2-acetylthiophene and could be assumed to form the same type of dimers in the crystal. However, no cyclic dimer of **52** was found in the crystal, but instead, the monomers are linked by a single hydrogen bond C=O···H−N, and the crystal packing is arranged in the X-pattern (Fig. 7).[82]

The condensation products of pyrrole-2-carbaldehyde, 3*H*-indole-3-carbaldehyde, quinoline-8-carbaldehyde and *p*-dimethylaminobenzaldehyde with 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **53**−**56** were synthesized and used as new chalcone ligands (Scheme 25).[83]

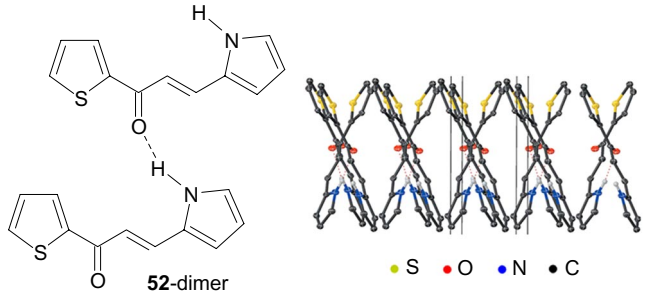
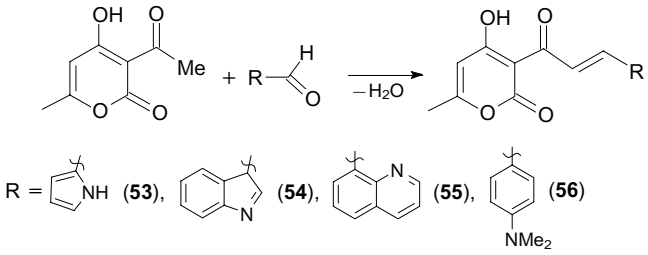


Figure 7. Molecular structure of the dimer of compound **52** and the X-pattern of crystal packing.[82] Reproduced from Gibbons *et al.*[82] with the permission of IUCr Journals.

Scheme 25



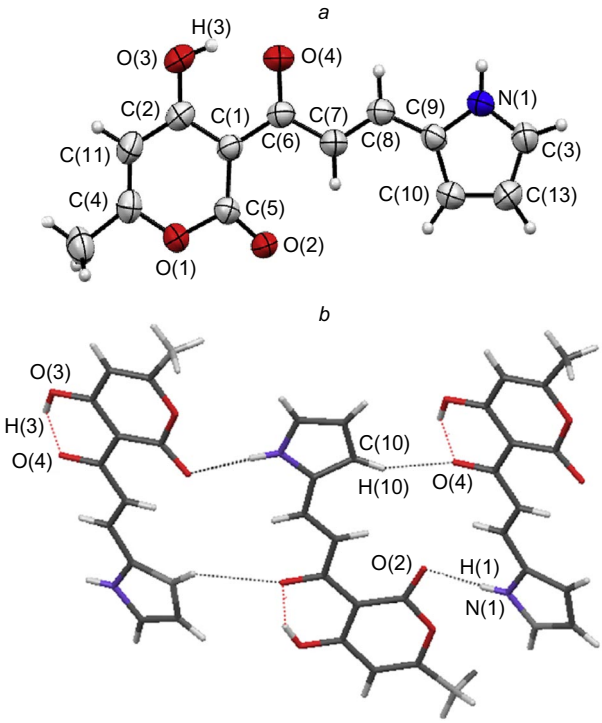


Figure 8. Molecular structure of monomeric molecule **53** (*a*) and its associate formed by intermolecular C=O···H−N and bifurcated O−H···O···H−C hydrogen bonds (*b*). The figure was prepared by the authors using the data from the study.[83]

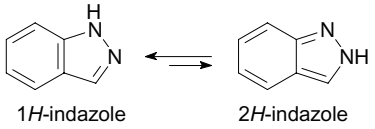
In the crystal, compounds **53**−**56** form different associates stabilized by various hydrogen bonds, both two-centered and bifurcated three-centered, as exemplified in Fig. 8.

Summing up this Section, it can be concluded that the relative stability of *E*- and *Z*-monomers and the dimers (or higher H-bonded associates) formed thereof is determined by the relative strength of the intramolecular hydrogen bonds in the monomers and intermolecular hydrogen bonds in the associates. It also depends on packing effects in the crystal and the possible equilibrium between self-associates and H-bonded solvates in solution. Overall changes can be either symbate or antibate, depending on the relative contribution of different factors.

