Chemometric characterization of the hydrogen bonding complexes of secondary amides and aromatic hydrocarbons

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Abstract

This paper reports the results of the study of hydrogen bonding complexes between secondary amides and various aromatic hydrocarbons. The possibility of using chemometric methods was investigated in order to characterize N–H···π hydrogen bonded complexes. Hierarchical clustering and Principal Component Analysis (PCA) have been applied on infrared spectroscopic and Taft parameters of 43 N-substituted amide complexes with different aromatic hydrocarbons. The results obtained in this study are in good agreement with conclusions of other spectroscopic and thermodynamic analysis.

Keywords: hydrogen bonding; secondary amides; aromatic hydrocarbons; principal component.

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Hydrogen bonding of the amide group is an important factor that affects the structure of polypeptides and proteins. N-substituted amides are the simplest model molecules having a peptide group, and consequently, many studies have been devoted to the hydrogen bonding of N-substituted amides [1–5]. It is also well known that aromatic hydrocarbons can act as the proton acceptors and participate in hydrogen bonding with various phenols and amines [6]. The knowledge of weak N–H···π interactions on the molecular level contributes to a better understanding of their possible role in many biological systems [7]. In our laboratory, during a continuous and extensive research of N-substituted amides and their interactions in solutions, N–H···π, complexes were investigated using IR technique [8–11]. Chemometric methods are successfully applied to various chemical data, including the spectroscopic ones [12–14]. Consequently, it seems reasonable and interesting to treat IR spectroscopic data of N–H hydrogen bonds on the basis of chemometrics.

In this work, chemometric methods have been used for comparison of hydrogen-bonded complexes of different N-substituted amides with aromatic donors. Such chemometric identification has not been reported previously. We believe it can be useful in qualification of different hydrogen bonded systems. Principal component analysis (PCA) and hierarchical cluster analysis were applied in order to visualize multivariate spectroscopic data and to find relationships among variables.

EXPERIMENTAL

Materials and methods

Various N-monosubstituted formamides, acetamides, and propionamides, of general formula $HCONHR$, CH_3CONHR, and CH_3CH_2CONHR, wherein R is methyl, ethyl, *n*-butyl, sec-butyl, isobutyl, tert-butyl, cyclohexyl, were synthesised by Schotten–Baumann reaction of acylation of the corresponding amines with alkyl chloride [15,16]. The purity of these N-monosubtituted amides was checked by GC and mass spectrometry. For all samples used in this work the purities were estimated to be 99.2% or better. The aromatic hydrocarbons were obtained from commercial sources (Frinton, Fluka, >97%) and have been used without further purification.

Hydrogen bonding parameters of investigated complexes are summarized in Table 1.

In order to avoid self-association, amide concentration in carbon tetrachloride solutions was below 0.003 mol dm^3. Concentration of the aromatic hydrocarbons varied between 0.2 and 1 mol dm^{-3}.

Infrared spectra have been obtained using Bomem MB 100 FTIR spectrophotometer with 1 cm UVIRSIL cell and measurements have been performed at 298 K. The reported frequencies and half-widths were reproducible within 0.2 and 1 cm^{-1}, respectively. The integrated molar absorption coefficients were obtained within ±5%. The equilibrium constants were determined with average relative standard deviation of 6%. The uncertainties in ΔH are within ±0.25 kJ mol^{-1}, respectively.

Deconvolution of the partially overlapped complex and free ν(NH) bands and calculation of spectroscopic variables (Δ$ν$, $ν_{1/2}$ and B) was done using PeakFit software (Aspire Software International's, Ashburn, USA). The formation constants were determined from the

