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Theoretical modeling of electrocyclic 2*H*-pyran and 2*H*-1,4-oxazine ring opening reactions in photo- and thermochromic spiropyrans and spirooxazines

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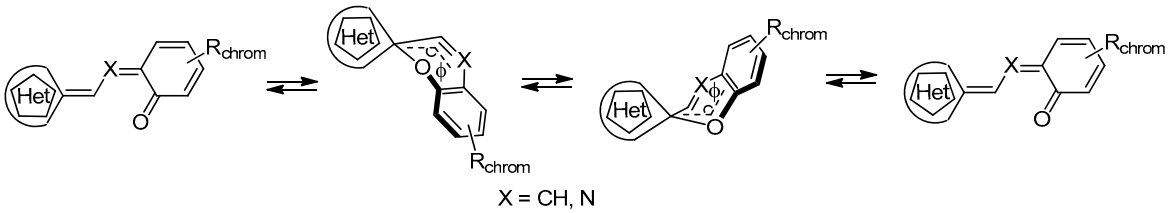

The detailed mechanism of thermal ring opening reactions of 2*H*-pyran and 2*H*-1,4-oxazine systems in a broad range of spiropyran and spiro-1,4-oxazine derivatives was studied by density functional methods (PBE0/6-311+G(d,p)). The study revealed mechanistic features and the dependence of activation parameters of this electrocyclic reaction on the steric and electronic properties of spiroconjugated fragments of the studied compounds.

Keywords: spirooxazines, spiropyrans, DFT calculations, electrocyclic reaction, photochromism, thermochromism.

Among the various pericyclic reactions of heterocyclic compounds, thermal and photoinduced ring opening reactions of spirocyclic compounds, derivatives of spiropyrans and spiro-1,4-oxazines hold a special place. Such reactions define the intramolecular isomerization processes of these bistable compounds, leading to substantial structural changes and switching their physicochemical properties.[1–3] The key step of these reactions involves cleavage of the relatively weak C_{spiro}–O bond, followed by conformational changes, generally resulting in opening of pyran ring of the chromene system and the formation of colored isomers with conjugated merocyanine structure. Depending on the structure of the latter, these reactions may be thermally or photochemically reversible. The described properties (bistability) of spirocyclic compounds opens broad possibilities for their applications as optical switches,[4] chemosensors,[5–8] materials for molecular electronics,[9–11] regulators and markers for enzyme reactions and other dynamic biological processes.[12–14] Mechanistic study of ring opening reactions in spirocyclic compounds is highly important, as it provides basis for rational design of new thermo- and photochromic compounds and expanding the areas of their practical application.

Despite the relatively long history of experimental and theoretical studies regarding spiropyrans and spirooxazines,[15–31] many mechanistic details of processes occurring during the conversion of cyclic form to the open merocyanine form both in the ground state and, especially, in the excited states remain unknown. Furthermore, the computational studies in this direction were performed either with model compounds containing isolated fragments of the actual molecules,[21,22] or, in the majority of cases, with spirobenzopyrans and spirobenzoxazines of indoline series.[23–31]

In the current work, we relied on the density functional theory (DFT), using PBE0 hybrid functional and 6-311+G(d,p) basis set to study thermal ring opening reactions in a wide range of spiropyrans **1**–**9** and spirooxazines **10**–**15** with various heterocyclic and 2*H*-chromene ring systems (Fig. 1) in order to establish the dependence of mechanism and activation parameters of these reactions on the structure of spiroheterocycles, as well as the position and electronic properties of substituents (using the examples of spirobenzopyrans **1a**–**c** and spironaphthopyrans **2a**–**c**).

The obtained results are expected to provide an opportunity not only to establish mechanistic features of thermal opening reactions of spiropyrans and spirooxazines, but also will serve as the basis for further studies of photophysical and photochemical mechanisms of photochromic transformations in these systems. The energy profiles of the studied reactions on the potential energy surfaces of ground and excited states will provide the most complete mechanistic understanding of these highly

