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Chem. Ind. Chem. Eng. Q. 17 (3) 307–314 (2011) CI&CEQ

ALEKSANDAR D. MARINKOVIĆ
JELENA NEDELJKOVIĆ
DUŠAN Ž. MIJIN
NATAŠA ILIĆ
SLOBODAN D. PETROVIĆ

Faculty of Technology and Metallurgy, University of Belgrade, Belgrade, Serbia

SCIENTIFIC PAPER

UDC 547.057:547.8

DOI 10.2298/CICEQ110302016M

CORRELATION ANALYSIS OF IR, ^{1}H- AND ^{13}C-NMR SPECTRAL DATA OF *N*-ALKYL AND *N*-CYCLOALKYL CYANOACETAMIDES

Linear free energy relationships (LFER) were applied to the IR, ^{1}H- and ^{13}C--NMR spectral data in N-alkyl and N-cycloalkyl cyanoacetamides. N-alkyl and N-cycloalkyl cyanocetamides were synthesized from corresponding amine and ethyl cyanoacetate. A number of substituents were employed for alkyl substitution, and fairly good correlations were obtained, using simple Hammett equation. In N-alkyl and N-cycloalkyl cyanoacetamides substituent cause SCS of N-H hydrogen primarily by steric interaction, polar subtituent effect influences SCS shift of C=O carbon, while steric effect of N-alkyl substituent causes IR stretching frequencies of N-H, C=O and CN group. The conformations of investigated compounds have been studied by the use of semiempirical PM6 method, and together with LFER analysis, give a better insight into the influence of such a structure on the transmission of electronic substituent effects. Negative ρ values for several correlations (reverse substituent effect) were found.

Key words: N-alkyl cyanoacetamides; N-cycloalkyl cyanoacetamide; LFER analysis; IR and NMR spectra; SCS shift; Hammett equation.

Cyanoacetamides as well as many derivatives show diverse biological activity [1-6]. They are also used as intermediates for the preparation of various organic and often heterocyclic compounds due to its high reactivity [7,8]. Some derivatives are also used as dyes [9,10].

Analysis of both ^{1}H- and ^{13}C-NMR substituent chemical shifts (SCS) and IR absorption frequencies is based on the principles of linear free energy relationships (LFER). It was always initially attempted to use a simple Hammett equation as presented in Eq. (1) (single substituent parameter equation - SSP) which is usually given in the literature in general form:

$$s = \rho\sigma + h \quad (1)$$

where s are the substituent chemical shifts SCS or absorption frequencies, ν, ρ is the proportionality constant reflecting the sensitivity of the ^{1}H- and ^{13}C-NMR chemical shifts and IR frequencies to the substituent effects, σ are the corresponding substituent constant (σ^* - polar constant, E_s - steric constant and υ - Charton's steric constants), and h is the intercept (*i.e.*, describes unsubstituted member of series) [11]. For the correlation of spectral data for *N*-alkyl and *N*-cycloalkyl cyanoacetamides we tried to use Charton's steric constants υ and corrected υ (υ_{corr}) for the -C-C- branching in the the corresponding alkyl group [12]. The υ_{corr} parameter stands for $\upsilon(n_1+n_2)$, n_1 and n_2 being the number of branch points at the *alpha*- and *beta*-C-atoms in the alkyl groups, respectively. In some instances, we considered it appropriate to take into account the conformational effects described in that manner, because of the close proximity of the alkyl groups and the N-H proton. This model using υ_{corr} parameters failed, as the steric effect probably does not largely depend on alkyl branching. Interestingly, instead of these, a constant correlation with steric parameters for alkylamino group, defined by Charton [13], gave excellent results which will be discussed later in the paper.

So far, our investigations in the chemistry of different amides included the synthesis and identification of new compounds, as well as the mass spectral study [14,15]. Also, UV absorption spectra of *N*-(4-substituted phenyl)-2,3-diphenyl-propanamides [16] and *N*-(4-substituted phenyl)-benzamides [17] in various solvents have been investigated.

Correspondening author: A.D. Marinković, Faculty of Technology and Metallurgy, University of Belgrade, P.O. Box 3503, 11120 Belgrade, Serbia.
E-mail: marinko@tmf.bg.ac.rs
Paper received: 2 March, 2011
Paper revised: 4 April, 2011
Paper accepted: 8 April, 2011

In the first part of this work, a series of *N*-alkyl and *N*-cycloalkyl cyanocetamides was synthesized (Figure 1), and corresponding substituents are given in Table 1.

