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Hydrolysis of Benzopyrylium Dyes – An Application of the Concept of Chemical Hardness

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Abstract. A systematic study on the relationship between the substitution pattern, the pK_a values, and spectral properties of flavylium cations and the respective $-(CH_2)_2-$ bridged analoga (5,6-dihydrobenzo[c]xanthylium cations) is given in order to find rules concerning their spectral behaviour and their chemical reactivity.

Our results show that the concept of chemical hardness can explain the different reactivity of 4'- and 7-substituted flavylium ions against HO^-. The pK_a values of these species, which can act as a measure of reactivity with respect to a nucleophile, correlate linearly with the absolute hardness calculated from half the energy gap between the frontier orbitals. Since the longest-wavelength UV/VIS absorption maximum is mainly determined by the HOMO-LUMO transition, an analogous linear correlation is obtained between the spectral 0–0 transition and the pK_a value. Deviations from these correlations are assumed to be due to steric effects.

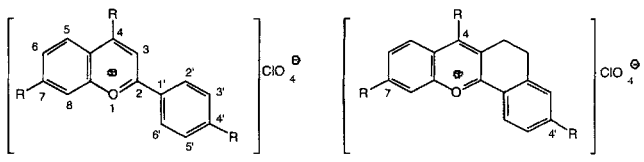
Benzopypylium dyes are known to show valuable properties for special applications. In particular, the 4'- and 7-substituted flavylium cations **1a–l** and their bridged derivatives (5,6-dihydrobenzo[c]xanthylium ions) **2c,g,k** are often able to show a photochromic behaviour. In aqueous solutions they are hydrolysed resulting in colourless or yellow products [15]. Some of them can be converted back to the initial benzopyrylium compound by light, thus, constituting a photochromic system [3, 4].

The strong fluorescence, especially of the bridged methoxy substituted benzopyrylium salts, accompanied by sufficient stability in solution and against light implies an application as laser dyes, too [6, 7].

In contrast to dyes acting as photochromic materials, a laser dye must not undergo any conversions in solution for long times. The instability of many benzopyrylium salts seems to be the main limitation for their application as laser dyes.

Our study reports on the influence of substituents as well as the $-(CH_2)_2-$ bridge on the reactivity of benzopyrylium ions in aqueous solutions and the longest-wavelength UV/VIS transition. The aim of our investigations is the design of benzopyrylium dyes for application both as photochromic materials and laser dyes.

The benzopyrylium dyes studied in this work are compiled in Scheme 1.



1a–m **2c,g,k,m**

	R^7	$R^{4'}$	R^4
a	H	H	H
b	H	Me	H
c	H	OMe	H
d	H	NMe_2	H
e	OMe	H	H
f	OMe	Me	H
g	OMe	OMe	H
h	OMe	NMe_2	H
i	NEt_2	Me	H
j	NMe_2	OMe	H
k	NEt_2	OMe	H
l	NMe_2	NMe_2	H
m	OMe	OMe	Ph

Scheme 1

Experimental

Melting points were determined with a Kofler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a 400 MHz Bruker spectrometer (AMX 400) in DMSO with TMS as internal standard. Absorption and fluorescence measurements were made with a Perkin Elmer Lambda 16 or

an LS 50 spectrometer, respectively. The pH measurements were performed by means of a Schott pH-meter CG 825 and a glass electrode N 42 A.

The benzopyrylium salts were synthesized as described in [8] and [9]. In all cases their anion is ClO_4^-.

The hydrolysis of the 7,4'-dimethoxyflavylium perchlorate (**1g**) has been performed as follows: 100 ml of 1 M aqueous solution of sodium acetate as buffer were added to 20 ml of a saturated solution of 7,4'-dimethoxyflavylium perchlorate (**1g**) in ethanol. After standing for at least three days in the dark its hydrolysis product (**5a**) was separated and recrystallized from methanol. *m.p.* 147–149 °C.

The *trans* geometry of the product (**5a**) was established by the coupling constant of the vinylic H-atoms in the ^1H NMR spectrum, which was $^3J = 15.6$ Hz.

