The Topology and the Aromaticity of Coumarins (1)

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2*H*-1-benzopyran-2-one (coumarin), its isomers and derivatives are considered as aromatic or potentially aromatic chemical species and analyzed as such by use of standard and parameter-varying graph-theoretical procedures. Theoretical results are interpreted within the bounds set by existing chemical evidence.

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There has always been some use for coumarins (4-6). Their conspicuous presence in plants is well recognized if not quite satisfactorily explained. Their early acknowledged physiological activities, frequently correlated with their physicochemical properties (7,8), range from anticoagulants to potent inhibitors of DNA supercoiling and catenation (9). Other uses are as *p*H indicators (10) and lasing materials (11,12). These examples are mostly uses of α-pyrone compounds although the γ-pyrone derivatives have not been of lesser significance. Figure 1 shows common structural formulae and corresponding graph representations of the four basic coumarins, (**1a**, **2a**, **3a**, **4a**) and (**1b**, **2b**, **3b**, **4b**), respectively.

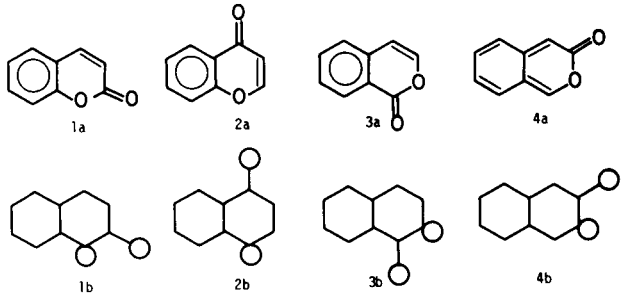


Figure 1. Structural formulae of the four basic coumarins and the corresponding graphs.

It is interesting to note that, whereas coumarin (**1a**) is a naturally occurring compound, unsubstituted chromone (**2a**) has not yet been isolated from natural sources, but it is well known in the form of its substituted 2-phenyl and 3-phenyl derivatives, flavons and isoflavons (13).

The coumarins in Figure 1 may be conveniently represented as permutation isomers (14). If 2*H*-1-benzopyran-2-one or coumarin (**1a**) is to be taken as the identity permutation isomer, E, then 4*H*-1-benzopyran-4-one or chromone (**2a**) is (*12*) isomer while 3*H*-2-benzopyran-3-one (**4a**) is (*132*) permutation isomer. The isomerisation can be associated with appropriate permutation patterns (15) as is given, within the graph representation, in Figure 2.

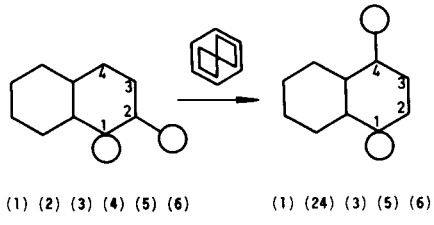


Figure 2. The E → (*24*) interconversion.

The early recognition of the E → (*24*) interconversion and the significance of this for much of the chemistry of coumarins has usually been treated on the basis of existing chemical evidence for the α- and γ-pyrons. The aromaticity of coumarins, either in the ground state or in excited states, has frequently been questioned (16-18). This and the few existing theoretical treatments of coumarins gave us a motive to use our graph-theoretical method in an analysis of the aromatic properties of these conjugated compounds (19).

Aromaticity, as treated in this work, refers to the familiar idea elaborated through the work done by Breslow (20), Dewar (21), Hess and Schaad (22-25), Herndon and Párkányi (26) and many others. The method in the present paper is exposed elsewhere (27-34) and is based on chemical graph theory (35). It originated by injecting the idea of linear reference structure (20,21) into an existing body of graph-theoretical applications in chemistry (35-39). The resulting topological resonance energy, TRE, is given by the expression,

(1)

$$\mathrm{TRE} = \left\langle \ln \left| \frac{P(G; ix)}{A_o(G; ix)} \right| \right\rangle \qquad (1)$$

where P(G; x) and A_o(G; x) are characteristic polynomials of the molecular and reference graphs, respectively (29). The above integral formula is transformed (31) into the following expression which is used in the numerical work (28-34, 40),