Alkyl-NHCOCH$_2$CN Cycloalkyl-NHCOCH$_2$CN

1 **2**

*Figure 1. General structures of investigated N-alkyl (**1**) and N-cycloalkyl cyanocetamides (**2**).*

In the second part of the work, linear free energy relationships (LFER) were applied to the ν, ^{1}H- and ^{13}C--NMR spectral data in the *N*-alkyl and *N*-cycloalkyl cyanoacetamides, with the aim to get an insight into the factors determining chemical shifts in investigated compounds. Semi-empirical MO-PM6 calculations were performed to obtain optimal geometries of *N*-alkyl and *N*-cycloalkyl cyanoacetamides (Figure 2). The optimization results was used to discuss transmission of substituent effect in relation to such defined geometries.

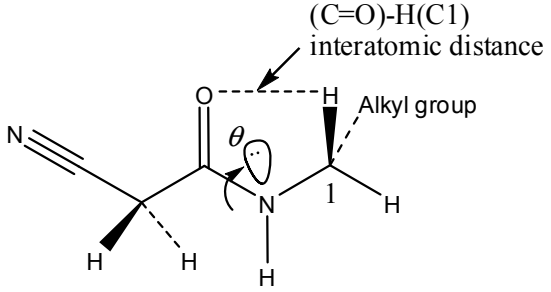

Figure 2. General structure of the N-alkyl cyanoacetamides.

EXPERIMENTAL

Materials

Ethyl cyanoacetate and amines used in synthesis were purchased from Fluka.

Methods of synthesis of N-alkyl and N-cycloalkyl cyanoacetamides

All investigated amides were synthesized by known method [18].

Yields and melting points of synhtesized cyanoacetamides are given in Table 1.

Instrumental techniques

The IR spectra were recorded on a Bomem MB 100 FTIR spectrophotometer (Hartmann & Braun) in the form of KBr pellet.

^{1}H- and ^{13}C-NMR spectra were determined in $CDCl_3$ solvent on a Varian-Gemini 200 MHz spectrometer (Varian) using TMS as internal standard. The chemical shifts are expressed in ppm values referenced to TMS (δ_H = 0 ppm) in ^{1}H-NMR spectra, and the residual solvent signal (δ_C = 39.5 ppm) in ^{13}C-NMR spectra. All spectra were recorded at ambient temperature.

Geometry optimization

The starting conformations of the both *E* and *Z* forms of studied molecules were sketched in Isis Draw 2.5, and optimised on MO semi-empirical level, by PM6 method [23], to root-mean-square gradient bellow 0.01 kcal/mol, using eigen-vector following gradient with implicit $CDCl_3$ solvation for *N*-alkyl and N-cycloalkyl-cyanoacetamides (COSMO) (Keywords: EF, GNORM =

Table 1. Yields and melting point of N-alkyl and N-cycloalkyl cyanoacetamides

Compound	Substituent	Literature m.p., °C	M.p., °C	Yield, %
1a	Me	80 [18]	84-86	63.1
1b	Et	74 [18]	70-72	47.2
1c	*n*-Pr	45-46 [19]	44-46	54.9
1d	*i*-Pr	74 [20]	66-67	72.4
1e	*n*-Bu	53-54 [18]	59-60	43.9
1f[a]	s-Bu[a]	-	40-41	49.0
1g	*i*-Bu	45-46 [19]	37-39	57.6
1h	n-Pe	53 [20]	52-53	-
1i	n-He	74-75 [21]	73-75	-
1j	Heptyl	74-75 [20]	72-74	45.3
1k	Octyl	67-69 [20]	66-68	43.1
1l	Decyl	78-79 [22]	77-79	58.9
2a	Cyclopropyl	103-105 [20]	105-106	70.5
2b	Cyclopentyl	87-88 [20]	85-87	41.0
2c[a]	Cyclohexyl[a]	-	132-134	55.2

[a]New compounds

= 0.01, EPS = 4.8 ($CDCl_3$) and NSPA = 92) using the MOPAC2009^{TM} program package. The VEGA ZZ 2.3.2 was used as the graphical user interface (GUI) [24]. The geometries of all molecular species, corresponding to the energy minima in vacuum, were optimised by the PM6 method.

^{1}H- and ^{13}C-NMR spectral data

*N-methylcyanoacetamide (**1a**)*. ^{1}H-NMR ($CDCl_3$): δ 2.89 (3H, *d*, J_{HH} = 5.2 Hz, CH_3), 3.40 (2H, *s*, CH_2), 6.34 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 26.65 (CH_3), 26.95 ($\underline{C}H_2$-CN), 114.83 (CN), 161.55 (CO).

*N-ethylcyanoacetamide (**1b**)*. ^{1}H-NMR ($CDCl_3$): δ 1.18 (3H, *t*, J_{HH} = 7.2 Hz, CH_3), 3.33 (2H, *m*, $C\underline{H}_2$-CH_3), 3.50 (2H, *s*, CH_2-CN), 7.22 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 14.06 (CH_2-$\underline{C}H_3$), 25.78 ($\underline{C}H_2$-CN), 35.01 ($\underline{C}H_2$-CH_3), 115.03 (CN), 161.72 (CO).