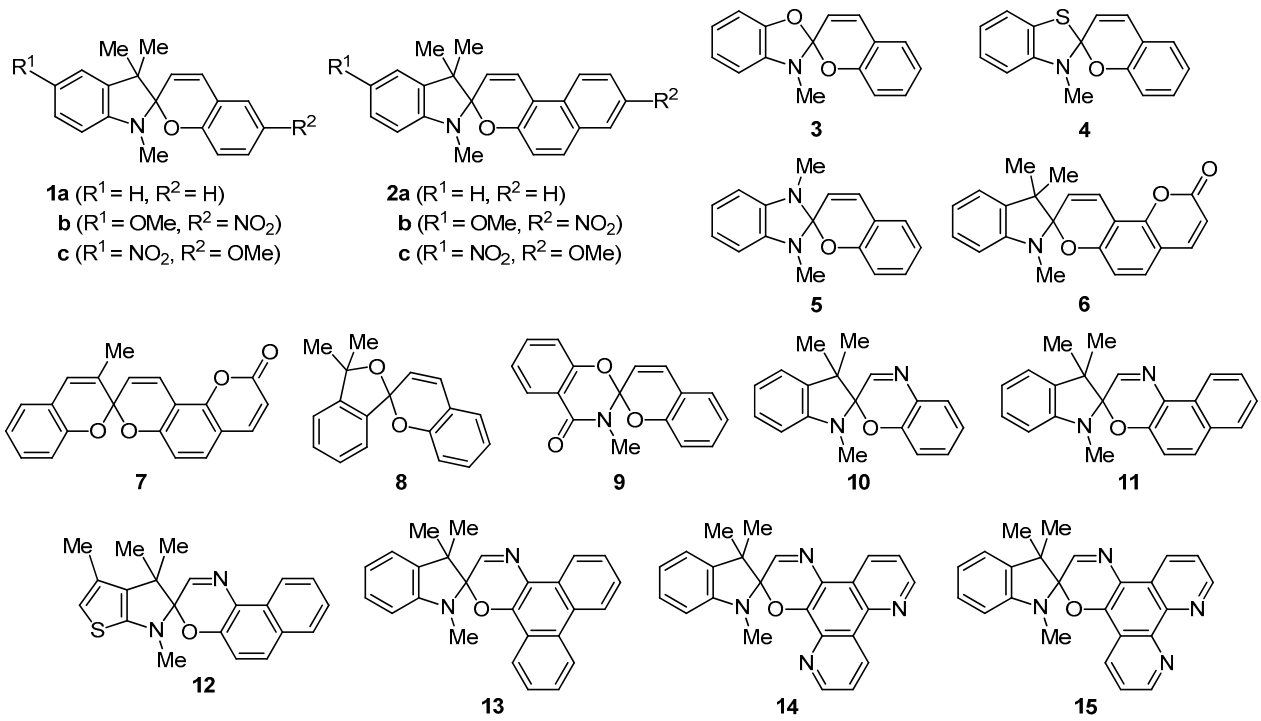

Figure 1. The structures of studied spiropyrans **1**–**9** and spirooxazines **10**–**15**.

important photoinitiated processes and will allow to establish certain structure–activity relationships, indicating the best approaches to the synthesis of desired products.

Calculated energetic characteristics of stationary points on the thermal ring opening reaction pathways of the studied compounds are shown in Table 1 and Figures 2–6.

As previously established by us[26] and later confirmed by other authors,[28] the structural flexibility of cyclic spiropyran and spirooxazine isomers, associated with slight conformational changes in the chromene or 1,4-benzoxazine rings (Scheme 1, Het – heterocyclic system) creates two reaction pathways on the potential energy surface for thermal ring opening reactions in these systems. Depending on the initial configuration of the cyclic isomer (**Sp-c** or **Sp-t**), the reaction may result in the formation of merocyanine isomers of the starting spirocyclic structures – **CTC** (*cis-trans-cis*) or **TTC** (*trans-trans-cis*) (Scheme 1).

The calculated bending angles in the chromene system of cyclic isomers of the studied compounds varied from 149.4° for isomer **Sp-t** of spiropyran **4** to 169.8° for the analogous isomer of spiropyran **1b**. The results of computational modeling showed that the form **Sp-c** was preferable, except in the case of spiropyrans **2c**, **3**, **4**, **6**, **8**, **9** and spirooxazine **10**. Both cyclic isomers (**Sp-c** and **Sp-t**) of spiropyran **5** were a pair of enantiomers, while the respective merocyanines (**CTC** and **TTC**) were identical.