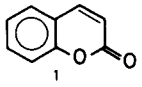
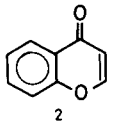
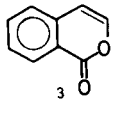
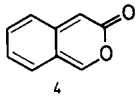
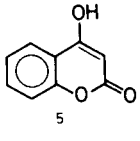
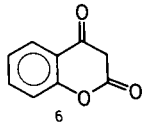
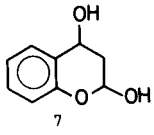
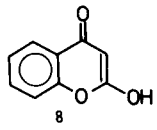
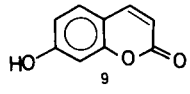
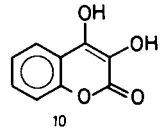
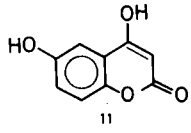
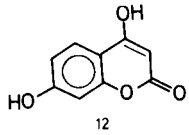
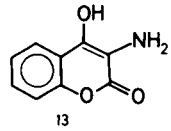
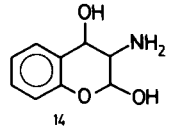
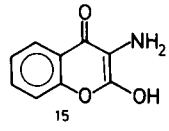
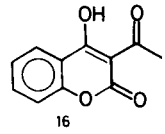
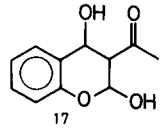
(2)

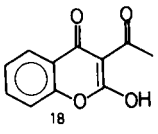
$$TRE = \sum_{i=1}^{N} g_i x_i - \sum_{j=1}^{N} g_j x_j' \qquad (2)$$

where x_i and x_j' are the roots (eigenvalues) of the characteristic polynomials of the molecular and reference graphs, respectively.

In the Table given are calculated values of the topological resonance energy of some coumarins.

Table

	I Δ TRE	II TRE	III %B	%CB
 1	ΔC -0.132 ΔA -0.103	0.244	44.68	
 2	ΔC -0.142 ΔA -0.133	0.256	46.90	
 3	ΔC -0.174 ΔA -0.187	0.230	42.23	
 4	ΔA 0.033 ΔA 0.020	0.090	16.56	
 5	ΔC -0.124 ΔA 0.124	0.120	20.26	
 6	ΔC -0.000 ΔA 0.000	0.256	43.38	
 7	ΔC -0.376 ΔA 0.376	-0.151		3.79
 8	ΔC -0.128 ΔA 0.128	0.128	21.63	
 9	ΔC -0.136 ΔA 0.136	0.107	18.05	
 10	ΔC -0.181 ΔA 0.120	0.003	0.54	
 11	ΔC -0.164 ΔA 0.129	-0.014		0.32
 12	ΔC -0.178 ΔA 0.127	-0.012		0.94
 13	ΔC -0.211 ΔA 0.090	0.062	9.82	
 14	ΔC -0.093 ΔA 0.189	-0.150		3.50
 15	ΔC -0.296 ΔA 0.035	0.186	29.28	
 16	ΔC -0.106 ΔA 0.001	0.238	32.77	
 17	ΔC -0.270 ΔA 0.000	0.223	30.65	



18	ΔC -0.101 ΔA 0.000	0.255	32.06

Topological resonance energies for some coumarins

I column: changes in TRE upon loosing (ΔC) or getting (ΔA) a π-electron; II column: TRE values; III column: TRE(PE) values given as percentages of benzene TRE(PE) value (%B) or as percentages of cyclobutadiene TRE(PE) value (%CB).

The positive or negative values are, as usual, associated with species considered as aromatic or antiaromatic, respectively. This classification of topological resonance energy values has been justified by many examples (29-34). A common way to display TRE values for molecular systems with different characteristics (41,42) is to give TRE per electron, TRE(PE) (29). According to this procedure, species having TRE(PE) equal or larger than 0.01 are considered to be of prevailing aromatic character. On the other hand, when TRE(PE) is -0.01 or smaller, the species is considered antiaromatic (43). Species having TRE(PE) values in the open interval (-0.01, +0.01) are either ambivalent or non-aromatic conjugated compounds. An attempt to make more stringent quantification of TRE values however, has been faced with some conceptual difficulties (44-46).