Table 1. Hydrogen bonding parameters of investigated complexes

Amide	No.	Electron donor	Δv cm^{-1}	$v_{1/2}$ cm^{-1}	$B^{\times}10^6$ cm mol^{-1}	K dm^3 mol^{-1}	$-\Delta H$ KJ mol^{-1}	$\Sigma\sigma$	ΣEs
N-t-Butyl formamide	**1**	Benzene	23	20	5.14	0.26	5.0	−0.79	−2.78
	2	Toluene	29	25	5.73	0.31	5.3	−1.28	−4.02
	3	Ethylbenzene	30	25	5.89	0.33	5.5	−1.38	−4.09
	4	n-Propylbenzene	30	26	5.98	0.33	5.5	−1.4	−4.38
	5	n-Butylbenzene	31	26	6.07	0.35	5.5	−1.41	−4.41
	6	o-Xylene	31	26	6.11	0.35	5.4	−1.77	−5.26
	7	Mesytilene	38	31	6.82	0.43	6.0	−2.26	−6.5
	8	Durene	42	34	7.35	0.50	6.2	−2.75	−7.74
	9	Pentamethylbenzene	47	37	8.71	0.59	6.5	−3.24	−8.98
	10	Hexamethylbenzene	50	39	9.05	0.67	6.7	−3.73	−10.22
N-Cyclohexyl formamide	**11**	Benzene	23	27	9.43	0.19	5.1	−0.64	−2.03
	12	Toluene	28	30	10.93	0.26	5.3	−1.13	−3.27
	13	Ethylbenzene	30	34	11.33	0.27	5.5	−1.23	−3.34
	14	n-Propylbenzene	31	36	11.85	0.25	5.5	−1.25	−3.63
	15	n-Butylbenzene	32	37	12.46	0.28	5.7	−1.26	−3.66
N-ethyl acetamide	**16**	Benzene	19	21	7.25	0.29	4.8	−0.59	−1.31
	17	Toluene	24	25	7.95	0.37	5.1	−1.08	−2.55
	18	Ethylbenzene	25	26	8.02	0.38	5.2	−1.18	−2.62
	19	n-Propylbenzene	27	28	8.32	0.40	5.3	−1.2	−2.92
	20	Xylene	30	30	8.82	0.48	5.5	−1.57	−3.79
	21	Mesytilene	35	36	9.56	0.59	5.8	−2.06	−5.03
N-methyl propanamide	**28**	Benzene	19	19	7.29	0.23	4.8	−0.49	−1.24
	29	Toluene	24	23	7.98	0.28	5.1	−0.98	−2.48
	30	Ethylbenzene	26	24	8.22	0.32	5.2	−1.08	−2.55
	31	n-Propylbenzene	28	26	8.42	0.35	5.4	−1.1	−2.84
	32	Xylene	31	29	8.84	0.38	5.6	−1.47	−3.72
	33	Mesytilene	36	34	9.65	0.48	5.9	−1.96	−4.96
N-n-Butyl propanamide	**34**	Benzene	19	19	7.26	0.23	4.8	−0.49	−1.24
	35	Toluene	24	23	7.99	0.28	5.1	−0.98	−2.48
	36	Ethybenzene	26	24	8.26	0.32	5.2	−1.08	−2.55
	37	n-Propylbenzene	28	26	8.43	0.35	5.4	−1.1	−2.84
N-Isobutyl propanamide	**38**	Benzene	23	23	8.12	0.22	4.8	−0.615	−2.17
	39	Toluene	29	26	8.51	0.26	5.3	−1.105	−3.41
	40	Ethylbenzene	30	27	9.11	0.31	5.5	−1.205	−3.48
	41	n-Propylbenzene	31	29	9.42	0.34	5.5	−1.225	−3.77
N-sec-Butyl propanamide	**42**	Benzene	21	25	6.73	0.19	4.3	−0.7	−2.46
	43	Toluene	27	28	7.26	0.22	4.8	−1.19	−3.7
	44	Ethylbenzene	28	28	7.88	0.24	4.9	−1.29	−3.77
	45	n-Propylbenzene	29	30	8.19	0.27	4.9	−1.31	−4.06
N-t-Butyl propanamide	**46**	Benzene	18	19	6.36	0.16	3.8	−0.79	−2.78
	47	Toluene	23	22	6.84	0.20	4.3	−1.28	−4.02
	48	Ethylbenzene	25	24	7.02	0.20	4.4	−1.38	−4.09
	49	n-Propylbenzene	26	25	7.25	0.23	4.5	−1.4	−4.38

monomer absorbency using Becker's procedure [17]. The enthalpies of hydrogen bonded complex formation ΔH were calculated using the dependence of the equilibrium constants on temperature.