The local minima on potential energy surface corresponding to the structures of conformational isomers **Sp-c** and **Sp-t** were located at a relatively flattened region, while the relative energy values of these minima were very small (Table 1). Due to the flattened potential energy surface in the vicinity of the cyclic isomers, only one of the possible cyclic forms could be localized for spiropyrans **3**, **4**, **6**–**9**. Nevertheless, the cleavage of C_{spiro}–O bond in spiropyran or spirooxazine according to one or the other reaction pathway in any case was preceded by the respective structural transformations of pyran or oxazine ring.

The main common feature of the described reactions was that they occurred in two steps. The first step involved cleavage of C_{spiro}–O bond, followed by *cis-trans* isomerization in the second step, associated with rotation of the chromene moiety relative to the central bond of =CH–X= motif (Scheme 1). The potential energy surface regions corresponding to these reaction stages, as a rule,

Scheme 1

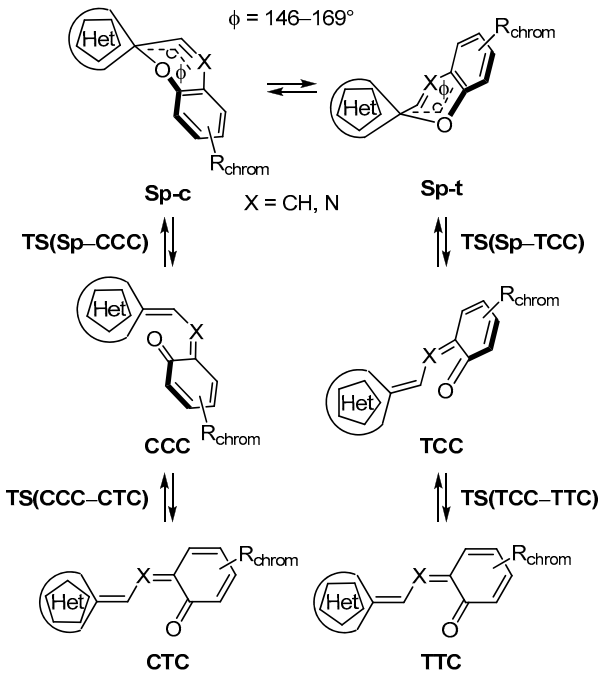

Table 1. The relative energies (*E*, kcal/mol) with zero-point energy correction (*ZPE*) of the structures, corresponding to local minima and transition states (**TS**) on the routes of ring opening reactions of spiropyrans **1**–**9** and spirooxazines **10**–**15**, according to PBE0/6-311+G(d,p) calculations in gas phase

Isomer or transition state	Compound																		
	1a	**1b**	**1c**	**2**	**3**	**4**	**5a**	**5b**	**5c**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
CTC	13.8	9.4	17.6	16.2	14.1	5.5	9.6	7.6	11.5	8.1	7.2	17.0	23.6	12.9	7.7	6.8	4.1	6.2	3.3
TS(CCC–CTC)	30.2	31.7	31.0	34.9	32.7	29.7	23.6	25.3	22.3	28.8	26.9	31.5	37.2	36.0	26.6	26.9	21.3	24.6	21.9
CCC	17.2	12.1	21.1	17.7	16.3	–	12.3	9.9	14.1	12.5	16.7	23.2	26.1*	22.8	17.0	16.0	13.6	15.2	12.7
TS(Sp–CCC)	18.5	12.7	22.9	17.9	17.2	–	15.1	11.9	17.9	13.5	18.9	24.0	26.1	23.0	19.0	18.1	16.8	17.3	15.8
Sp-c	0.0	0.0	0.0	–	–	0.0	0.0	0.0	–	–	0.0	–	–	0.1	0.0	0.0	0.0	0	0.0
Sp-t	0.1	0.0	0.1	0.0	0.0	0.0	0.1	0.2	0.0	0.0	–	0.0	0.0	0.0	0.2	0.1	0.2	0.2	0.2
TS(Sp–TCC)	–	–	29.6*	–	18.7	–	19.4*	–	21.7	–	18.8*	25.7	25.5	–	–	23.1	21.3	22.5	20.4
TCC	–	–	29.6	–	16.8	–	19.4	–	20.6	–	18.8	21.9	25.4	–	23.7	23.0	19.9	22.0	19.4
TS(TCC–TTC)	29.5	31.1	30.3	32.6	29.0	29.7	22.9	24.5	21.4	28.1	30.6	30.0	33.9	35.6	26.3	26.8	21.3	24.3	21.7
TTC	11.2	7.1	14.9	10.9	8.4	5.5	7.0	5.3	8.6	6.0	12.4	12.8	16.5	11.9	6.1	5.4	2.7	4.6	1.8

* The energy difference of intermediate and transition state was less than 0.1 kcal/mol.

were separated by a flattened area even in the case when the intermediate minimum could not be located in this region (for example, for the benzimidazole spiropyran **5**).