The hydrolysis product of the bridged homologue has been prepared from 3,10-dimethoxy-5,6-dihydrobenzo[c]xanthylium perchlorate (**2g**) in the same way as that of the non-bridged form. *m.p.* 163–165 °C.

The ^{13}C NMR spectrum of the final product of hydrolysis (**6a**) gives a $\delta = 185.53$ ppm, indicating its structure as a chalcone. By a NOESY experiment, showing the neighbourship in space between a H-atom of the phenyl ring and one of the $-(CH_2)_2-$ bridge in a cross peak, it was verified that the *trans* isomer is the only final product.

(*trans*)-3,4-dihydro-2-((2,4-dimethoxyphenyl)methylene)-1(2H)-7-methoxynaphthalenone (**6b**) has been synthesized by a base-catalyzed aldol condensation of 2,4-dimethoxybenzaldehyde and 7-methoxy-1-tetralone as described in [3]. *m.p.* 114 °C. – Anal. Calcd. for $C_{20}H_{20}O_4$: C 74.06 H 6.21 Found: C 73.76 H 6.51. The *trans* geometry has been established by the NOESY experiment as above mentioned.

The pK_a values of the flavyium compounds were determined in an aqueous medium. 1 ml aliquotes of the stock solution (1 mg of the benzopyrylium salt in 25 ml 0.1 M aqueous HCl) were diluted to 10 ml with aqueous buffer consisting of 2.4 ml glacial acetic acid, 2.7 ml 85 mass% phosphoric acid, 2.47 g crystalline boric acid per liter. The pH was adjusted with 3 M aqueous sodium hydroxide solution.

For the observation of the effect of bridging and the influence of the 4-phenyl substituent, a mixture consisting of the above mentioned buffer solution and 20% acetonitrile was used. After standing for 6 to 7 hours in the dark at room temperature the determination of the pK_a values was carried out UV/VIS spectroscopically.

In all studied benzopyrylium cations the hydrolysis reaction is completely reversible and the equilibrium is not complicated by pH dependent consecutive or side reactions. This is revealed by the presence of good isosbestic points in the pH dependent reaction spectra (Fig.1). The pK_a values were calculated according to equation (1).

$$pK_A = pH - \lg\frac{A_H^0 - A_H}{A_H} \qquad (1)$$

A_H^0 and A_H refer to the absorbances of the benzopyrylium cation at the longest-wavelength absorption band in the initial pure state and in the thermal equilibrium, respectively. The standard deviation is ± 0.08.

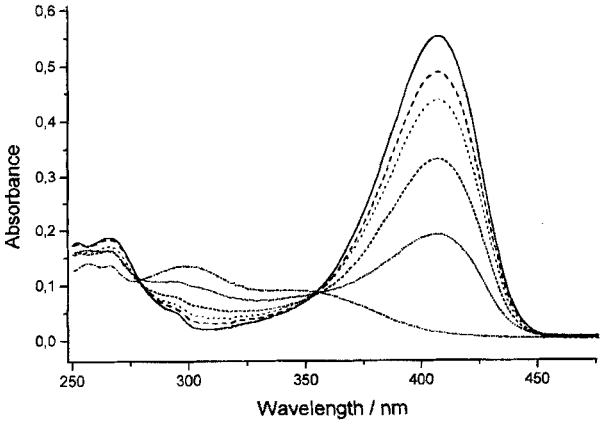


Fig. 1 Thermal equilibrium between the benzopyrylium dye **1b** and the 2-hydroxychalcone as a function of pH in aqueous solution. Solid line: pH=1.70, dashed line: pH=2.53, dotted line: pH=2.88, short-dashed line: pH=3.23, short-dotted line: pH=3.81, dot-dash line: pH=6.84.

The optimized molecular geometry, the electron affinity, A, the ionization potential, I, and the energies of the frontier orbitals, E_{HOMO} and E_{LUMO}, were obtained from MNDO-PM3 calculations within the MOPAC6 package, version 6.30 [10]. The keywords PM3, EF, and PRECISE were used.