*N-propylcyanoacetamide (**1c**)*. ^{1}H-NMR ($CDCl_3$): δ 0.94 (3H, *t*, J_{HH} = 7.8 Hz, CH_3), 1.56 (2H, *m*, $C\underline{H}_2$-CH_3), 3.25 (2H, *q*, J_{HH} = 6.2 Hz, $C\underline{H}_2$-NH), 3.48 (2H, *s*, CH_2-CN), 7.10 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 11.11 (CH_3), 22.21 ($\underline{C}H_2$-CH_3), 25.80 ($\underline{C}H_2$-CN), 41.88 (CH_2-N), 115.03 (CN), 161.79 (CO).

*N-i-propylcyanoacetamide (**1d**)*. ^{1}H-NMR ($CDCl_3$): δ 1.20 (6H, d, J_{HH} = 6.6 Hz, CH_3), 3.48 (2H, *s*, CH_2-CN), 4.00 (1H, *m*, $\underline{CH}$-NH), 7.04 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 21.98 ($2CH_3$), 25.89 ($\underline{C}H_2$-CN), 42.35 (CH-N), 115.09 (CN), 160.88 (CO).

*N-butylcyanoacetamide (**1e**)*. ^{1}H-NMR ($CDCl_3$): δ 0.93 (3H, t, J_{HH} = 6.4 Hz, CH_3), 1.35 (2H, *m*, -$C\underline{H}_2$-CH_3), 1.49 (2H, *m*, $C\underline{H}_2$-CH_2-N), 3.26 (2H, *q*, J_{HH} = = 6.6 Hz, $C\underline{H}_2$-NH), 3.49 (2H, *s*, CH_2-CN), 7.15 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 13.46 (CH_3), 19.76 ($\underline{C}H_2$-CH_3), 25.80 ($\underline{C}H_2$-CN), 30.92 ($\underline{C}H_2$-CH_2-CH_3), 39.88 (CH_2-N), 115.03 (CN), 161.75 (CO).

*N-i-butylcyanoacetamide (**1f**)*. ^{1}H-NMR ($CDCl_3$): δ 0.93 (6H, *d*, J_{HH} = 6.2 Hz, CH_3), 1.83 (H, *m*, H_2C-$C\underline{H}$-$(CH_3)_2$), 3.09 (2H, *t*, J_{HH} = 6.8 Hz, $C\underline{H}_2$-NH), 3.50 (2H, *s*, CH_2-CN), 7.12 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 19.85 ($2CH_3$), 25.82 ($\underline{C}H_2$-CN), 28.09 ($\underline{C}H$-$(CH_3)_2$), 47.49 ($\underline{C}H_2$-N), 115.07 (CN), 161.88 (CO).

*N-s-butylcyanoacetamide (**1g**)*. ^{1}H-NMR ($CDCl_3$): δ 0.92 (3H, *t*, J_{HH} = 7.2 Hz, CH_3), 1.16 (3H, *d*, J_{HH} = = 6.8 Hz, $C\underline{H}_3$-CH-CH_2), 1.51 (2H, *m*, $C\underline{H}_2$-CH_3), 3.47 (2H, *s*, CH_2-CN), 3.86 (1H, *m*, $C\underline{H}$-NH), 6.73 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 10.16 (CH_2-$\underline{C}H_3$), 19.78 (CH-$\underline{C}H_3$), 25.95 ($\underline{C}H_2$-CN), 29.02 ($\underline{C}H_2$-CH_3), 47.77 ($\underline{C}H$-N), 115.07 (CN), 160.95 (CO).

*N-pentylcyanoacetamide (**1h**)*. ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H, *t*, J_{HH} = 6.2 Hz, CH_3), 1.30 (4H, *m*, $(C\underline{H}_2)_2$-CH_3), 1.54 (2H, *m*, $C\underline{H}_2$-CH_2-N), 3.30 (2H, *m*, $C\underline{H}_2$-NH), 3.48 (2H, *s*, CH_2-CN), 7.06 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 13.77 (CH_3), 22.10 ($\underline{C}H_2$-CH_3), 25.82 ($\underline{C}H_2$-CN), 28.64 ($\underline{C}H_2$-CH_2-CH_3), 28.76 ($\underline{C}H_2$-CH_2-N), 40.20 ($\underline{C}H_2$-N), 115.02 (CN), 161.66 (CO).