In this work, following the accepted elementary standards of aromaticity and antiaromaticity, the TRE values of coumarins are expressed with respect to the "internal standard"; these are the values in the last column of the Table. There are actually two such standards: benzene (B) as a representative aromatic compound and cyclobutadiene (CB) as its antiaromatic counterpart.

In the Table eighteen different coumarins are given, with an accent on the α- and γ-pyrone and their derivatives. First are the four basic coumarins (**1**, **2**, **3**, **4**), following are various ol/one derivatives (**5**, **6**, **7**, **8**, **9**) and diol derivatives (**10**, **11**, **12**). The notable process of α/γ-pyrone conversion is dissected and represented graphically by 4-hydroxycoumarin (**5**), 2-hydroxychromone (**8**), with dione-derivative (**6**) and diol-anion (**7**) as two possible intermediary species. This sequence, (**5**), (**7**) and (**8**) is repeated with 3-amino derivatives (**13**, **14**, **15**) and 3-acetyl derivatives (**16**, **17**, **18**).

It should be understood that the topological resonance energy values, TRE, as given in the middle column of the Table represent a combinatorial interplay of basically three factors: (i) chemical topology (47), that is, the number and the arrangement of atomic centers and associated chemical bonding, (ii) the values of the real field parameters assigned to particular graph elements, and (iii) the number of π-electrons present in a species under analyses.

The topology of species is expressed algebraically by characteristic polynomials which are basic for the TRE values. Its influence on the TRE can be seen in four permutation isomers (**1**, **2**, **3**, **4**). All four compounds have twelve π-electrons over a bicyclic network. The TRE values of the first three, *i.e.* coumarin, chromone and isocoumarin are almost the same, indicating aromaticity and high chemical similarity. This is in accord with certain facts but does not correlate with all facts germane to the chemistry of the coumarins. The TRE value of 4*H*-1-benzopyran-4-one (**2**) is indeed the highest in this series which is consistent with most of the chemical evidence. However, the differences between TRE values are not very indicative of the predominant olefinic character of the C(3)-C(4) bond in the lactone rings of 2*H*-1-benzopyran-2-one (**1**) and 1*H*-2-benzopyran-1-one (**3**). The low TRE value of 3*H*-2-benzopyran-3-one (**4**) denotes an absence of significant aromatic stabilization; a result in concordance with the classical quinonoid structure of the compound. There is also a corroborating absence of evidence of the reported successful synthesis of this compound.

An even better example of the influence of chemical topology on the TRE values is given by the three permutation isomers of dihydroxycoumarins (**10**, **11**, **12**). Their TRE values are basically the same and thus neglect chemical and positional differences among 3,4-diols and 4,6- and 4,7-diphenols. A finer chemical differentiation should comprise a distinction between the phenolic character of the 6- or the 7-hydroxyl group and the enolic 4-hydroxyl group.

All of these examples are not the pure topological variants; their TRE values are influenced by the parameters used. The origin of these parameters is in the following: the graphs representing coumarins are weighted graphs (48-50). They are introduced as a natural need to make a distinction between homocyclic and heterocyclic compounds. By analogy with the isometric Hückel MO method, parameters associated with electronegativities of non-carbon atoms and the lengths of carbon-heteroatom bonds (51,52) are introduced. The essence of the graph-theoretical method is not changed by this mutation, only the self-loops appear as linear (53,54) countable elements. Using the standard set of parameter values (23,55), the heterogeneity of corresponding species is quantified within the prescribed metric of the MO method; the price is, however, the loss of the intrinsic non-parametric quality of the topological resonance energy.

The parameters used in the analysis of coumarins are basically of two types: those corresponding to singly bound oxygen and those referring to doubly bound oxygen. The influence of those parameters on TRE is carefully analyzed in the case of furan and cyclopentadienone as examples of singly- and doubly-bound oxygen, respectively. Some of the results are given in Figure 3 and Figure 4.