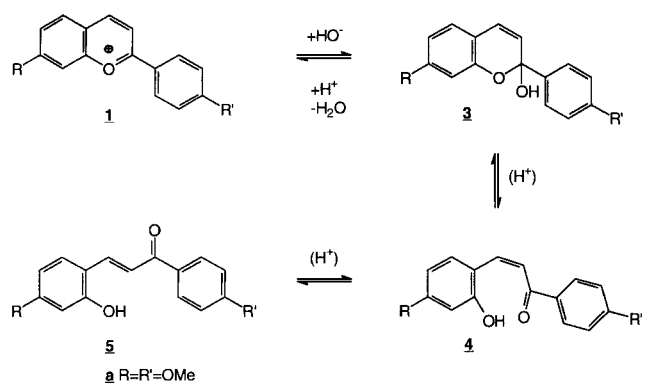
The spectral transitions were calculated from the optimized MOPAC6 geometries by means of VAMPC, PC-version 4.56 [11], using the keywords INTENS and C.I.=6. All calculations were performed on a PC 486 DX-33.

Results and Discussion

In aqueous solutions all studied benzopyrylium dyes undergo a thermal degradation. It leads generally to their decolouration caused by the formation of colourless or yellow flavenes and 2-hydroxychalcones. The final hydrolysis products of these benzopyrylium salts are usually trans 2-hydroxychalcones [1–5]. In the literature [3] the mechanism given in scheme 2 is supposed to occur at pH 3–6. In aqueous solutions the addition of the HO^- in 2-position of the benzopyrylium unit converts the flavylium cation to a 2-hydroxyflavene (**3**). The subsequent reaction steps are acid catalyzed. Being an acetal, the 2-hydroxyflavene reacts to the corresponding *cis* 2-hydroxychalcone (**4**) as the tautomeric carbonyl compound which is readily transformed into its *trans* isomer (**5**).

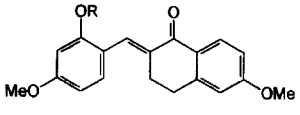
Furthermore, it is evident from kinetic studies that in more basic solution (pH=12) the nucleophile can alternatively add in 4-position of the benzopyrylium unit to form a 4-hydroxyflavene [1]. This species occurs, however, as a kinetic product only.

We verified the structures of the final products of **1g** and **2g**, being **5a** and **6a**, by means of ^1H and ^{13}C NMR spectroscopy. For comparison of the UV/VIS spectra of **6a** the respective 2-methoxychalcone **6b** was synthe-



Scheme 2

sized. The chromophore system should not be changed significantly if the 2-OH substituent is replaced by a OMe group. The UV/VIS spectra of both **6a** and **6b** are found to be identical (in acetonitrile λ_{max}=343 nm).



6 a: R = H
b: R = Me

The synthesis of an authentic sample of **6a** according to [3] failed due to the poor reactivity of the 2-hydroxy-4-methoxybenzaldehyde in basic solution.

The products of the other benzopyrylium dyes **1a–m** and **2c,g,k,m** were only identified by UV/VIS spectroscopy and the behaviour at higher pH values. In basic medium (pH up to 10) the hydrolysis products of the 4'- and 7-substituted benzopyrylium cations **1a–l** and **2c,g,k** show a bathochromic shift of the longest-wavelength absorption band, which indicates the deprotonation of the phenolic OH group. It follows that 2-hydroxychalcones are formed.

On the contrary, the products of the 4-phenyl substituted species, **1m** and **2m**, absorb both at a relatively short wavelength and remain unchanged at higher pH values. That means, 2-hydroxychalcones are not formed as hydrolysis products. Here it is more likely that hydroxyflavenes are the final products.

For all flavylium cations, F^+, studied here, an acidity constant can be defined according to reaction (2). It refers to the first step of the hydrolysis reaction of the benzopyrylium ions, the formation of the corresponding hydroxyflavene, FOH.

$$F + H_2O \rightleftharpoons FOH + H^+ \qquad (2)$$

We only investigated those benzopyrylium cations which show clear isosbestic points in the pH dependent spectra, so that pH dependent side and other subsequent reactions can be neglected. Therefore, the acidity constants are equal to the overall equilibrium constants.