*N-hexylcyanoacetamide (**1i**)*. ^{1}H-NMR ($CDCl_3$): δ 0.89 (3H, *t*, J_{HH} = 6.6 Hz, CH_3), 1.30 (6H, *m*, $(C\underline{H}_2)_3$-CH_3), 1.53 (2H, *m*, $C\underline{H}_2$-CH_2-N), 3.30 (2H, *q*, J_{HH} = = 7.2 Hz, $C\underline{H}_2$-NH), 3.48 (2H, *s*, CH_2-CN), 7.12 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 13.80 (CH_3), 22.32 ($\underline{C}H_2$-CH_3), 25.82 ($\underline{C}H_2$-CN), 26.31 ($\underline{C}H_2$-CH_2-CH_3), 28.90 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 31.21 ($\underline{C}H_2$-CH_2-N), 40.22 ($\underline{C}H_2$-N), 115.02 (CN), 161.72 (CO).

*N-heptylcyanoacetamide (**1j**)*. ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H, *t*, J_{HH} = 6.8 Hz, CH_3), 1.29 (8H, *m*, $(C\underline{H}_2)_4$-CH_3), 1.53 (2H, m, $C\underline{H}_2$-CH_2-N), 3.26 (2H, *q*, J_{HH} = 6.8 Hz, $C\underline{H}_2$-NH), 3.46 (2H, *s*, CH_2-CN), 6.94 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 13.87 (CH_3), 22.40 ($\underline{C}H_2$-CH_3), 25.82 ($\underline{C}H_2$-CN), 26.64 ($\underline{C}H_2$-CH_2-CH_3), 28.73 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 28.98 ($\underline{C}H_2$-CH_2-CH_2-N), 31.54 ($\underline{C}H_2$-CH_2-N), 40.28 ($\underline{C}H_2$-N), 114.98 (CN), 161.54 (CO).

*N-octylcyanoacetamide (**1k**)*. ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H, *t*, J_{HH} = 6.8 Hz, CH_3), 1.28 (12H, *m*, $(C\underline{H}_2)_5$-CH_3), 1.53 (2H, *m*, $C\underline{H}_2$-CH_2-N), 3.25 (2H, *q*, J_{HH} = 6.2 Hz, $C\underline{H}_2$-NH), 3.45 (2H, *s*, CH_2-CN), 6.92 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 13.93 (CH_3), 22.47 ($\underline{C}H_2$-CH_3), 25.84 ($\underline{C}H_2$-CN), 26.71 (($\underline{C}H_2$)$_2$-CH_2-CH_3), 29.04 (($\underline{C}H_2$)$_2$-CH_2-CH_2-N), 31.62 ($\underline{C}H_2$-CH_2-N), 40.29 ($\underline{C}H_2$-N), 114.98 (CN), 161.52 (CO).

*N-decylcyanoacetamide (**1l**)*. ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H, *t*, J_{HH} = 6.8 Hz, CH_3), 1.26 (14H, *m*, $(C\underline{H}_2)_7CH_3$), 1.53 (2H, *m*, $C\underline{H}_2$-CH_2-N), 3.27 (2H, *q*, J_{HH} = 7.4 Hz, $C\underline{H}_2$-NH), 3.41 (2H, *s*, CH_2-CN), 6.55 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 14.00 (CH_3), 22.56 ($\underline{C}H_2$-CH_3), 25.82 ($\underline{C}H_2$-CN), 26.73 ($\underline{C}H_2$-CH_2-CH_3), 29.10 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 29.13 (($\underline{C}H_2$)$_2$-CH_2-CH_2-CH_2-CH_3), 29.42 (($\underline{C}H_2$)$_2$-CH_2-CH_2-N), 31.77 ($\underline{C}H_2$-CH_2-N), 40.37 ($\underline{C}H_2$-N), 114.94 (CN), 161.12 (CO).

*N-cyclopropylcyanoacetamide (**2a**)*. ^{1}H-NMR ($CDCl_3$): δ 0.60 (2H, *m*, CH_2 ring), 0.84 (2H, *m*, CH_2 ring), 2.75 (1H, *m*, CH ring), 3.37 (2H, *s*, $C\underline{H}_2$-NH), 6.45 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 6.46 (2C ring), 23.23 (1C ring), 25.71 ($\underline{C}H_2$-CN), 114.74 (CN), 162.32 (CO).

N-cyclopentylcyanoacetamide (**2b**). ^{1}H-NMR ($CDCl_3$): δ 1.48 (2H, *m*, CH_2 ring), 1.60 (4H, *m*, CH_2 ring), 1.95 (2H, *m*, CH_2 ring), 3.45 (2H, *s*, CH_2-CN), 4.15 (1H, *m*, CH ring), 6.93 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 23.50 (2C ring), 25.89 ($\underline{C}H_2$-CN), 32.48 (2C ring), 51.96 (1C ring), 115.09 (CN), 161.12 (CO).