5. Unusual tautomerism of indazole derivatives

All condensation products of indanones **1a**,**b** with heterocyclic aldehydes having the CHO group at the α-position to the nitrogen atom (HetCHO, Het is 2-pyridyl, 2-pyrrolyl, 2-pyrazolyl, 4-imidazolyl) can adopt the configuration stabilized by the formation of the 7-membered ring closed by an intramolecular N−H···O=C hydrogen bond provided that the heterocyclic ring has properly oriented NH and C=O groups. Less evident is the situation with the products of condensation with indazole-3-carboxaldehyde, for which two tautomeric forms can be envisaged. The problem of 1*H*- *vs* 2*H*-tautomers of indazole and its derivatives has been explored by many authors, particularly due to the biological activity of such compounds. Thus, Os^{IV} complexes with different tautomers of indazole showing antiproliferative activity in human cancer cell lines have been studied,[84,85] and it was specifically emphasized that metal coordination imparts an unprecedented stability to the 2*H*-indazole tautomer.[84] Continuing the study of indazole tautomerization in coordination compounds, the kinetics of the process was measured, and the formation of 1*H*- or 2*H*-tautomers was shown to depend on pH.[86] On the one hand, it is generally accepted that, regardless of solvent[87] or ring substituent,[88] 1*H*-tautomers of indazole are much more stable than their 2*H*-counterparts,[89–91] which are less stable due to loss of aromaticity in the quinoid structure (Scheme 26).[92]

Scheme 26



In a series of works, Catalan *et al.*[93–95] both experimentally and theoretically studied the acidity, basicity, aromaticity, relative stability, dimerization and tautomerism of indazoles in the ground and excited states. Theoretical analysis showed the 1*H*-tautomer to be 2.3–3.6 kcal mol^{-1} more stable than its 2*H*-counterpart depending on the level of theory but irrespective of the ground or excited state. This energy difference may decrease due to the solvation effect but cannot be reversed, always remaining in favour of the 1*H*-tautomer. Electronic spectra provided experimental evidence for a clearly pronounced predominance of 1*H*-indazole in the gas phase. No tautomerization of 1*H*- into 2*H*-indazole occurs in either the ground or the excited state; however, in complexes, such tautomerization can take place in full agreement with the results of the studies.[84–86]

On the other hand, the 1*H*-tautomer of the condensation product of indazole-3-carbaldehyde with indanones or indane-1,3-diones should be destabilized by the repulsion of lone electron pairs of nitrogen and oxygen (**A**), whereas its 2*H*-analogue (**B**) can exist in the intramolecularly H-bonded form, thus stabilizing the otherwise elusive 2*H*-tautomer (Fig. 9).

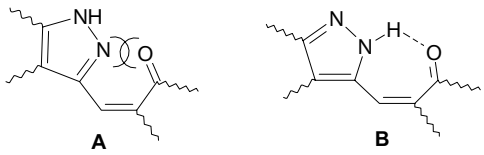
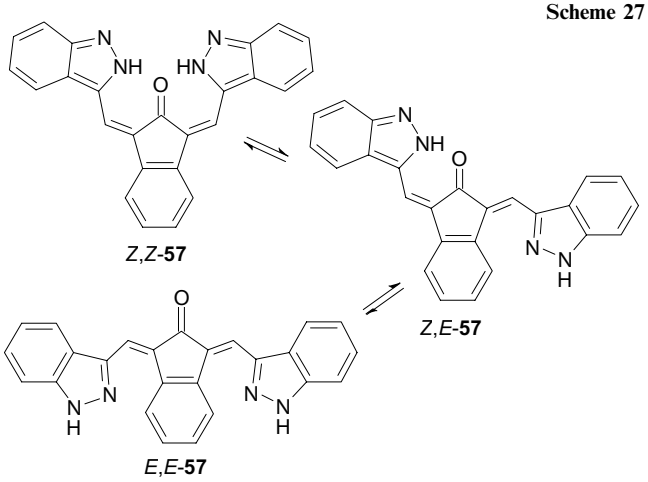


Figure 9. A schematic representation of the 1*H*- (**A**) and 2*H*-tautomers (**B**) of the condensation products of indazole-3-carbaldehyde with indanone derivatives.

In addition to bis-azolylmethylidene-2-indanones **17**–**19** (see Scheme 11), their indazolyl analogue, 1,3-bis[(1*H*-indazol-3-yl)methylene]-1*H*-inden-2(3*H*)-one **57**, was prepared from 2-indanone and 1*H*-indazole-3-carbaldehyde.[51] Three isomers are possible for compound **57** (Scheme 27); their existence was confirmed by IR and NMR data.

Scheme 27



As in the case of compounds **18** and **19**, the relative stability of the *Z*,*Z*-, *Z*,*E*- and *E*,*E*-isomers of compound **57** strongly depends on solvent participation, which was taken into account explicitly in the form of complexes with DMSO, or in the PCM model, or both (Table 2).

Experimentally, the freshly prepared compound **57** consists mainly of the *Z*,*E*-isomer with an intramolecular hydrogen bond with one indazole motif having the 2*H*-tautomer structure. In polar media, it isomerizes into the *E*,*E*-isomer, which has both indazole motifs in the 1*H*-form (see Scheme 27).[51] The isomerization is almost completed after 1 h of heating a solution of compound **57** in DMSO-d_6.