Data analysis

The 43 hydrogen bonded complexes are characterized by five spectroscopic parameters and two Taft steric and inductive constants: 1) complex band shift,

$\Delta\nu$, 2) half width of complex band, $\nu_{1/2}$, 3) the integrated molar absorption coefficient of complex band, B, 4) the equilibrium constant of hydrogen bonded complex formation K, 5) the enthalpy of hydrogen bonded complex formation, ΔH, 6) sum of Taft electronic coefficients for proton donor and acceptor substituents, $\Sigma\sigma$ and 7) sum of Taft steric coefficients for proton donor and acceptor substituents ΣEs [18].

Hierarchical clustering and principal component analysis (PCA) [19] have been used for examination of all measurements.

Hierarchical grouping or cluster analysis involves a number of different classification algorithms that put objects into clusters when one does not have any *a priori* hypotheses. It displays data in 2D space, qualitatively, in a form of dendograms with similarities among samples. Hierarchical cluster analysis was performed using Euclidean distance and Ward method of linkage.

Principal components analysis (PCA) is a well-known technique for reducing the dimensionality of multivariate data by transforming them into orthogonal principal components (PCs), which are linear combinations of the original variables while preserving most of the variance. Prior to hierarchical clustering and PCA, data were preprocessed using column standardization. This scaling procedure ensures that all the variables have the same weighting in the PC model. After the pretreatment, the appropriately formatted data were analyzed by Statistica 8.0 (StatSoft, Tulsa, USA).

RESULTS AND DISCUSSION

The correlation coefficients between different hydrogen bond complex parameters obtained by FTIR spectroscopy are presented in Table 2.

The correlation coefficients between the used hydrogen bond parameters confirm that the variables contain similar information. The complex band shift, $\Delta\nu$, exhibits the highest correlation with all other parameters, whereas the integrated molar absorption coefficient of complex band B exhibits the lowest correlation.

Hierarchical cluster analysis

In order to evaluate possible classes among samples considered, a clustering method was carried out before PCA. For the present study, the Euclidean distance and Ward method were used. Figure 1 shows the dendrographic classification of hydrogen bonded complexes and, as it can be seen, three main clusters can be observed.

Cluster A contains all benzene complexes and complexes with short alkyl chains (toluene, ethylbenzene). Cluster B includes 100% n-butyl benzene, xylene and 87.5% n-propylbenzene complexes. The cluster C reflects high similarity between complexes of amides with polymethyl substituted benzenes.

The two main clusters (A and B) could be additionally separated into two sub-clusters each forming in this way an entity of four clusters. Subcluster a1 contains dominantly complexes with benzene as the proton acceptor. Subcluster a2 contains complexes of N-sec-butyl and t-butyl propanamides. Parts of N-t-butyl formamide complexes are grouped in subcluster b1. Subcluster b2 joins a part of N-cyclohexyl formamide complexes.

Main clusters are formed according to proton acceptors, whereas subclusters are formed according to proton donors. The same separation pattern could be obtained even if the equilibrium constant that is often used for complex comparison was removed for the analysis.

Principal component analysis

PCA was used in order to visualize multivariate data, to identify possible classes and to find relationships among variables. When PCA was applied to the standardized data matrix, two principal components with eigenvalues exceeding one were extracted. The choice of significant number of PC is validated by the estimation of the eigenvalues (only values higher than 1.00 are taken into account). The scree plot is shown in Figure 2.

The scores plot for the first two principal components is shown in Figure 3.