Another common feature of the investigated processes was linked to the very low activation energy barriers to the recyclization of cisoid intermediates **CCC** and **TCC** (Scheme 1, Table 1). For the thermodynamically and kinetically more stable **CCC** isomers, the activation energy barriers of the reverse reaction did not exceed 3.8 kcal/mol, while for the majority of **TCC** isomers (except for the spiropyran **8**) the energy barriers were much lower. Furthermore, for spiropyrans **1a**,**b**, **2b**, **5**, **6** and the spirooxazine **10** the **TCC** structures could not be located on the potential energy surface. All these facts mean that the cisoid isomers (**CCC**, **TCC**) would practically never accumulate during the reaction, and the two-stage process must be kinetically similar to a single-stage reaction. Thus, it is pointless to attempt to identify the limiting, i.e., the slowest stage of the investigated reactions, since the reaction rate will be quite accurately determined by the sum of activation barriers for C_{spiro}–O bond cleavage and *cis-trans* isomerization.

By studying the reaction mechanisms of ring opening in unsubstituted and substituted derivatives of spiropyrans and spirooxazines **1a**–**c** and **2a**–**c** containing electron-donating and electron-withdrawing substituents (Fig. 2), we established some correlation between the activation energy barriers of the first and second stage of this reaction.

In those cases when the cleavage of C_{spiro}–O bond required overcoming a relatively high energy barrier, the subsequent step as a rule had lower activation energy parameters. The main reason determining such energy profile of the investigated reactions was the partial rotation of one moiety of the spiropyran or spirooxazine molecule relative to the other during the stretching and cleavage of C_{spiro}–O bond.

The high activation energy barrier for bond cleavage corresponded to longer C_{spiro}–O distance and larger torsion angle between the parts of molecule in the transition state and the intermediate structures. Besides that, an increase of torsion angle can be linked to substantial repulsion between the chromene and heterocyclic moieties in the cisoid intermediate, caused by the presence of bulky substituents in these moieties. Some examples of such systems include the **TCC** isomers of spiropyrans **1a**–**c**, **2a**–**c**, **6** and spirooxazines **10**–**15**.

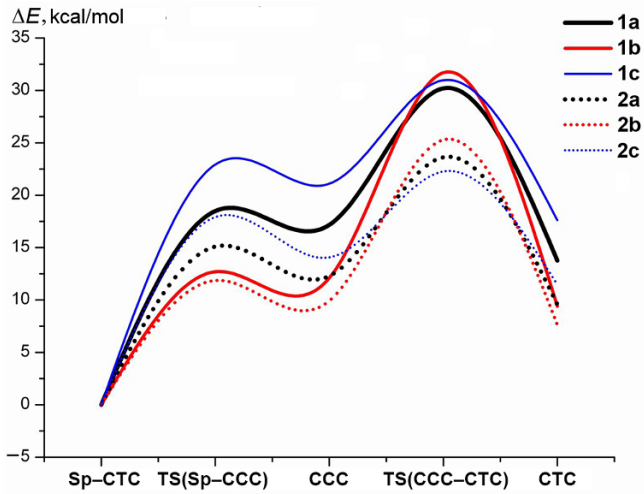

Figure 2. The energy profiles of ring opening reactions in **Sp-c** isomer of spirobenzopyrans **1a**–**c** and spironaphthopyrans **2a**–**c**, according to the data of PBE0/6-311+G(d,p) calculations.

Thus, in this case the heterocyclic (Het) and chromene (benzoxazine) parts of the molecules are already sufficiently rotated one relative to the other and provide for the low energy barrier to the subsequent *cis-trans* isomerization. On the other hand, the cleavage of C_{spiro}–O bond with low energy barrier occurred at smaller torsion angles between the parts of the molecules. At the same time, in the absence of steric hindrance the possibility arised for effective conjugation between the =CH–X= moiety (Scheme 1) and the π-electron system of the rest of the molecule, resulting in a double bond character in the central part of this motif. This, in turn, led to increased activation energy of the *cis-trans* isomerization process.