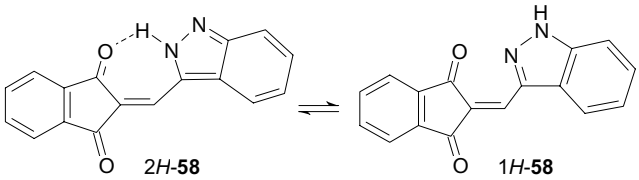
Table 2. The relative energies (kcal mol^{-1}) of the isomers of compound **57** and their solvate complexes with DMSO in the gas phase and in solution.[51]

Form of compound **57**	*Z*,*Z*	*Z*,*E*	*E*,*E*
Isolated molecules	0.0	2.1	5.7
PCM	0.0	0.4	1.9
DMSO-PCM	4.4	0.0	2.2
2DMSO-PCM	7.7	3.3	0.0

It is noteworthy that such isomerization occurs even for a solid sample: ~90% of *E*,*E*-**57** was observed within 6 months.[51]

For comparison, we obtained condensation products of 3-indazolcarbaldehyde with 1,3-indandione and 1-indanone.[96] Since no geometric isomers are possible for compound **58** bearing an indazolyl moiety and symmetric residue of 1,3-indandione, $1H \leftrightarrows 2H$ tautomerization is not complicated by isomerization and can be investigated in pure form (Scheme 28).

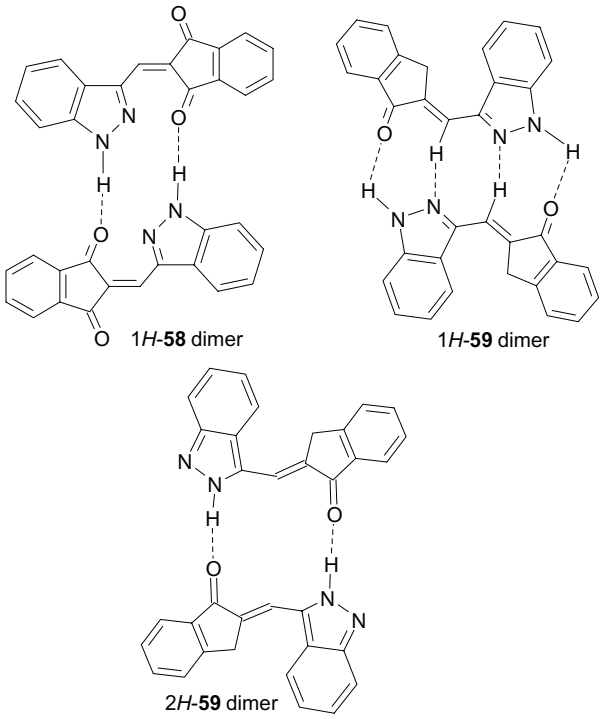
Scheme 28



The existence of two tautomers of **58** in the crystal was proved by X-ray diffraction analysis, namely, by disordering of the NH proton between the positions at the N1 and N2 atoms. In solution, the 2*H*-tautomer is the only tautomer in $CDCl_3$ (broad downfield signal at δ_{NH} 15.4 ppm), whereas both tautomers are visible in DMSO-d_6, and the δ_{NH} signal in the 1*H*-tautomer appears in a higher field at 14.4 ppm (Fig. 10). The cleavage of the intramolecular hydrogen bond in 2*H*-**58** and its replacement by an intermolecular H-bond with the solvent is even more pronounced in the pyridine-d_5 solution. The AA′BB′ splitting pattern of the indandione aromatic protons in the ^{1}H NMR spectrum of compound **58** is indicative of fast (on the NMR timescale) rotation about the formally double exocyclic C=C bond, which results in pairwise averaging of the signals for the *ortho*- and *meta*-protons. Apparently, the averaging is due to the fast NH proton exchange between the solute (compound **58**) and the solvent (pyridine), which lowers the C=C bond order and, hence, the barrier to rotation.[96]

2-(Indazol-3-yl)methylene-2,3-dihydro-1*H*-inden-1-one **59** is formed in the reaction of condensation in the form of the *E*-isomer, as proved by X-ray diffraction analysis.[96]

Structures 58, 59



However, X-ray analysis revealed that compound **59** crystallizes in two forms, yellow and red, with different crystal structures, which is a very rare case of tautomeric polymorphism.[97] Although this phenomenon was reported for 3-substituted indazoles,[98] the polymorphs differed only by crystal packing, both being 1*H*-indazole derivatives. The red form was shown to be a mixture of the 1*H*-**59** and 2*H*-**59** tautomers, as evidenced by the disordering of the NH proton between the N(1) and N(2) atoms, while the yellow form was a pure 1*H*-**59** tautomer. Since none of them can be stabilized by an intramolecular H-bond with the carbonyl oxygen, the presence of the 2*H*-**59** tautomer was explained by the formation of an intermolecular H-bond in the dimer.