This score graph of first two principal components accurately represents the seven-dimensional original data space since it describes 91.4% of the total variance, which indicates that the data compression is very efficient. The first principal component, PC1, accounts

Table 2. The correlation coefficients between different hydrogen bond complex parameters

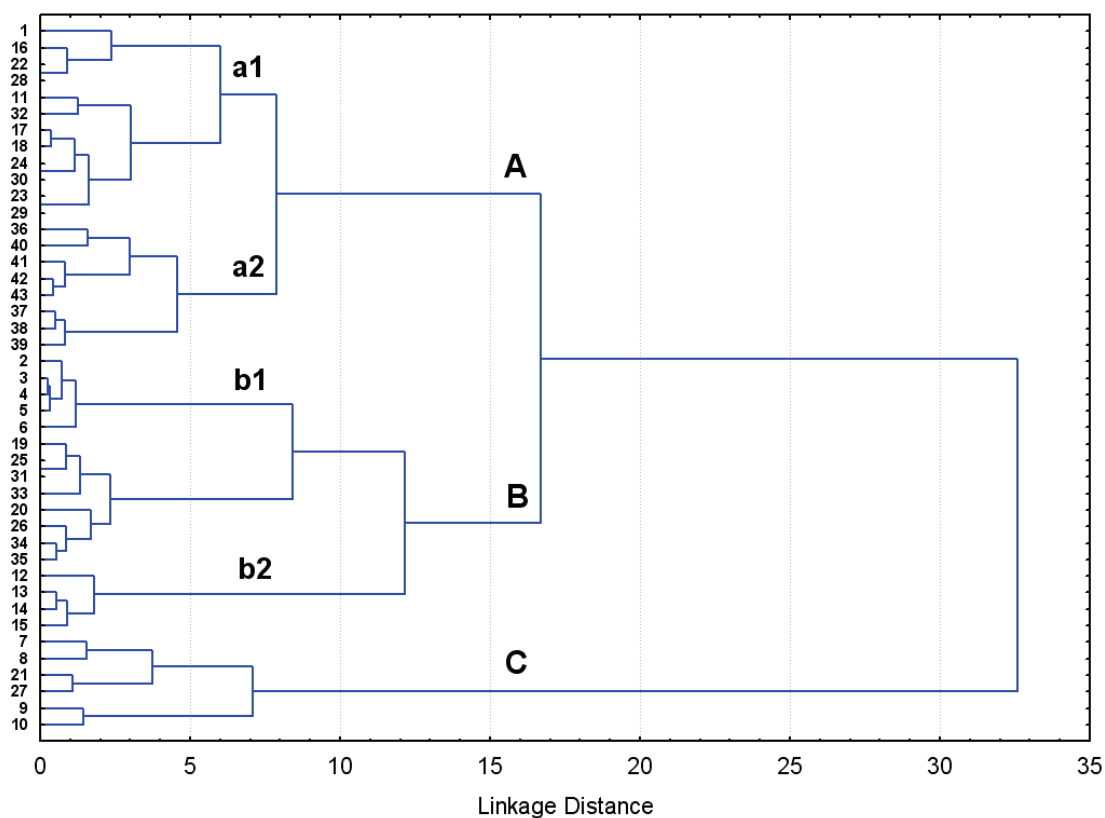|	$\Delta\nu$	$\nu_{1/2}$	B	K	ΔH	ΣEs	$\Sigma\sigma$
$\Delta\nu$	1.000	0.848	0.286	0.830	0.892	−0.948	−0.930
$\nu_{1/2}$		1.000	0.661	0.667	0.771	−0.742	−0.704
B			1.000	0.184	0.377	−0.121	−0.044
K				1.000	0.852	−0.838	−0.734
ΔH					1.000	−0.767	−0.699
ΣEs						1.000	−0.978
$\Sigma\sigma$							1.000