According to the results of calculations (Table 1, Fig. 2), the introduction of electron-donating methoxy substituent in the heterocyclic (Het) part of the molecule and electron-withdrawing nitro substituent in the 2*H*-chromene part of compounds **1a** and **2a** (Scheme 1) led to lower activation energy barriers for the cleavage of C_{spiro}–O bond by 5.8 and 3.2 kcal/mol, respectively. At the same time, the energy barriers to *cis-trans* isomerization increased by 6.7 and 4.1 kcal/mol (the energy profiles for compounds **1b** and **2b** are given in Fig. 2). The structures corresponding to intermediates **CCC** showed a shortening of the central bond in =CH–X= moiety (with X = CH) from 1.393 to 1.376 Å (compounds **1a**–**c**) and from 1.400 to 1.388 Å (compounds **2a**–**c**), indicating enhanced conjugation in this part of the molecule. On the other hand, when the positions of substituents in these systems were switched to the opposite (curves **1c**, **2c**, Fig. 2), the activation energy barrier for the bond cleavage was increased by 10.2 and 6 kcal/mol, and the energy barrier of the subsequent isomerization step decreased by 9.7 and 4.1 kcal/mol. The opposite effect was also observed as changes of bond lengths in the =CH–X= moieties.

The substituent effect was much more pronounced in the spirobenzopyran system of compound **1a**, compared to the spironaphthopyran system of compound **2a**. The possible reason for such result is associated with the fact that the extended π-electron system in these compounds allows for partial compensation of structural changes in the molecule *via* effective redistribution of electron density.

Indeed, according to computer modeling data, the stepwise expansion of π-electron system of the 2*H*-chromene moiety in the series of spiropyrans **1a**, **2a** and spirooxazines **10**, **11**, **13** leads to lowering of activation energy barriers both at the stage of C_{spiro}–O bond cleavage and the subsequent *cis-trans* isomerization (Fig. 3). The calculated changes of energy barrier at the first stage of the reaction were 3.4 kcal/mol in spiropyran series, as well as 4.0 and 1.7 kcal/mol in spirooxazine series. The energy barriers to *cis-trans* isomerization decreased by 1.7 kcal/mol in spiropyran series, as well as by 3.7 and 1.8 kcal/mol in spirooxazine series.

The change from benzene ring to thiophene in the heterocyclic part (Het) of spirooxazine **11** molecule (curve **12**, Fig. 4) and aza-substitution in the chromene system of spirooxazine **13** (curves **14**, **15**) only insignificantly changed the activation parameters of reaction.

In comparison to spiropyrans, derivatives of spirooxazines were generally characterized by higher activation energy values at each step of thermal electrocyclization reaction. This result can be linked to some degree of shortening and, therefore, increased strength of the C_{spiro}–O bond in spirooxazine ring compared to the analogous spiropyrans.

Based on the obtained results, we can formulate conclusions about the effect of various heterocyclic (Het) and 2*H*-chromene (benzoxazine) groups with different electron-donating or electron-withdrawing properties in molecules of spiropyrans and spirooxazines, which affect the energy profile of the considered electrocyclic reactions. It was established that changing from benzochromene system in an indoline type spiropyran to coumarin system with stronger electron-withdrawing properties lowered the energy barrier of C_{spiro}–O bond cleavage by 5 kcal/mol (curve **6**, Fig. 5). At the same time, the change of indoline part in compound **6** to a more electron-withdrawing