The freshly prepared red sample turns yellow upon standing, indicating a slow transformation of the red poly-

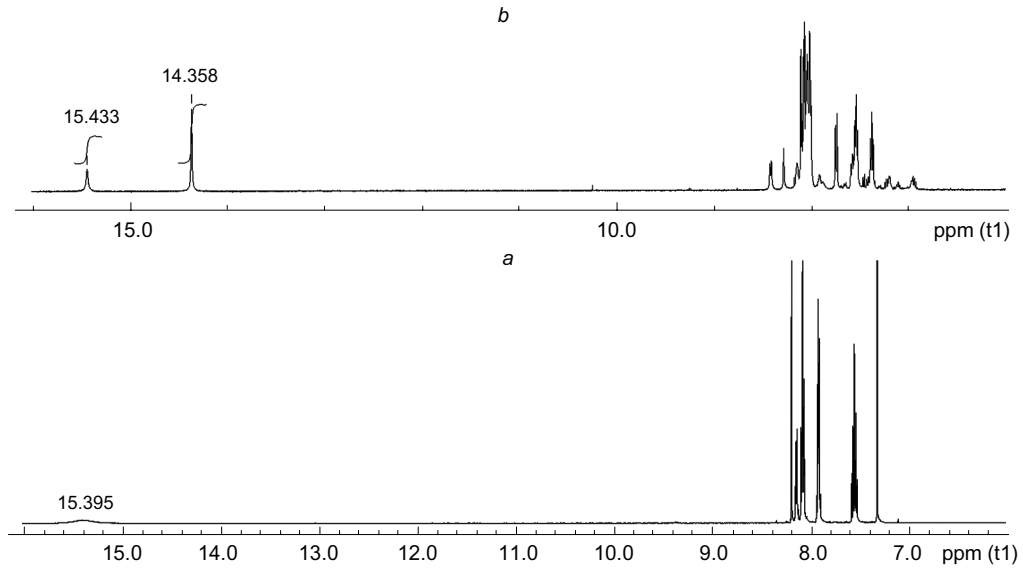
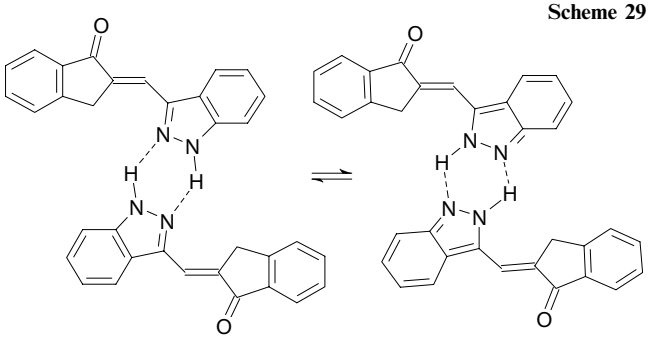


Figure 10. ^{1}H NMR spectra of compound **58** in $CDCl_3$ (*a*) and DMSO-d_6 (*b*). The ratio of tautomers 2*H*-**58** : 1*H*-**58** measured from the intensities of the NH signals is 0.45 : 1. The figure is reproduced from Sigalov *et al.*[96] with the permission of the American Chemical Society.

Scheme 29

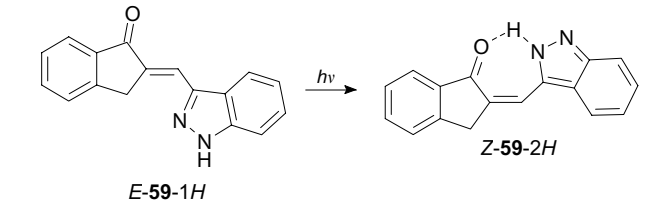


morph to a yellow polymorph (2*H*-**59** → 1*H*-**59**). Scheme 29 shows another type of dimer that can explain the transformation of the 1*H*- and 2*H*-tautomers of compound **59**, represented by a centrosymmetric structure closed by two N–H···N hydrogen bonds.

The presence of the less stable tautomer 2*H*-**59** seems to be due to its higher dimerization energy, which outweighs the higher stability of monomeric 1*H*-**59**. For a large series of compounds having hydrogen bonds involving the pyrrolic NH proton, it has been shown that the hydrogen bond energies lie within the range of 5–9 kcal mol^{-1}.[99,100] Apparently, such gain in energy at least partly counterbalances the loss of aromaticity of the 2*H*-tautomer. Therefore, 2*H*-indazole tautomers can be stabilized not only by intra- but also by intermolecular hydrogen bonds.