N-cyclohexylcyanoacetamide (**2c**). ^{1}H-NMR ($CDCl_3$): δ 1.53 (3H, *m*, CH_2 ring), 1.67 (5H, *m*, CH_2 ring), 1.92 (2H, *m*, CH_2 ring), 3.46 (2H, *s*, CH_2-CN), 4.18 (1H, *m*, CH ring), 6.98 (1H, *s*, NH). ^{13}C-NMR ($CDCl_3$): δ 23.49 (2C ring), 25.89 ($\underline{C}H_2$-CN), 32.48 (3C ring), 51.93 (1C ring), 115.07 (CN), 161.14 (CO).

RESULTS AND DISCUSSION

In order to get better insight into transmission modes of particular substituent effects, as well influence of their optimal geometry, an analysis of substituent effect on absorption frequencies ν of N-H, CN and C=O groups, as well as ^{1}H- and ^{13}C-NMR chemical shifts of N-H proton and C=O carbon, was performed.

The chemical shifts (SCS) of the N-H proton and C=O carbon of all cyanoacetamides are given in Table 2, in terms of the substituent chemical shifts (SCS) relative to the parent compound. Also, the IR stretching frequencies of characteristic groups N-H, CN and C=O of *N*-alkyl and *N*-cycloalkyl cyanoacetamides are shown in Table 2.

The general conclusion derived from the data in Table 2 is that alkyl and cycloalkyl substituents influence, *via* their electronic and steric effects, the value of ν as well as SCS of N-H proton and C=O carbon. Among factors contributing differences in ν and SCS values (Table 2), the geometry of the investigated compounds plays an important role regarding elements of their geometry. Thus, a definite molecular geometry has been achieved as a consequence of the particular transmission modes of the substituent electronic effects.

LFER analysis of the ^{1}H- and ^{13}C-NMR data in *N*-alkyl and *N*-cycloalkyl cyanoacetamides

Study of the transmission of substituent effect in *N*-alkyl and *N*-cycloalkyl cyanoacetamides was dificult task regarding choice of alkyl substituent constant which could give reasonable correlations. It could be expected that alkyl substituents cause SCS values of N-H proton primarily by their steric effect, described by constants υ, *Es* and υ_{corr} values, and considering that they shows rather weak electronic effects. However, the model using Charton constant υ and υ_{corr} failed. It appears that υ_{corr} constants, corrected for the C-C branching at the *alpha*- and *beta*-carbons in the substituent alkyl groups, which also account for the hyperconjugation and its effect on the electron density changes, could not satisfactory described *N*-alkyl substituent influences on SCS N-H and C=O atoms. This could be consistent to the somewhat restricted free rotation of the alkyl groups [12], or such geometrical arrangement which could not allow larger extent of hyperconjugative resonance interaction. In order to study electronic and structural effect of alkyl group on the electronic character of the carbonyl unit, we have used different alkyl and cycloalkyl groups (series **1** and **2**), which express different Taft's polar substituent constant σ^{*} for *R* and varies from 0 to 0.22. The most succesfull correlations obtained for N-H proton and C=O carbon are given in Table 3.

The neccessity to include the steric factor in the correlation of the SCS for the N-H proton shows that a steric interference of the bulky alkyl groups with N-H proton occurs. An attempt to correlate *SCS* value of N-H proton with *Es* parameters gave three separate correlation lines (Table 3, lines 1-3), which further confirms the importance of conformational effects of alkyl substituent, also indicating that spatial arrange-

Table 2. IR streching frequencies of N-H, CN and C=O groups and ^{1}H-NMR (N-H) and ^{13}C-NMR (C=O) chemical shifts in N-alkyl and N-cycloalkyl cyanoacetamides

Compound	Substituent	ν_{N-H} / cm^{-1}	ν_{CN} / cm^{-1}	ν_{CO} / cm^{-1}	SCS_{N-H}[a] / ppm	$SCS_{C=O}$[b] / ppm
1a	Me	3290.18, 3109.82	2260.69	1658.56	6.34	161.55
1b	Et	3256.98, 3083.10	2261.28	1673.31	0.88	0.17
1c	*n*-Pr	3298.06, 3084.94	2261.29	1665.11	0.76	0.24
1d	*i*-Pr	3304.05, 3078.97	2259.48	1561.25	0.70	-0.67
1e	*n*-Bu	3302.59, 3092.47	2258.96	1655.57	0.81	0.20
1f	s-Bu	3314.36, 3091.22	2259.09	1665.14	0.39	-0.60
1g	*i*-Bu	3303.07, 3085.21	2260.16	1654.19	0.78	0.33
1h	*n*-Pe	3297.73 3098.33	2261.57	1653.66	0.72	0.11
1i	*n*-He	3303.56 3094.67	2259.71	1653.59	0.78	0.17
1j	Heptyl	3297.06, 3096.55	2261.03	1656.78	0.60	-0.01
1k	Octyl	3302.88, 3095.73	2260.64	1649.9	0.58	-0.03
1l	Decyl	3300.45, 3094.24	2261.42	1651.62	0.21	-0.43
2a	Cyclopropyl	3299.76, 3070.05	2257.82	1656.45	0.11	0.77
2b	Cyclopentyl	3283.73, 3094.29	2260.67	1650.3	0.59	-0.43
2c	Cyclohexyl	3281.73, 3088.58	2261.5	1654.19	0.64	-0.41