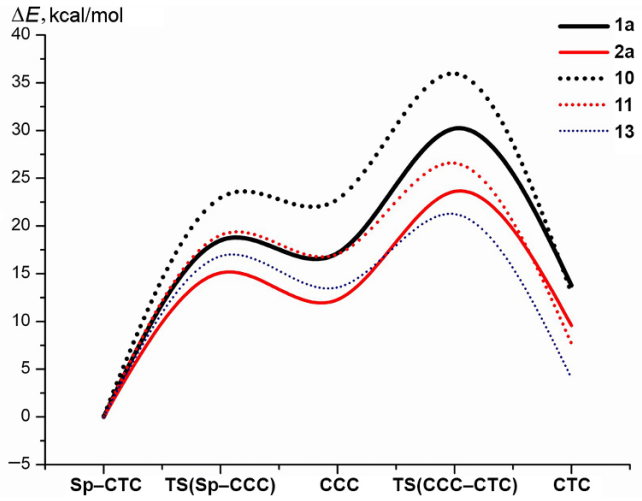

Figure 3. The energy profiles of ring opening reactions in **Sp-c** isomers of spiropyrans **1a**, **2a** and spirooxazines **10**, **11**, **13** according to the data of PBE0/6-311+G(d,p) calculations.

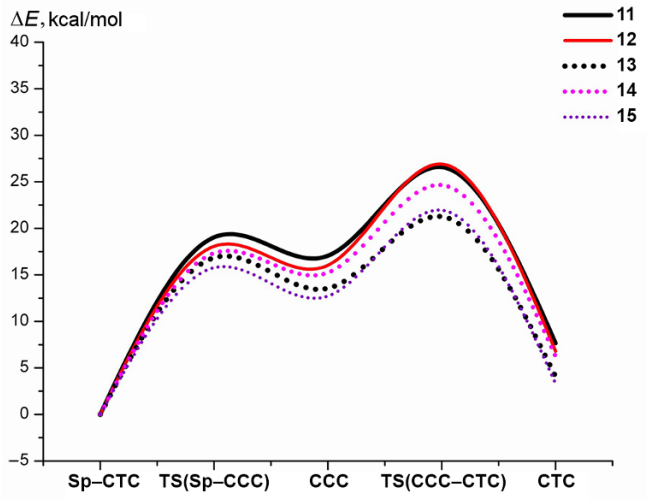

Figure 4. The energy profiles of ring opening reactions in **Sp-c** isomers of spirooxazines **11**–**15** according to the data of PBE0/6-311+G(d,p) calculations.

benzochromene system (curve **7**, Fig. 5) largely cancelled the effect of previous structural modification.

On the other hand, the change of indoline system in the heterocyclic part of compound **1a** to the more electron-withdrawing isobenzofuran and benzoxazine systems (curves **8**, **9**, Fig. 6) noticeably increased the energy barrier to the cleavage of C_{spiro}–O bond (by 5.5 and 7.6 kcal/mol, respectively), while the benzoxazole and benzothiazole analogs of compound **1a** (curves **3**, **4**, Fig. 6) had lower activation energy values (by 0.6 and 1.3 kcal/mol, respectively) at this stage of the reaction. For the subsequent *cis-trans* isomerization of **CCC** isomers of compounds **3**, **4**, **8**, **9** the energy barriers were higher by 4.2 and 3.4 kcal/mol for spiropyrans **3**, **4** and lower by 4.8 and 2.0 kcal/mol for compounds **8**, **9**. Qualitatively similar results were obtained by variation of substituents with different properties in the series of benzo- and naphthopyrans **1** and **2** (Fig. 1).

In conclusion, it should be noted that the steric factors associated with the presence of bulky substituents in the heterocyclic (Het) and (or) 2*H*-chromene (1,4-benzoxazine) systems of spiropyrans and spirooxazines, which interfere with the stabilization of cisoid intermediates, largely prevail over the effect of electronic factors at some stages of the reactions. For example, the ring opening in **Sp-t** isomers of spiropyrans and spirooxazines belonging to indoline series, having two methyl groups in the chromene part that create steric obstacles to the formation of intermediates **TCC**, often proceeds as a single-step process with a relatively high energy barrier, combining the cleavage of C_{spiro}–O bond and *cis-trans* isomerization (Table 1).