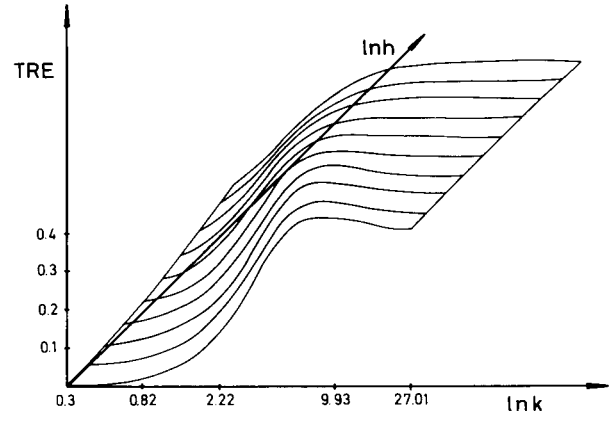


Figure 3. The influence of heteroatom (h) and heterobond (k) parameters on TRE values of furan.

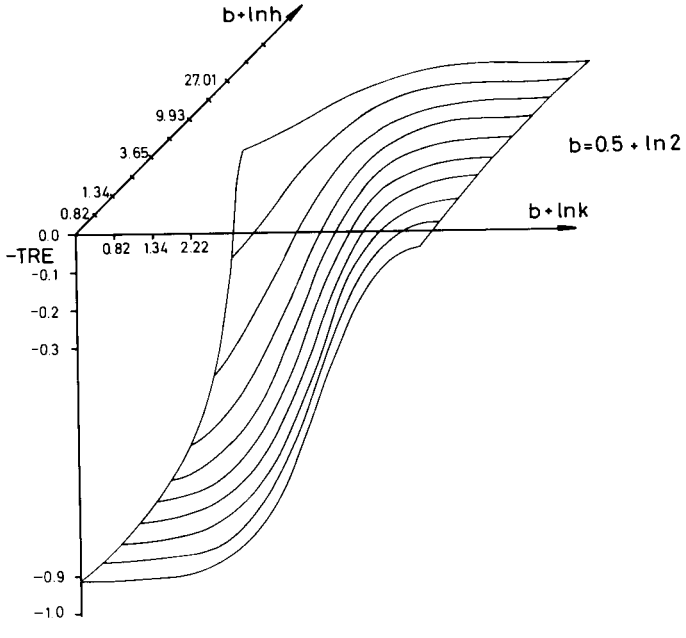


Figure 4a and b. The influence of heteroatom (h) and heterobond (k) parameters on TRE values of cyclopentadienone.

Obviously each h,k pair associated with an atom and bond (56), respectively, induces a specific TRE plane for a prescribed number of π-electrons. The planes that best mimic the experimental physical and chemical properties give the most usable set of heteroparameters for the species under consideration (57,58). In this work, however, the standard set of heteroparameters (23,55) was used in order to check the TRE procedure in its original form.

A combination of these parameters is used in calculating TRE values for models of species involved in the coumarin/chromone tautomerism, or E→(*24*) permutation isomerization. 4-hydroxy-2*H*-1-benzopyran-2-one (**5**) and 2-hydroxy-4*H*-1-benzopyran-4-one (**8**) are two boundary