Table 3. Correlation results of the SCS values for N-akyl and N-cycloalkyl cyanoacetamides obtained by the use of SSP Eq. (1)

Atom	Scale	ρ	h	r	*S.d.*	F	n
N-H	E_s	-0.379 (±0.582)	-0.422 (±0.110)	0.967	0.074	43	5[a]
	E_s	-0.325 (±0.063)	0.068 (±0.115)	0.947	0.033	26	5[b]
	E_s	0.443 (±0.020)	1.461 (±0.031)	0.998	0.006	486	4[c]
C=O	σ^*	-15.331 (±0.792	2.215	0.997	0.043	373	4[d]
	σ^*	-14.256 (±0.511)	2.415 (±0.105)	0.996	0.032	777	7[e]

[a] **1a**, **1f**, **1l**, **2a**, **2c**; [b] **1g**, **1h**, **1j**, **1k**, **2b**; [c] **1d**, **1c**, **1i**, **1b**; [d] **1g**, **1e**, **1l**, **1d**; [e] **1h**, **1i**, **1j**, **1k**, **2b**, **2c**, **1f**

ment could cause attenuation of the hyperconjugative resonance effect transmission.

Excellent correlation was obtained for C=O carbon with Taft set of polar constants σ^* for alkyl and cycloalkyl substituents. These value quantitavely describe polar, steric and resonance component of alkyl substituent. The correlation of *SCS* of C=O with σ^* shows a good correlation with a negative slope for both series (Table 3, rows 4 and 5). The carbonyl carbon resonates on the higher field, indicating increased shielding at the C=O carbon as long as the more electron-withdrawing alkyl group is present. Substituents in their close vicinity exert only steric influence on *SCS* of N-H, while alkyl substituent produces more significant polar effect (field effect) at C=O carbon. It could be supposed that transmission of alkyl substituent effect cause mainly degree of resonance interaction in amide group (Figure 3, structure a). The relatively high value of the slope of the *SCS* dependence with respect to σ^* for C=O (Table 3, rows 4 and 5) indicates that there is a significant influences of substituent effect of alkyl group attached on amide nitrogen.

Reverse substituent chemical shift effects have been previously detected for some unsaturated carbons in the side chains of aromatic rings. The behavior has most often been explained by the effect of so-called π-polarization. The substituent dipole is thought to polarize each π-unit as a localized system. It could be supposed that carbonyl group is subjected to the polarization through the space (field effect). The π-polarization mechanism was criticized [25], but no alternative explanation was given.

Considering the wave function presented by the structure in Figure 3b, a dipole on *N*-alkyl (or near to that bond) could is induced, and interaction of this dipole through molecular cavity results in the polarization of π-electron of carbonyl group (localized polarization), casuing reverse polarization of that group. The negative sign means reverse behaviour, *i.e.*, the value of *SCS* of C=O carbon decreases, although the electron-withdrawing ability of the substituents, measured by σ^*, increases.

Resonance interaction (*n*,π-conjugation) within the amide group, presented by the wave function in Figure 3a, is of appropriate significance. The net result that the substituent of higher electron-donating capabilities decreases the shielding of C=O carbon, and the opposite effect is exerted by electron-acceptor. According to the presented result, it could be accepted that the extent of resonance interaction within π-electronic system of amide group is of utmost significance for transmission of alkyl substituent effect through investigated molecules.

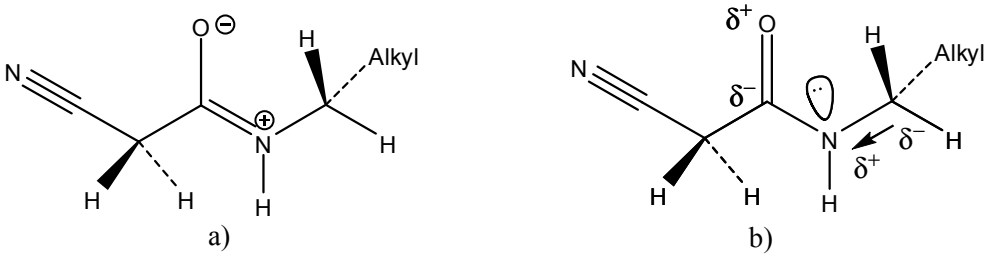

Figure 3. Resonance interaction within amide group (a), and contribution of π-polarization mechanism causing reverse polarization of carbonyl group (b).