The acidity constant of the benzopyrylium ions can serve as a measure of their thermodynamic stability in aqueous solutions and express the tendency to nucleophilic addition of HO^- to the aromatic benzopyrylium cation. Thus, the higher the pK_a the more stable is the compound in aqueous solutions.

The donor substituents and the $-(CH_2)_2-$ bridge influence the reactivity of the benzopyrylium cations and their UV/VIS absorption and fluorescence spectra. Also the band structure and the Stokes shift may be changed. In order to get a unified measure of the spectral transition we consider only the wavenumber of the 0–0 transition. This is obtained from the average of the wavenumbers of the lowest-energy absorption and the highest-energy fluorescence transition. The latter ones were estimated with the help of band analyses.

As seen in Table 1, the donor substituents in 7- and 4'-position lead generally to a shift of the 0–0 transition to lower wavenumbers. A donor group in 4'-position brings about, however, a larger effect than the same substituent in 7-position.

Considering the sensitivity against hydrolysis, the 4'-substitution also causes a higher stability than the 7-one. But, a species with a methoxy substituent in 7-position destabilizes the flavylium system against a nucleophilic attack. Thus, concerning the behaviour against HO^-, compound **1e** is thermodynamically the least stable flavylium ion of all studied ones. An analogoues destabilizing effect has previously been observed in the case of a 7-OH group [5].

In contrast to the donor substituents in 4'- and 7-position the 4-phenyl group does not affect the longest-wavelength absorption and fluorescence bands. Therefore, the 0–0 transition of the 4-phenyl substituted benzopyrylium cations, **1m** and **2m**, and the respective species without the 4-phenyl group, **1g** and **2g**, are identical.

However, the reactivity of the 4-phenyl substituted species with the nucleophile decreases dramatically. The pK_a values of **1m** and **2m** are found three pH units higher than that ones of **1g** and **2g**.

The insertion of a $-(CH_2)_2-$ bridge between the 3-position of the benzopyrylium and the 2'-position of the phenyl unit leads to a bathochromic shift of the absorption and fluorescence maximum by 15–20 nm. The pK_a values of the bridged species, however, increase considerably, by about two pH units (see Table 1).

The effect of destabilization by a methoxy substituent in 7-position is also shown in the bridged benzopyrylium ions.

As our calculations show, the bathochromic shift of the longest-wavelength absorption band can essentially be explained by the mesomeric and inductive effects

Table 1 Relevant data of the benzopyrylium cations. The pK_a values were obtained in aqueous buffer solution. The longest-wavelength absorption and fluorescence band, λ_a, and λ_f (nm) were measured in dichloromethan. The wavenumber of the 0–0 transition, $\tilde{\nu}_{0-0}$ (cm^{-1}), were calculated by band analysis of the absorption and fluorescence band. The energies of the frontier orbitals, E_{HOMO} and E_{LUMO}, and the absolute hardness, η, are given in eV.

	pK_a	λ_a	λ_f	$\tilde{\nu}_{0-0}$	η	$-E_{HOMO}$	$-E_{LUMO}$
1a	2.62	404	434	23183	3.54	13.18	6.09
1b	3.43	424	455	22504	3.43	12.86	6.00
1c	3.95/3.70[a])	462	502	20585	3.31	12.49	5.86
1d	5.97	537sh573	669	16866	3.02	11.47	5.43
1e	2.54	441	474	21740	3.40	12.72	5.90
1f	2.69	457	480	21428	3.35	12.52	5.82
1g	3.08/2.41[a])	480	502	20230	3.26	12.23	5.71
1h	4.83	569	607	16838	2.99	11.32	5.34
1i	5.25	527sh555	598	17202	3.12	11.66	5.42
1j	5.51	558	593	17221	3.07	11.55	5.40
1k	5.28[a])	534sh561	598	17031	3.07	11.53	5.35
1l	6.10	606	633	16185	2.92	11.04	5.20
1m	5.44[a])	477	491	20248	3.26	12.05	5.53
2c	5.56[a])	476	499	20524	3.30	12.38	5.78
2g	4.79[a])	497	512	19733	3.24	12.10	5.63
2k	7.84[a])	583	611	16760	3.06	11.38	5.26
2m	7.01[a])	491	510	19846	3.25	11.95	5.46