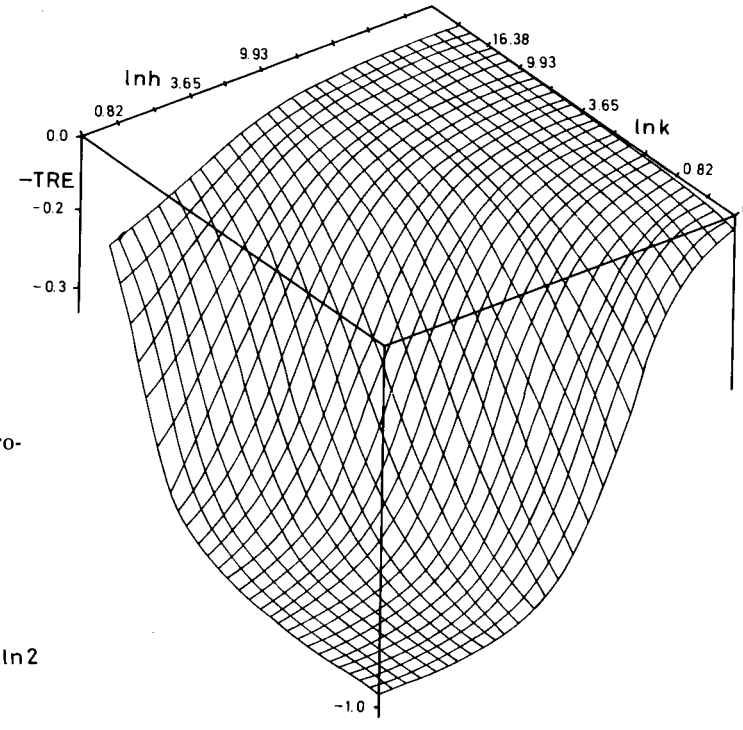


Figure 4 b

state forms. The corresponding TRE values are almost the same which is in accordance with most of the chemical evidence. The difference between the TRE values of (**5**) and (**8**), TRE(**8**) - TRE(**5**) > 0, however small and inconclusive places the 2-hydroxy-4*H*-1-benzopyran-4-one tautomer against the experimental evidence. The third tautomer (**6**) is in equilibrium with (**5**) and (**8**), however, it is by no means more aromatic than the other tautomers, as the corresponding TRE values would suggest. The 2,4-dione derivative (**6**) is either a nonconjugated species or a biradical; the latter fact has been largely ignored by the TRE procedure (59,60). Hence the unjustifiably high TRE values of (**6**). A possible intermediate is represented by the 2,4-diol derivative (**7**). A high positive difference between TRE values of the neutral and the anionic form, ΔA, indicates that the diol exists as an anion. According to the classical approach (61) to coumarin/chromone tautomerism, 4-hydroxy-2*H*-1-benzopyran-2-one exchanges with 2-hydroxy-4*H*-1-benzopyran-4-one. The reaction pathway is based on the loss of a proton and formation of the intermediary 2,4-diol anion. This path given a graph-theoretical treatment is schematized by the following sequence of TRE values:

$$[\mathrm{TRE}(\mathbf{5})^- = 0.244] \rightarrow [\mathrm{TRE}(\mathbf{7})^- = 0.225] \rightarrow [\mathrm{TRE}(\mathbf{8})^- = 0.257] \quad (3)$$

The graph-combinatorial treatment of the "tautomeric triad", *i.e.* 4-hydroxy-2*H*-1-benzopyran-2-one (**5**), 2,4-dihydroxy-2*H*-1-benzopyryl anion (**7**), and 2-hydroxy-4*H*-1-benzopyran-4-one (**8**), respectively, has been expanded to

the 3-amino derivatives (**13**, **14**, **15**) and 3-acetyl derivatives (**16**, **17**, **18**). Corresponding TRE values are given in the Table; in certain aspects they mimic the TRE values of the original triad and in certain aspects they do not. It is interesting to note that the TRE values of both series of derivatives, like those of the original species, suggest greater aromaticity of the 2-hydroxy derivative with respect to the 4-hydroxy derivative. The TRE differences between these two series are small, however, the chemical evidence requires different ordering (62). The TRE value of 3-amino-2*H*-1-benzopyran-2-one indicates rather an absence of aromatic stabilization though the substance is thermodynamically stable. Deprotonation of 2,4-dihydroxy-3-acetyl-1-benzopyran (**17**) is, according to the negligibly small ΔA value, not a favourable process as is the case with the acetyl-unsubstituted diol (**7**). The acetyl diol is expected to be stable enough even in the neutral form. On the other hand, the process of tautomerization, given by the sequence of TRE values for the 3-acetyl derivatives follows scheme (3) very closely, as given by the scheme below,

$$[TRE(\mathbf{16})^- = 0.239] \rightarrow [TRE(\mathbf{17})^- = 0.223] \rightarrow [TRE(\mathbf{18})^- = 0.255] \quad (4)$$

The low TRE value of the 3-amino-2,4-dihydroxyl-1-benzopyryl anion (**17**)$^-$, TRE = 0.03832 and TRE(PE) = 0.00255, with respect to the TRE values of (**16**)$^-$ and (**18**)$^-$, indicates that the diol may not be an intermediate in a tautomeric exchange, if there is any.