Based on the results of our study, we have reached the following general conclusions. Electrocyclic ring opening reaction in spiropyrans and spirooxazines occurs by two routes, as a consequence of structural flexibility in the 2*H*-chromene (1,4-benzoxazine) system in the spirocyclic form of these compounds, leading to the existence of conformational isomers with similar energy. The reaction proceeds in two stages: dissociation of C_{spiro}–O bond and *cis-trans* isomerization of the first intermediate, but its kinetics are similar to a single-stage process, due to the very low energy barriers to recyclization of cisoid intermediates. Increasing the electron-donating properties of the heterocyclic part and the electron-withdrawing properties of the 2*H*-chromene (1,4-benzoxazine) part decreased the activation energy barrier to the cleavage of C_{spiro}–O bond and simultaneously increased the barrier to the subsequent isomerization through stronger conjugation in the =CH–X= moiety (X = CH, N) of cisoid intermediates with the π-electron system of the rest of the merocyanine molecule. The extended π-electron systems of chromene and benzoxazine rings in spiropyrans and spirooxazines, respectively, had lower activation barriers for both reaction stages due to the ring fusion and suppressed the influence of the substituents. The steric obstacles to the formation of cisoid intermediates on the reaction pathway of spiropyran and spirooxazine ring opening led to the combination of C_{spiro}–O bond cleavage and *cis-trans* isomerization steps in one process. The activation barriers to thermal isomerization of spirooxazines, as a rule, were higher than the respective barriers for structurally analogous spiropyrans.

Computational modeling. The mechanistic pathways of 2*H*-pyran and 2*H*-1,4-benzoxazine ring opening in the series of spiropyran and spirooxazine derivatives **1**–**15** were studied by DFT calculations using GAUSSIAN 09 software suite.[32] The PBE0 hybrid functional[33] and 6-311+G(d,p) basis set were used in the calculations. The nature of identified stationary points on the reaction routes was confirmed by calculation of the intrinsic Hessian matrix values.

Supplementary information file containing full and relative energy values for the stationary points on the potential energy surface of investigated transformations, as

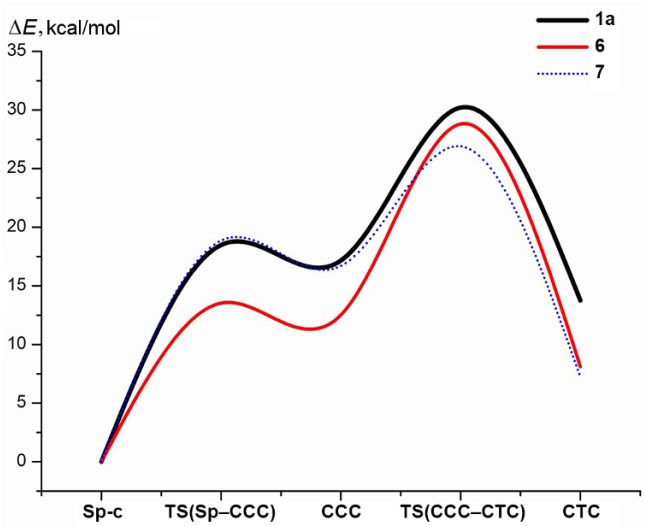

Figure 5. The energy profiles of ring opening reactions of isomers **Sp-c** of spiropyrans **1a**, **6**, **7**, according to the data of PBE0/6-311+G(d,p) calculations.

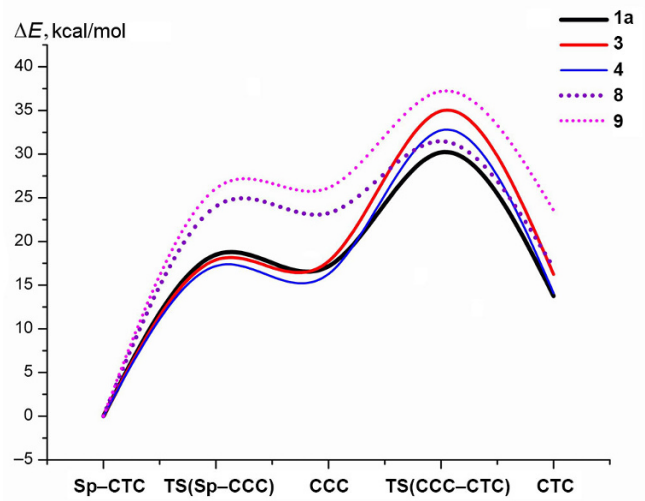

Figure 6. The energy profiles of ring opening reactions of isomers **Sp-c** of spiropyrans **1a**, **3**, **4**, **8**, **9**, according to the data of PBE0/6-311+G(d,p) calculations.

well as the imaginary vibrational frequencies of transition state structures, is available at http://link.springer.com/journal/10593.

The Cartesian coordinates of all optimized structures can be provided at request.

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