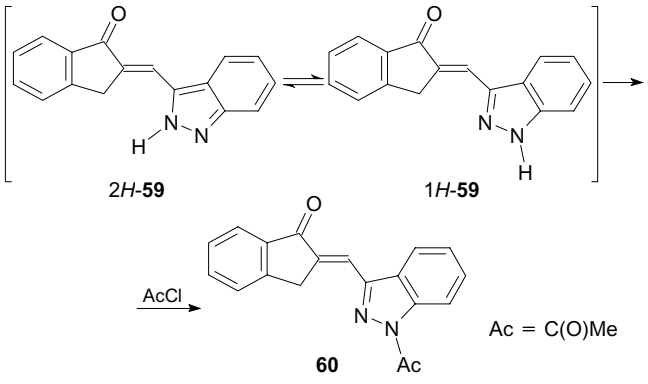
The two polymorphs give different NMR spectra in various solvents (acetone-d_6, C_2D_5OD, CD_3CN, DMSO-d_6), which is the first experimental observation of different spectra in solution for two crystalline polymorphs. As a rule, polymorphs differing in the crystal become identical in solution.[101] The observed unusual behaviour is due to the slow isomerization 1*H*-**59** → 1*H*-**59** in the dimers of compound **59** linked by N···H···N intermolecular hydrogen bonds. In contrast, in pyridine-d_5, the two polymorphs give the same ^{1}H NMR spectrum due to fast proton exchange between the solute and solvent. Upon UV irradiation, tautomer 1*H*-**59** undergoes photoinduced $E \rightarrow Z$ isomerization with simultaneous 1*H* → 2*H* tautomerization, as evidenced by the appearance of a downfield signal (15.7 ppm) from a proton involved in the strong N–H···O intramolecular H-bond in the *Z*-isomer of the 2*H*-**59** tautomer (Scheme 30).

Scheme 30



The 1*H*-**59** ⇆ 2*H*-**59** equilibrium with the more stable first tautomer was also proved chemically by treating a mixture of the red and yellow forms with acetyl chloride and isolating compound **60** acylated at the N1 atom; its structure was proved by NMR spectroscopy (Scheme 31).[96]

Scheme 31



6. Conclusion

The chemistry of compounds with a chalcone motif, *i.e.*, a three-carbon α,β-unsaturated carbonyl system, has attracted much attention of researchers for many years because of its presence in many natural products as well as its structural and electronic effects in the conjugated system. The present review focuses on previously undeservedly ignored chalcone-type indanone derivatives with a fixed *s-cis* configuration of the vinyl ketone fragment bearing various azolyl substituents at the C=C double bond. The performed analysis clearly demonstrated a variety of synthetic routes for the condensation reaction of cyclic ketones with heterocyclic aldehydes, including unexpected spontaneous oxidation of the intermediate condensation products. Structural and theoretical analysis of the newly synthesized compounds revealed numerous hydrogen-bond-assisted transformations, such as the formation of unusual tautomers, *E*/*Z*-isomerization determined by homo- and heteroassociation, and a new type of π-conjugation ('roundabout conjugation'). In this review, these effects are considered in interrelation with each other and, therefore, can be useful and interesting to researchers in various fields of structural and theoretical chemistry.

From a practical point of view, the ability of some of the studied compounds to undergo UV-induced *E*/*Z*-isomerization makes them potentially useful as reversible molecular photoswitches, colourimetric anion sensors, semiconductors, in forensic chemistry for fingerprint detection, and reagents for the synthesis of new products, drugs and dyes.

7. References

1. V.Lokshin, L.Bekere, V.Khodorkovsky. *Dyes and Pigments*, **145**, 570 (2017)
2. Y.Lv, Y.Guo, J.Xu, S.Shao. *J. Fluorine Chem.*, **132**, 973 (2011)
3. T.Du, R.Gao, Y.Deng, C.Wang, Q.Zhou, Y.Geng. *Angew. Chem., Int. Ed.*, **59**, 221 (2020)
4. R.Pluskota, M.Koba. *Mini-Reviews in Medicinal Chemistry*, **18**, 1321 (2018)
5. C.H.Son, S.Thogiti, R.K.Chitumalla, G.Koyyada, R.Cheruku, J.Jang, J.H.Jung, J.H.Kim. *Jpn. J. Appl. Phys.*, **57**, 122302 (2018)
6. M.Levin-Elad, Y.Liptz, K.L.Bar-Or, J.Almog. *Forensic Sci. Int.*, **271**, 8 (2017)
7. M.V.Sigalov, B.A.Shainyan. In *A Closer Look at Hydrogen Bonds*. (Ed. M.Waechter). (New York: Nova Science Publishers, 2020). P. 111
8. Z.Rozmer, P.Perjési. *J. Pharm. Biopharm. Res.*, **2**, 118 (2020)
9. J.C.J.M.D.S.Menezes. *RSC Advances*, **7**, 9357 (2017)