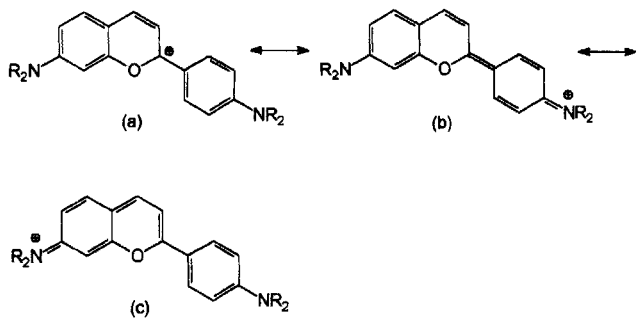
[a]) measured in a mixture from aqueous buffer and 20% acetonitrile

of the bridge. We simulated the effect of bridging by calculating the absorption bands of the non-bridged flavylium cations, unsubstituted and 3- and 2'- methyl substituted. Since the geometry optimization reveals that in the bridged species, a dihedral angle of 13.8° occurs between the benzopyrylium unit and the phenyl group; this angle was fixed during all calculations. As a result, we observed that methyl substution in both cases leads to a bathochromic shift of the longest-wavelenght absorption band. For the non-bridged flavylium ion we observed 369 nm, whereas for the 3-Me and the 2'-Me substituted ones we got 380 and 386 nm, respectively. The magnitude of the bathochromic shift is comparable to the experimental shift between the non-bridged and the bridged flavylium ions.

Absolute Hardness

A consideration of the hydrolysis products of the benzopyrylium cations suggests that the nucleophilic attack of HO^- occurs at 2-position of the benzopyrylium unit. Therefore, one may assume that an increasing donor strength of the substituent in 4'- and/or 7-position decreases the positive atomic charge at C–2 according to the mesomeric formulas (**b**) and (**c**). However, this is not the case (see Table 2). Also, no correlation exists between the pK_a values and the heats of formation of the benzopyrylium cations.

However, we find a statistically evident relationship between the pK_a and the 0–0 transition as well as the energy gap between the frontier orbitals. These relationships can reasonably be explained within the concept of chemical hardness which justifies Pearson's HSAB Principle.



The absolute hardness, η, of an atom or a molecule has been defined as the second derivative of the electronic energy, E, with respect to the number of electrons, N, at a constant external potential, v [13, 14].

$$\eta = \frac{1}{2}\left(\frac{\delta^2 E}{\delta N^2}\right)_v = \frac{1}{2}\left(\frac{\delta \mu}{\delta N}\right)_v \qquad (3)$$

Since the first derivative of the electronic energy with respect to the number of electrons is the chemical potential, μ, the hardness can be explained as the sensitivity of the chemical potential to changes in the number of electrons. That means the chemical hardness characterizes the resistence of a chemical species to changes in its electronic configuration [13, 15].

Table 2 Atomic charges at C-2, $q_{C\text{-}2}$, and heats of formation, ΔH_f, of the benzopyrylium cations

	ΔH_f [kcal mol^{-1}]	$q_{C\text{-}2}$
1a	201.1631	0.322
1b	190.1415	0.324
1c	159.5452	0.328
1d	189.4657	0.315
1e	159.9674	0.313
1f	149.1315	0.317
1g	118.7341	0.323
1h	149.2545	0.318
1i	168.3228	0.283
1j	149.2922	0.297
1k	136.2248	0.294
1l	180.8761	0.310
1m	141.6729	0.315
2c	149.0041	0.329
2g	108.3920	0.324
2k	126.7040	0.291
2m	133.2455	0.315