LFER analysis of IR absorption frequencies in *N*-alkyl cyanoacetamides

The IR stretching frequencies of characteristic groups in *N*-alkyl and *N*-cycloalkylcyanoacetamides are shown in Table 2. The best correlations, and significantly better statistical than with other steric parameters, was obtained with υ steric parameters for alkylamino group, defined by Charton [13], and they are presented in Table 4.

The neccessity to include the steric factor in the correlation of the υ for N-H bond shows that an steric interference of the bulky alkyl groups with N-H proton occurs, what is in accordance with weak electronic effect of those group, and also with previous discussion on substituent effect on SCS of N-H hydrogen. An attempt to correlate N-H stretching vibration with υ steric substituent values gave two separate correlation lines for symmetric and asymmetric N-H vibrations, which further confirms the importance of the steric substiuent effect depending on their spatial conformation. Substituent effect on ν values of C=O and CN groups shows complex influences which are very difficult to interpret.

Results of geometry optimization

An analysis of optimized geometries of investigated compounds could help understanding transmission modes of substituent effects through such defined spatial arrangement. Estimation of substituent effect on the polarization of C=O bond could be obtained from calculation of optimized geometries (angles θ, bond length C=O, (C=O)-N and N-C1, as well (C=O)-H(C1) interatomic distance, obtained by the use semi-empirical PM6 method, and results are presented in Table 5. The optimized structures of all cya-

Table 4. Correlation results of the υ values for N-akyl and N-cycloalkyl cyanoacetamides obtained by the use of SSP equation

Atom	*ρ*	*h*	*r*	*S.d.*	*F*	*n*
N-H (sym)	-61.72	3135.63	0.982	1.75	184	9[a]
	(±4.54)	(±3.12)				
N-H (asym)	30.53	3279.60	0.929	2.34	57	11[b]
	(±4.06)	(±2.97)				
C=O	-8.881	1661.80	0.961	0.692	25	4[c]
	(±1.793)	(±1.293)				7[d]
	-364.79	1894.655	0.996	3.614	645	
	(±14.359)	(±9.940)				
CN	2.61	2259.68	0.988	0.06	82	4[e]
	(±0.29)	(±0.17)				
	-2.96	2262.34	0.964	0.20	13	3[f]
	(±0.82)	(±0.77)				
	-38.03	2285.50	0.972	0.26	52	5[g]
	(±5.27)	(±3.49)				

[a]**1a**, **1d**, **1e**, **1g**, **1h**, **1i**, **1j**, **1k**, **1l**; [b]**1a**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**, **1l**; [c]**1a**, **1g**, **1e**, **2c**; [d]**1b**, **1c**, **1i**, **2c**, **1k**, **1l**, **1d**; [e]**1a**, **1b**, **1c**, **1j**; [f]**1g**, **1d**, **1f**; [g]**1c**, **1h**, **1k**, **1l**, **2c**

Table 5. Elements of optimized geometry of N-alkyl and N-cycloalkylcyanoacetamides obtained by the use of semi-empirical PM6 method

Compound	C=O (Å)	(C=O)-N (Å)	N-C1 (Å)	(C=O)-H(C1) (Å)	*θ*	$\Delta H^{\#}$ / kJ mol^{-1}
1a	1.2285	1.3748	1.4778	2.4056	2.38	-116.52
1b	1.2271	1.3801	1.4890	2.4138	8.22	-143.70
1c	1.2275	1.3795	1.4870	2.4103	8.01	-167.19
1d	1.2286	1.3752	1.4988	2.3739	1.52	-183.76
1e	1.2273	1.3798	1.4873	2.4079	7.87	-188.34
1f	1.2287	1.3748	1.4973	2.3689	2.54	-198.42
1g	1.2274	1.3788	1.4850	2.4203	6.62	-193.02
1h	1.2273	1.3798	1.4874	2.4098	8.04	-207.28
1i	1.2274	1.3799	1.4875	2.4101	8.05	-228.97
1j	1.2274	1.3797	1.4774	2.4097	7.94	-250.24
1k	1.2274	1.3800	1.4876	2.4127	8.07	-271.54
1l	1.2275	1.3802	1.4876	2.4115	8.07	-283.23
2a	1.2257	1.3826	1.4615	2.4056	1.12	-39.45
2b	1.2250	1.3787	1.4901	2.4761	2.68	-170.26
2c	1.2279	1.3753	1.4966	2.3778	1.34	-210.55

noacteamides conform *trans*-conformation, exampled by *N*-n-propyl cyanoacetamide, given in Figure 4.