Figure 1. Dendrographic classification of hydrogen bonded complexes using the Euclidean distance and applying the Ward linkage method.
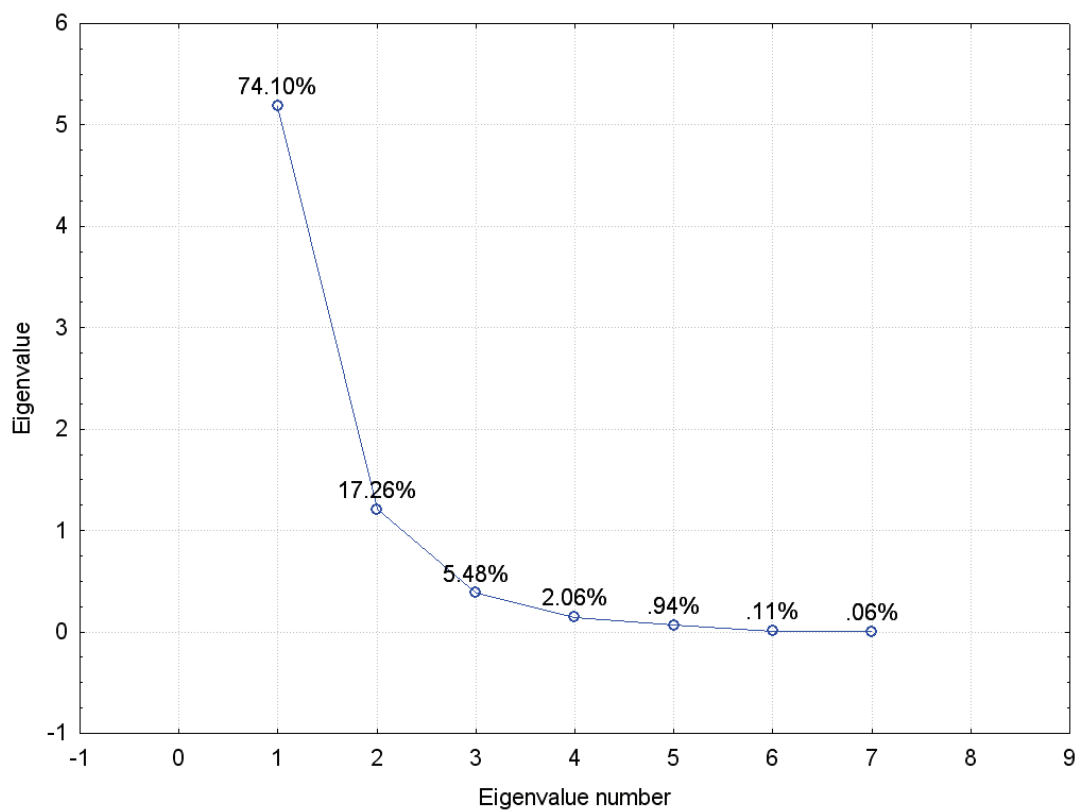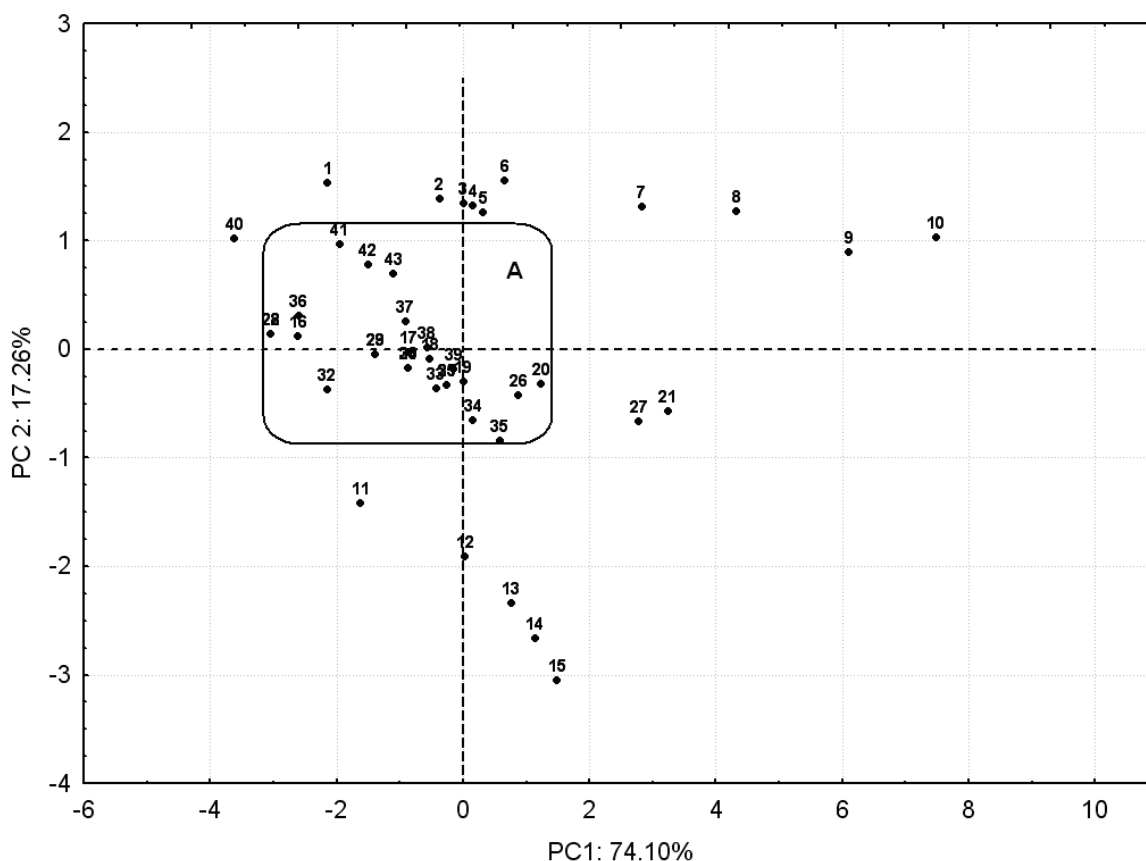