The finite differences approximation supplies a working definition for the absolute hardness of a molecule. That way, the absolute hardness is easily obtained from the difference between the ionization potential, I, and the electron affinity, A, or the energy gap between the highest occupied molecular orbital, E_{HOMO}, and the lowest unoccupied molecular orbital, E_{LUMO}, respectively, according to equation (4):

$$\eta = \frac{1}{2}(I - A) = \frac{1}{2}(E_{LUMO} - E_{HOMO}) \qquad (4)$$

Due to the large size of the benzopyrylium cations and their easily polarizable conjugated π-electronic systems the hardness of the benzopyrylium cations is found in the region of soft molecules [13, 14, 16]. HO^- belongs to hard bases [13].

Regarding the 7- and/or 4'-substituted flavylium ions we found that a growing donor strength of the substituents causes a decreasing energy gap between the frontier orbitals. That means the stronger the donor ability of these substituents the softer is the benzopyrylium ion. In accordance with the HSAB principle that hard/soft bases prefer to coordinate with hard/soft acids, we found that the reactivity increases with an increasing absolute hardness of the benzopyrylium cation. As presented in Fig. 2, we obtained a fairly good linear relationship between the absolute hardness and the pK_a value. The correlation coefficient r is −0.9937 when the 7-methoxy substituted flavylium ions are excluded from this group and treated separately. The negative correlation coefficient occurs since a small pK_a characterizes a high reactivity.

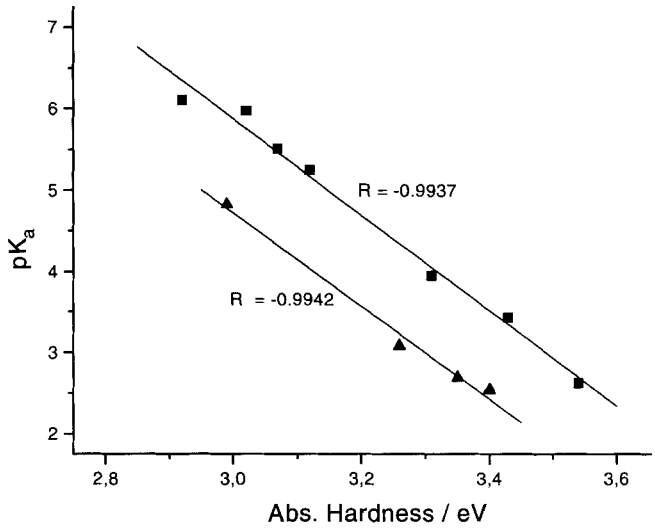


Fig. 2 Plot of the pK_a value of the 4',7-substituted non-bridged flavylium cations in water versus the absolute hardness, h, calculated using the MNDO-PM3 Hamiltonian. – Squares: 4',7-substituted non-bridged flavylium cations without the 7-OMe group. – triangles: 7-OMe substituted species **1e–h**.

The 7-methoxy substituted species **1e–h** are found generally below the regression line of the other 7- and 4'- substituted flavylium species **1a–d** and **1i–l**. By now, we can not give a reasonable explanation of this destabilization, but since it is also observed in the bridged derivatives, this phenomenon must be regarded as a general one. In the series of the 7-methoxy compounds, we also get a fairly good linear correlation between hardness and reactivity (r = −0.9942). The regression lines of the „normal" 7- and 4'-substituted flavylium cations and the 7-methoxy substituted ones run nearly parallel.

Since the lowest-energy absorption bands of all studied benzopyrylium systems are calculated to be mainly determined by the HOMO-LUMO transitions, the 0–0 transition correlates linearly with the absolute hardness. The correlation coefficient is r = 0.9877 (see Fig. 3).