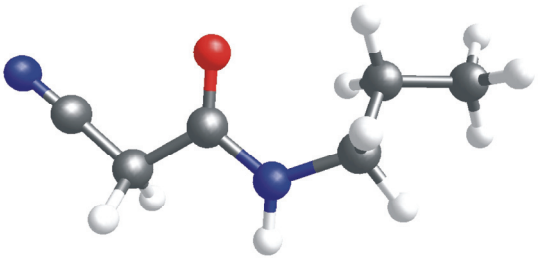

Figure 4. Optimized trans-conformation of N-n-propyl cyanoacetamide.

The presented results show that there are some significant variation of elements of optimized geometries of investigated componds. Conformational arangement could help the understanding of the extent of substituent effect transmission modes: steric and electronic. Variation of the elements of geometries (Table 5) indicates that there is a complex contribution of appropriate substituent effects which is quantified in the presented correlation results. It should be noticed that two effects exist, n,π-conjugation in amide group (Figure 3a) and substituent effects, in the investigated molecules is balanced causing appropriate conformational arrangement of investigated compounds.

CONCLUSION

Applied LFER analysis appears to be a straightforward method for correlations of SCS values of investigated molecules with appropriate substituent constants. The *N*-alkyl and *N*-cycloalkyl cyanoacetamides show a broad range of the properties. All correlations are of good quality, indicating that substituent effects on SCS are electronic in origin. There are possibilities for substituent interactions, both electronic and particularly steric, but the general trends of substituent effects were estimated. One conclusion is that in both *N*-alkyl and *N*-cycloalkyl cyanoacetamides, the substituent and amide group are nearly coplanar, conforming *E*-conformation, and the deviations, defined by the torsional angle θ, vary with the type of substitution. Reverse polarization is operative at carbonyl carbon, as a consequence of π-polarization.

Acknowledgments

The authors aknowledge the financial support by the Ministry of Education and Science of the Republic Serbia (Project Number 172013).

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ALEKSANDAR MARINKOVIĆ
JELENA NEDELJKOVIĆ
DUŠAN MIJIN
NATAŠA ILIĆ
SLOBODAN PETROVIĆ

Tehnološko-metalurški fakultet,
Univerzitet u Beogradu, Beograd

NAUČNI RAD

KORELACIONA ANALIZA IR, ^{1}H- I ^{13}C-NMR SPEKTALNIH PODATAKA *N*-ALKIL- I *N*-CIKLOALKILCIJANOACETAMIDA

Principi linearnih korelacija slobodnih energija (LFER) su primenjeni na IR, ^{1}H- i ^{13}C-NMR spektralne podatke N-alkil i N-cikloalkilcijanoacetamida. Širok opseg alkil i cikloalkil supstituenata je korišćen pri sintezi N-alkil i N-cikloalkilcijanoacetamida sa ciljem ispitivanja uticaja njihovih elektronskih i sternih efekata na IR, ^{1}H i ^{13}C NMR spektralne podatke. Zadovoljavajuće korelacije su dobijene primenom proste Hammett-ove jednačine. Na osnovu korelacionih rezultata uočen je primaran uticaj sternih efekata supstituenata na SCS (supstituent indukovana hemijska pomeranja) vrednosti N-H vodonika ispitivanih jedinjenja, što je posledica blizine i različitih konformacija N-alkil i N-cikloalkil supstituenata. Takođe se uočava reversni efekat supstituenata na SCS pomeranja karbonilnog C=O ugljenika, kao posledica π-polarizacije. Indukovani dipol na N-alkil ili N-cikloalkil supstituentu izaziva povećanje elektronske gustine karbonilnog ugljenika iako elektron-akceptorski efekat supstituenta raste. Može se zaključiti da se efekat π-polarizacije odražava na veličinu rezonancionog efekta amidne grupe. Polarni efekat N-alkil ili N-cikloalkil supstituenata se primarno prenosi efektom polja kroz prostor. Uticaj efekata N-alkil ili N-cikloalkil supstituenata na IR vibracije istezanja N-H (simetrične i antisimetrične), C=O i CN veze je prevashodno određen konformacionim (sternim) efektom supstituenata koji utiče na jačinu veze, a time i na položaj trake u odgovarajućem spektru.

Ključne reči: N-alkilcijanoacetamidi, N-cikloalkilcijanoacetamidi, LFER analiza, IR i NMR spektri, SCS pomeraj, Hammett-ova jednačina.