10. J.R.Dimmock, N.M.Kandepu, A.J.Nazarali, T.P.Kowalchuk, N.Motaganahalli, J.W.Quail, P.A.Mykytiuk, G.F.Audette, L.Prasad, P.Perjesi, T.M.Allen, C.L.Santos, J.Szydlowski, E.DeClercq, J.Balzarinir. *J. Med. Chem*., **42**, 1358 (1999)
11. M.S.Nel, A.Petzer, J.P.Petzer, L.J.Legoabe. *Bioorg. Chem*., **69**, 20 (2016)
12. S.Shanmugapriya, A.Anusha, M.V.Aanandhi, V.Ravichandiran. *Inventi Impact: Med. Chem*., 127 (2013)
13. A.C.Wei, M.A.Ali, Y.K.Yoon, R.Ismail, T.S.Choon, R.S.Kumar, N.Arumugam, A.Almansour, I.Abdulrahman, H.Osman. *Bioorg. Med. Chem. Lett*., **22**, 4930 (2012)
14. R.Bansal, G.Narang, C.Zimmer, R.W.Hartmann. *Med. Chem. Res*., **20**, 661 (2011)
15. H.F.Vischer, J.W.Hulshof, S.Hulscher, S.A.Fratantoni, M.H.P.Verheij, J.Victorina, M.J.Smit, I.J.P.deEsch, R.Leurs. *Bioorg. Med. Chem*., **18**, 675 (2010)
16. R.Karthik, S.R.Jasmin, S.Sasikumar, K.S.Betanabhatla, A.J.M.Christina, J.Athimoolam, K.S.Saravanan. *Pharmacologyonline*, 176 (2008)
17. H.N.Pati, U.Das, E.DeClercq, J.Balzarini, J.R.Dimmock. *J. Enzyme Inhib. Med. Chem*., **22**, 37 (2007)
18. B.Hallgas, Z.Dobos, E.Osz, F.Hollosy, R.E.Schwab, E.Z.Szabo, D.Eros, M.Idei, G.Keri, T.Lorand. *J. Chromatogr. B*, **819**, 283 (2005)
19. J.R.Dimmock, G.A.Zello, E.O.Oloo, J/W.Quail, H.-B.Kraatz, P.Perjesi, F.Aradi, K.Takacs-Novak, T.M.Allen, C.L.Santos, J.Balzarini, E.DeClercq, J.P.Stables. *J. Med. Chem*., **45**, 3103 (2002)
20. P.Perjési, J.Kubalková, Z.Chovanová, M.Mareková, Z.Rozmer, K.Fodor, Z.Chavková, Z. V.Tomečková, J.Guzy. *Pharmazie*, **63**, 899 (2008)
21. K.Fodor, V.Tomescova, T.Köszegi, I.Kron. P.Perjési. *Monatsh. Chem*., **142**, 463 (2011)
22. L.T.Higham, J.L.Scott, C.R.Strauss. *Cryst. Eng. Comm*., **12**, 2803 (2010)
23. M.Homocianu, D.Serbezeanu, A.M.Macsim, T.Vlad-Bubulac. *J. Mol. Liq*., **316**, 113888 (2020)
24. J.Kawamata, K.Inoue, H.Kasatani, H.Terauchi. *Jpn. J. Appl. Phys*., **31**, 254 (1992)
25. X.Fan, X.Hu, X.Zhang, J. Wang. *Aust. J. Chem*., **57**, 1067 (2004)
26. K.B.Manjappa, Y.-T.Peng, , W.-F.Jhang, D.-Y.Yang. *Tetrahedron*, **72**, 853 (2016)
27. M.Murali, A.B.Samui. *J. Mater. Chem*., **20**, 2714 (2010)
28. Gangadhara, K.Kishore. *Macromolecules*, **26**, 2995 (1993)
29. Gangadhara, K.Kishore. *Macromolecules*, **28**, 806 (1995)
30. M.-A.Tehfe, F.Dumur. B.Graff, D.Gigmes, J.-P.Fouassier, J.Lalevée. *Macromolecules*, **46**, 3332 (2013)
31. F.Dumur. *Eur. Polymer J*., **143**, 110178 (2021)
32. S.Z.Vatsadze, A.G.Golikov, A.P.Kriven'ko, N.V.Zyk. *Russ. Chem. Rev*., **77**, 661 (2008)
33. D.A.Evans, J.V.Nelson, T.R.Taber. In *Topics in Stereochemistry*. (Eds N.L.Allinger, E.L.Eliel, S.H.Wilen). Vol. 13. (Hoboken, NY: John Wiley & Sons, Inc., 1982)
34. C.H.Heathcock. In *Asymmetric Synthesis*. (Ed. J.D.Morrison). (Orlando, NY: Academic Press, 1984). P. 111
35. C.Palomo, M.Oiarbide, J.M.Garcia. *Chem. Soc. Rev*., **33**, 65 (2004)
36. V.Khodorkovsky, R.A.Mazor, A.Ellern. *Acta Crystallogr*., **C52**, 2878 (1996)
37. L.Geita, I.Dalberga, G.Vanags. *Latvijas PSR Zinatnu Akad. Vestis, Kimijas Serija*, 1, 70 (1996)
38. F.Nemati, M.M.Heravi, R.S.Rad. *Chin. J. Catal*., **33**, 1825 (2012)
39. C.Franz, G.Heinisch, W.Holzer, K.Mereiter, B.Strobl, C.Zheng. *Heterocycles*, **41**, 2527 (1995)
40. M.V.Sigalov, B.A.Shainyan. *Russ. J. Org. Chem*., **57**, 1887 (2021)