Figure 2. Scree plot for PCA.

Figure 3. The score plot of the hydrogen bonded complexes in the plane of the first two principal components.

for 74.1% of the total data variance, whereas the second principal component, PC2, accounts for 17.26%.

The corresponding loading plots (Figure 4) show the parameters responsible for segregation of the complexes. The first two principal components are given by the following equations:

$$PC1 = 0.432\Delta v + 0.387v_{1/2} + 0.159B + 0.387K + {} \\ +0.398\Delta H - 0.394\Sigma\sigma - 0.414\Sigma Es \tag{1}$$

$$PC2 = 0.069\Delta v - 0.351v_{1/2} - 0.836B + 0.133K - {} \\ -0.075\Delta H - 0.299\Sigma\sigma - 0.242\Sigma Es \tag{2}$$

Complexes of N-substituted propionamides and acetamides with monosubstituted benzenes are close together along the first two principal components and form general cluster A. Complexes with polymethyl substituted benzenes (samples **7–10**, **21** and **27**) are separated along the PC1. Formamide complexes with cyclohexyl (**11–15**) and with t-butyl (**1–6**) as N-substituents are well separated from the main cluster according to the second principal component PC2. Within cluster A, *N-t*-butyl complexes (**40–43**) are grouped together and separated. A similar separation pattern was obtained by cluster analysis.

Figure 4 shows the distribution and contribution of parameters to the first two principal components. Apart from the molar integral intensity B, all parameters significantly contribute to PC1, whereas the molar integral intensity B contributes most significantly to the second principal component. The second principal component is also strongly associated with the half width of complex band, $v_{1/2}$. From the correlation matrix it can be seen that integral intensity, B, has a significant correlation only with the half width of the complex band, $v_{1/2}$. Parameters Δv, K and ΔH are strongly associated on the loadings graph, which should not be surprising, because these parameters show strong correlation (Δv–ΔH 0.892, ΔH–K 0.852, Δv–K 0.830). Complex band shift Δv and Sum of Taft steric coefficients ΣEs are almost diametrically opposed, suggesting that they measure opposite properties. High Δv corresponds to low ΣEs. This relation indicates the importance of steric effects in weak N–H···π interactions.