When considering the multigrouped species, *eg.* (**13**) to (**18**), by correlating the TRE values with the chemical evidence, it is essential to understand that a possible correlation of this kind is influenced by a legion of factors (*vide infra*). In other words, a complexity of physicochemical properties, typical of multifunctional species, should be treated very carefully within the set of associated TRE values.

Much of the current work on coumarins emphasizes electronically excited states. As was stated, the TRE method is isometric with the Hückel MO method which technically means that the physics lying behind the HMO method is largely transplanted to the TRE method. Knowing the general characteristics of the HMO method one could conclude that the TRE method might not be a method of choice to analyse the excited states chemistry of coumarins. Some general rules, however, can be set by making simple extrapolations of the ground state properties. The hydroxyl derivatives are again more interesting than coumarin itself (63). The batochromism associated by the TRE HOMO-LUMO (64) gap though this difference varies with the position of the substituent. The TRE HOMO-LUMO gap of 4-hydroxycoumarin is approximately 1/5 smaller with respect to coumarin, which is in accord with the red shift of the maxima in absorption bands of the corresponding uv spectra (65,66).

Particularly interesting and enlightening is the variation in the acid/base properties of the pyrone part with respect to the benzene part of the molecule in the course of $\pi \rightarrow \pi^*$ excitation (67). Conjugate acid/base properties in the ground and excited state were found (12) to be responsible for the fluorescence of 4-methylumbelliferone, a well-known lasing species in tunable dye lasers. It may be interesting to correlate the TRE values with the pK_a's associated with deprotonation of the ground state and excited state umbelliferone, as shown in Figure 5.

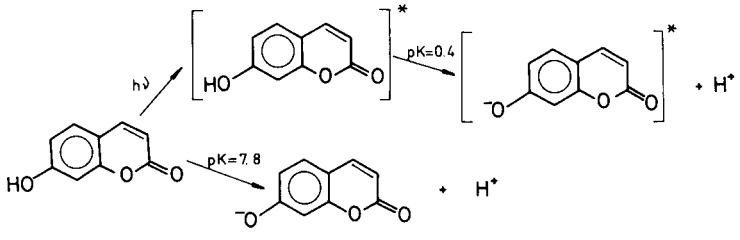


Figure 5. The pK_a values associated with deprotonation of umbelliferone in the ground state and excited state.

The proton release in both cases results in an anion; getting an electron has the same result. If the ΔA values are to be correlated with the ease of releasing one proton it follows that $\Delta A^* > \Delta A$. The ratio of the equilibrium constants for the two processes given in Figure 5 indicates that umbelliferone in the excited state is some $2 \cdot 10^7$ times more acidic than in the ground state (67). When the topologies of ground state and excited state umbelliferone are taken the same, the calculated ΔA TRE values do not corroborate the above reasoning; they are practically the same for both states.

The analogous process taking place on the pyrone part of the molecule is described by the dissociation of the protonated carbonyl oxygen cation. The ease of proton release is about $3 \cdot 10^4$ times smaller in excited state umbelliferone than in the ground state. This ratio is more modest in the case of coumarin and is two hundred. Consequently, the pyrone part in excited state of umbelliferone is about $10^{2.2}$ times more basic than it is in excited state of coumarin. Within the formalism of the applied graph-combinatorial procedure the process of protonating the pyrone carbonyl oxygen might be represented by appropriate ΔC values. Topological resonance energy values calculated in such a way do not, however, conform to the experimental facts (*vide supra*).