41. M.Sigalov, N.G.Lemcoff, B.Shainyan, N.Chipanina, T.Aksamentova. *Eur. J. Org. Chem*., 2800 (2010)
42. P.T.Chinh, P.T.Tham, N.V.Tuyen, D.H.Quynh, D.T.Van, D.N.Bang, V.T.Kien, B.D.Giang, N.T.Thuy1, B.T.Nhan, L.T.Giang. *Vietnam J. Chem*., **58**, 309 (2020)
43. B.Lantaño, J.M.Aguirre, E.V.Drago, M.Bollini, D.J.de la Faba, J.D.Mufato. *Synth. Commun*., **47**, 2202 (2017)
44. P.Camps, L.R.Domingo, X.Formosa, C.Galdeano, D.González, D.Muñoz-Torrero, S.Segalés, M.Font-Bardia, X.Solans. *J. Org. Chem*., **71**, 3464 (2006)
45. D.N.Dhar. *The Chemistry of Chalcones and Related Compounds*. (Hoboken, NY: JohnWiley & Sons, 1981). P. 168
46. P.Perjési. *Monatsh. Chem*., **146**, 1275 (2015)
47. D.N.Kevill, E.D.Weiler, N.H.Cromwell. *J. Org. Chem*., **29**, 1276 (1964).
48. J.-L.Imbach, A.E.Pohland, E.D.Weiler, N.H.Cromwell. *Tetrahedron*, **23**, 3931 (1967)
49. S.F.P.Braga, É.V.P.Alves, R.S.Ferreira, J.R.B.Fradico, P.S.Lage, M.C.Duarte, T.G.Ribeiro, P.A.S. Júnior, A.J.Romanha, M.L.Tonini, M.Steindel, E.F.Coelho, R.B.deOliveira. *Eur. J. Med. Chem*., **71**, 282 (2014)
50. M.Sigalov, B.Shainyan, N.Chipanina, L.Oznobikhina, N.Strashnikova, I.Sterkhova. *J. Org. Chem*., **80**, 10521 (2015)
51. M.V.Sigalov, B.A.Shainyan, N.N.Chipanina, L.P.Oznobikhina. *Eur. J. Org. Chem*., 1353 (2017)
52. J.Li, J.Nie, X.Zhu. *Progress in Organic Coatings*, **151**, 106099 (2021)
53. M.Ikegami, T.Arai. *Bull. Chem. Soc. Jpn*. **76**, 1783 (2003)
54. M.Ikegami, T.Arai. *Mol. Cryst. Liq. Cryst*., **431**, 445 (2005)
55. T.Arai, M.Ikegami. *Chem. Lett*. **28**, 965 (1999)
56. A.D.Laurent, J.-M.Andre, E.A.Perpete, D.Jacquemin. *Chem. Phys. Lett*., **436**, 84 (2007)
57. J.E.Zweig, T.R.Newhouse. *J. Am. Chem. Soc*., **139**, 10956 (2017)
58. J.E.Zweig, T.A.Ko, J.Huang, T.R.Newhouse. *Tetrahedron*, **75**, 130466 (2019)
59. X.Zhao, S.Yang. *J. Luminescence*, **220**, 116993 (2020)
60. C.Niebel, V.Lokshin, M.Sigalov, P.Krief, V.Khodorkovsky. *Eur. J. Org. Chem*., 3689 (2008)
61. M.V.Sigalov, E.P.Doronina, V.F.Sidorkin. *J. Phys. Chem. A*, **116**, 7718 (2012)
62. M.Ikegami, T.Suzuki, Y.Kaneko, T.Arai. *Mol. Cryst. Liq. Cryst. Sect. A*, **345**, 113 (2000)
63. M.V.Sigalov, B.A.Shainyan, I.V.Sterkhova. *J. Org. Chem*., **82**, 9075 (2017)
64. I.Rozas, I.Alkorta, J.Elguero. *J. Phys. Chem. A*, **102**, 9925 (1998)
65. M.Sigalov, B.Shainyan, I.Sterkhova. *J. Mol. Struct*., **1123**, 44 (2016)
66. N.N.Chipanina, L.P.Oznobikhina, M.V.Sigalov, B.A.Shainyan. *J. Phys. Org. Chem*., **32**, e3924 (2019)
67. M.V.Sigalov, B.A.Shainyan, N.N.Chipanina, L.P.Oznobikhina, A.V.Kuzmin. *Tetrahedron*, **76**, 131202 (2020)
68. J.Zhao, J.Zhao, X.He, Z.Tan, X.Cheng, Q.Han, C.Zhou. *J. Mater. Chem. C*, **9**, 1000 (2021)
69. M.Sigalov, B.Shainyan, N.Chipanina, I.Ushakov, A.Shulunova. *J. Phys. Org. Chem*., **22**, 1178 (2009)
70. M.V.Sigalov, B.A.Shainyan, N.N.Chipanina, L.P.Oznobikhina. *J. Phys. Chem. A*, **117**, 11346 (2013)
71. P.A.Gale, J.L.Sessler, V.Kral, V.M.Lynch. *J. Am. Chem. Soc*., **118**, 5140 (1996)
72. H.Miyaji, W.Sato, J.L.Sessler. *Angew. Chem., Int. Ed*., **39**, 1777 (2000)
73. R.Nishiyabu, R.P.Anzenbacher Jr. *J. Am. Chem. Soc*., **127**, 8270 (2005)
74. S.H.Kim, S.J.Hong, J.Yoo, S.K.Kim, J.L.Sessler, C.H.Lee. *Org. Lett*., **11**, 3626 (2009)
75. J.L.Sessler, S.Camiolo, P.A.Gale. *Coord. Chem. Rev*., **240**, 17 (2003)