The energy and stability of hydrogen bond N–H···π complexes depends strongly on many factors: acidity of the proton donor, basicity of the proton acceptor, steric and inductive effects on the proton donor and acceptor substituents. Several investigators [20–22] have obtained equilibrium constants for hydrogen bonding
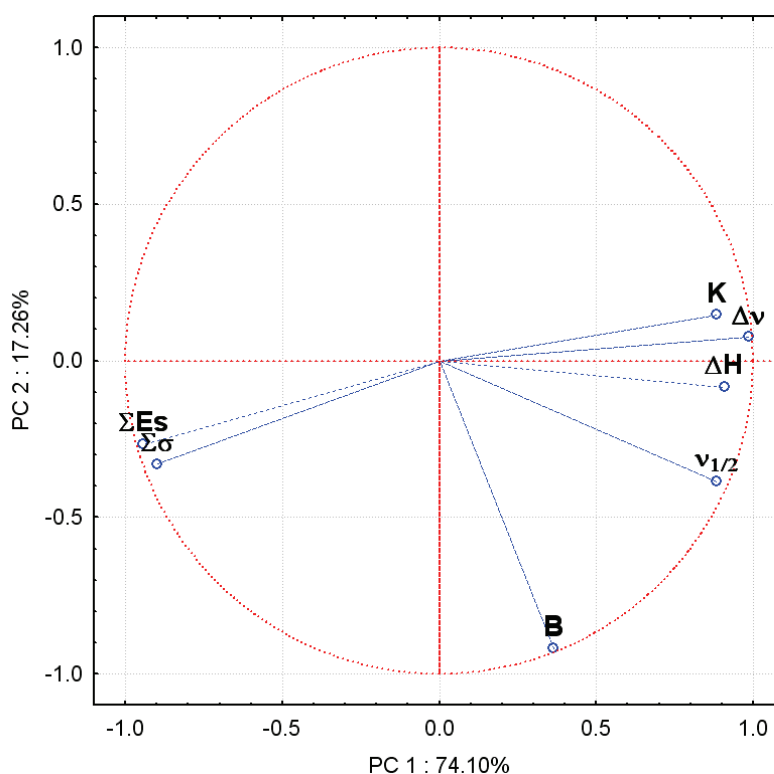
Figure 4. Loading plot of parameters on the first two principal components.

between phenols with various (cyclic and acyclic) ethers and they have established that donor-acceptor interactions are sensitive to both steric and electronic effects.

The main disadvantage of FTIR spectroscopy as a method for examining weak hydrogen bonds is the partial overlapping of monomer and complex bands. Deconvolution of partially overlapped bands is usually complicated, and includes great experimental error determining spectroscopic parameters, especially B and $v_{1/2}$. The influence of proton acceptor basicity on complex stability is explicit shown on the score graph. The electron-releasing effect of the methyl substituents increases the electron density in the π-system [23–25], and as a consequence, the monomer and complex bands are well separated and the spectroscopic parameters can be determined with more accuracy. This fact is responsible for the specific segregating effect in the dendrogram and score plot. Using the spectroscopic parameters of stronger hydrogen-bonded systems with clearly separated bands would give better separation on the score graph and give better insight into the relationships between the parameters in the loading graph.

CONCLUSIONS

The results of this work have shown that chemometric methods can be used to visualize similarities among hydrogen-bonded complexes according to the spectroscopic and theoretical parameters. It was possible to distinguish N–H···π complexes according to proton acceptor basicity, since good separation in the dendrogram and the scores plot was obtained. The results obtained in this report are in good agreement with conclusions of other spectroscopic and thermodynamic analysis. Hence, it follows that this could be an important tool to produce a higher level of understanding the hydrogen bonding of secondary amides.

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IZVOD

HEMOMETRIJSKA KARAKTERIZACIJA VODONIČNO-VEZANIH KOMPLEKSA SEKUNDARNIH AMIDA I AROMATIČNIH UGLJOVODONIKA

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(Naučni rad)

U ovom radu hemometrijski su okarakterisani vodonično vezani kompleksi sekundarnih amida i aromatičnih ugljovodonika. Metodama klaster analize i analizom glavne komponente utvrđene su razlike među N−H···π kompleksima na osnovu baznosti proton akceptora. Dobijeni rezultati se u dobroj meri slažu sa rezultatima spektroskopskih i termodinamičkih istraživanja.

Ključne reči: Vodonična veza • Sekundarni amidi • Aromatični ugljovodonici • Glavne komponente