It would certainly be unjustified and unfair to expect a single property, based on molecular connectivity only, to follow closely the changes in the pK_a's caused by electronic excitation of a molecule. However, the lack of any correlation between ΔpK_a's and ΔTRE's could indicate some deficiencies in the graph representation of coumarins. It certainly indicates deficiencies of a simple

monoelectronic method in an analysis of electronically excited states. This lack could originate from the variable chemical topology. Expressed in common words: coumarin is not a fully conjugated system in the ground state and its uniform graph representation is not quite justified. The incomplete conjugation has long been suspected and is corroborated by some chemical and physical evidence (68-70). This situation seems to be different in electronically excited states. According to SCF-MO-CI calculations (16) the α-pyrone part of a molecule undergoes specific transformations upon electronic promotion. Two of these are equalization of bond lengths between the centers C(3) and C(4) and C(4) and C(5) and spin delocalization. These suggestions fall in well with certain chemical facts (*vide supra*). In terms of simple MO methods, based on the nearest neighbor interactions, the first change - lengthening of a bond - has been commonly dealt with by associating a parameterized value to the resonance integral, C(4) -C(5) in this case. The parameter is varied as the system gets excited, as is schematically indicated in Figure 6.

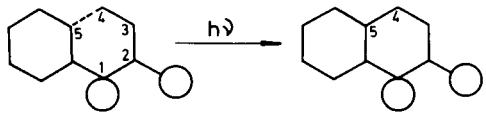


Figure 6. The change of the bond length and the value of the resonance integral of the C(4)-C(5) bond on excitation.

In terms of the graph-combinatorial approach a mutant graph is introduced. It is essential that the acyclic reference graph be mutated in the same way. The described procedure used within the Hückel MO formalism would probably give consistent results with a careful choice of parameters. In the case of the TRE method the situation is not so easy. Combinatorial properties of both molecular and reference graphs are connected in a complicated way. The procedure of variation of the parameter associated to centres C(4) and C(5) within common bounds (0.0, 1.0) does give the expected trend in the TRE values of simpler bicyclic systems, naphthalene for example. Variation of the parameter associated to the bond C(4) - C(5) in both molecular and reference graphs gives a ratio $(\Delta TRE)/(\Delta k_{45}) = +0.044$ for the k_{45} being varied within the bounds (0.67, 1.00). In the case of coumarin, however, the same variation does not give the expected trend in TRE values. Nevertheless, if such a mutation is used in representing the protonation/deprotonation processes of the ground state and excited state of coumarin, various results are obtained. It was found that deprotonation of the pyrone carbonyl oxygen cation is much less favoured in the excited state of coumarin thus requiring the ΔC in the ground state to be more negative. The mutated graph representation gives the expected trend in the TRE values. This is not the case when TRE values are correlated with the dissociation of the phenolic group of substituted coumarin. It appears that hardly any rules exist.

Conclusion.

In the present paper a topology-based method was used to calculate the π-electronic energies of coumarins. The method is essentially one-dimensional with restricted discrete metric. It is probably the most efficient (71) one-dimensional MO method. Its usefulness and simplicity in conjugated ring compounds has been proved many times. The method, however, is based on the essential prerequisite of chemical homogeneity of the compounds under consideration. The coumarins are obviously not a very "homogeneous" species, particularly as far as the pyrone part is considered. The lack of such a prerequisite can be cured by use of parameter-varying graphs. One can easily make further steps following this trend. A multivariable set of characteristic polynomials can be constructed. By a careful choice of parameters various effects could be simulated. Possible difficulties are of numerical character involving the search for minima in a multidimensional space. However, such a strategy is basically devoid of any deeper physical sense. Technically, it no longer has a graph-theoretical character.

The one-simensional topological representation of coumarin-like compounds can be used for a crude estimate of the chemical stability or reactivity. However, for the many-faceted chemistry of such multifunctional species as the coumarins, the topology-based representation is not sensitive enough.

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$$\alpha_X = \alpha_C + h_X\beta_{CC}$$

$$\beta_{CX} = k_{CX}\beta_{CC}$$

where α_C and β_{CC} are standard parameters for carbon compounds, while $h_X(=h)$ and $k_{CX}(=k)$ are parameters to be determined from the experimental properties of a particular class of heterocycles.

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