76. P.A.Gale. *Chem. Commun.*, 4525 (2008)
77. P.Dydio, D.Lichosyt, J.Jurchak. *Chem. Soc. Rev.*, **40**, 2971 (2011)
78. L.Yongjun, G.Yong, X.Jian, S.Shijun. *J. Fluorine Chem.*, **132**, 973 (2011)
79. M.V.Sigalov, B.A.Shainyan, N.N.Chipanina, L.P.Oznobikhina, I.V.Sterkhova. *Tetrahedron*, **77**, 131755 (2021)
80. S.G.Sweeting, C.L.Hall, J.Potticary, N.E.Pridmore, S.D.Warren, M.E.Cremeens, G.D.D Ambruoso, M.Matsumoto, S.R.Hall. *Acta Cryst.*, **B76**, 13 (2020)
81. I.-S.H.Lee, E.J.Jeoung, C.K.Lee. *Bull. Korean Chem. Soc.*, **34**, 936 (2013)
82. D.Gibbons, G.Emandi, M.O.Senge. *Acta Cryst.*, **E74**, 1463 (2018)
83. S.Thabti, A.Djedouani, S.Rahmouni, R.Touzani, A.Bendaas, H.Mousser, A.Mousser. *J. Mol. Struct.*, **1102**, 295 (2015)
84. G.E.Buchel, I.N.Stepanenko, M.Hejl, M.A.Jakupec, B.K.Keppler, V.B.Arion. *Inorg. Chem.*, **50**, 7690 (2011)
85. G.E.Buchel, I.N.Stepanenko, M.Hejl, M.A.Jakupec, B.K.Keppler, P.Heffeter, W.Berger, V.B.Arion. *J. Inorg. Biochem.*, **113**, 47 (2012)
86. B.Verdejo, L.Acosta-Rueda, M.P.Clares, A.Aguinaco, M.G.Basallote, C.Soriano, R.Tejero, E.García-España. *Inorg. Chem.* **54**, 1983 (2015)
87. V.I.Minkin, A.D.Garnovskii, J.Elguero, A.R.Katritzky, O.V.Denisko. *Adv. Heterocycl. Chem.*, **76**, 159 (2000)
88. C.Öğretir, N.F.Tay. *J. Mol. Struct. (Theochem)*, **588**, 145 (2002)
89. J.Elguero, C.Marzin, A.R.Katritzky, P.Linda. *The Tautomerism of Heterocycles*. (New York: Academic Press, 1976)
90. J.Elguero. In *Comprehensive Heterocyclic Chemistry*. (Eds C.W.Rees, A.R.Katrizky). (Oxford: Pergamon Press, 1984). P. 291
91. W.Stadlbauer. In *Science of Synthesis*. (Ed. R.Neier). (Stuttgart, New York: Georg-Thieme-Verlag, 2002). P. 227
92. A.Martínez, M.-V.Vázquez, J.L.Carreón-Macedo, R.Salcedo, L.E.Sansores. *Tetrahedron*, **59**, 6415 (2003)
93. J. Catalan, J.C.delValle, R.MClaramunt, G.Boyer, J.Laynez, J.Gómez, P.Jiménez, F.Tomás, J.Elguero. *J. Phys. Chem.*, **98**, 10606 (1994)
94. J.Catalan, J.L.G.dePaz, J.Elguero. *J. Chem. Soc., Perkin Trans. 2*, 57 (1996)
95. J.Catalan. *ARKIVOC*, 57 (2014)
96. M.V.Sigalov, A.V.Afonin, I.V.Sterkhova, B.A.Shainyan. *J. Org. Chem.*, **84**, 9075 (2019)
97. A.J.Cruz-Cabeza, C.R.Groom. *CrystEngComm.*, **13**, 93 (2011)
98. M.A.Garcia, C.Lopez, R.M.Claramunt, A.Kenz, M.Pierrot, J.Elguero. *Helv. Chim. Acta*, **85**, 2763 (2002)
99. A.V.Afonin, A.V.Vashchenko, M.V.Sigalov. *Org. Biomol. Chem.*, 11199 (2016)
100. A.V.Afonin, I.V.Sterkhova, A.V.Vashchenko, M.V.Sigalov. *J. Mol. Struct.*, **1163**, 185 (2018)
101. J.M.Bernstein. *Polymorphism in Molecular Crystals*. (Ed. J.M.Bernstein). (Oxford: Oxford University Press, 2002)