Therefore, the same picture as the relationship between hardness and pK_a is obtained when the absolute hardness is replaced by the wavenumber of the 0–0 transition from absorption and fluorescence (see Fig. 4). The correlation coefficients are r = −0.9889 in the „normal" and r = −0.9972 in the 7-methoxy substituted species. It shows that in the 7- and 4'-substituted flavylium ions a direct relationship exists between the lowest-energy UV/VIS transition and the reactivity. The relationship between hardness as well as 0–0 transition with the pK_a opens the opportunity to predict the sensitivity of the 4'- and 7-substituted flavylium cations against hydrolysis precisely. However, the prediction is limited to the non-bridged flavylium ions which do not bear additional substituents.

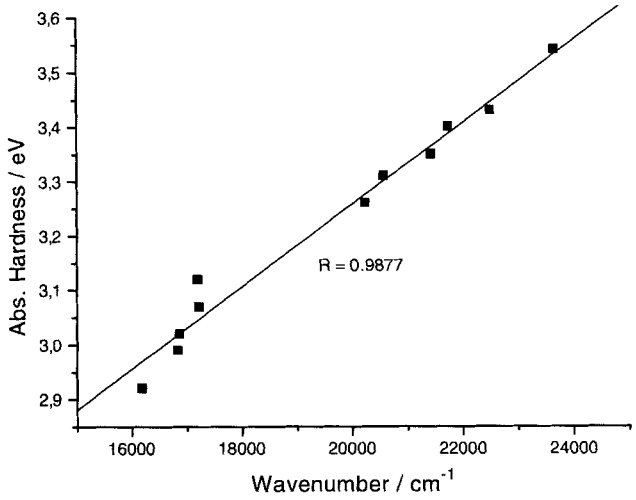


Fig. 3 Correlation between the absolute hardness calculated by means of the MNDO-PM3 Hamiltonian and the wavenumber of the 0–0 transition in dichloromethane.

The 4-phenyl substituted flavylium cations (**1m**) and the bridged ones (**2c,g,k,m**) are much more stable than expected from the above mentioned relationships. In these cases it is assumed that, in particular, steric factors are important for the stabilization.

In the bridged benzopyrylium cations the structural rigidization and the fact that the two methylene groups of the bridge are twisted out of the plane might cause a steric hindrance. The addition of a nucleophile can be complicated when the bridge forces the molecule in a rigid geometry, since the formation of the 2-hydroxyflavene as the first reaction step can only occur when the phenyl moiety is stronger twisted out of coplanarity with the benzopyrylium unit. Furthermore, the surrounding solvent molecules may also play a role in the stabilization. They are assumed to shield the bridged benzopyrylium ions more from the nucleophile than the non-bridged ones. In the bridged benzopyrylium cations, the solvent molecules cannot easily be pushed aside during the approach of the nucleophile because of the rigid geometry of the flavylium molecule and the methylene units of the bridge. This might result in a decreasing probability of an effective reaction.

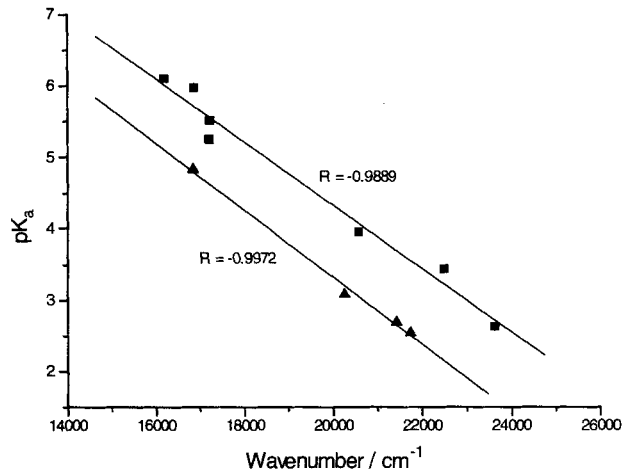


Fig. 4 Plot of the pK_a values of the 4',7-substituted non-bridged flavylium cations in water versus the wavenumber of the 0–0 transition in dichloromethane. – Squares: 4',7-substituted non-bridged flavylium cations without the 7-OMe group. – triangles: 7-OMe substituted species **1e–h**.

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