NUCLEOPHILICITY AND ITS PARAMETRIZATION

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The method of conjugate deviations based on the regression analysis has been suggested for construction of a new nucleophilicity scale. This method has been applied to a set of 28 nucleophiles participating in 47 physical and chemical processes described in literature. The two-parameter nucleophilicity scale obtained represents — in the parameter denoted as ND — the general tendency to form a bond to an electrophile predominantly on the basis of the orbital interaction and — in the parameter denoted as PD — the ability to interact with a centre similar to the proton (basicity). The linear correlation equation involving the ND, PD parameters and the charge appears to be distinctly better than the most significant relations used. The correlation dependences have the physico-chemical meaning. From the position of individual nucleophiles in the space of the ND and PD parameters, some general conclusions have been derived about the factors governing the reactivity of nucleophiles.

The nucleophilicity defined as the ability of the nucleophile to donate its free electron pair in a process of formation of a new covalent bond is a very complex quantity. In spite of much scientific effort spent on studies of nucleophilicity (as documented in a number of reviews[1-11]) the level of understanding reached so far is lower than that in the case of solvent or even substituent effects. This fact is due to simultaneous operation of many mutually interconnected factors[1,2,9,12,13] whose nature and contribution can sometimes be evaluated only with difficulties. As the nucleophilicity makes itself felt during the reaction course, properties of the substrate and medium are also significant beside the properties of nucleophiles (reagents). Considering the nucleophile, attention was mostly paid to the effect of free electron pairs adjacent to the reaction centre (the so-called α effect[7,14-19]) which causes anomalies in quantitative treatments. Another speciality is the ambident character of some nucleophiles[3]. Properties of substrates related to nucleophilicity were studied predominantly with respect to the role of leaving groups in substitution reactions (the so-called nucleofugacity[20-22]). The relations between reaction centres of nucleophiles and substrates are expressed in the HSAB theory (Hard and Soft Acids and Bases, see e.g. refs[23-25]). The effects of medium on nucleophilicity are given first of all by the solvent used[4,5,10]. The solvent molecules also can act as nucleophiles, as it is the case in solvolyses (e.g. refs[26-30]). The nucleophilic catalysis represents a special section (e.g. ref.[31]).

The above-mentioned complexity of the notion of nucleophilicity is fully mani-fested in its quantitative description[9]. Although the theoretical approach is successful sometimes, empirical correlation equations appear to be the most universal for the interpretation. Historically the oldest quantitative description is based on the Brönsted relation[32]

$$\log (k/q) = \beta \log (K_a \, p/q) + \log G \,, \tag{1}$$

where k is the nucleophilic reaction rate constant, K_a means the dissociation constant of the conjugate acid of the nucleophile, β is the so-called Brönsted coefficient, p and q stand for numbers of equilibrium acidic protons and basic centres, respectively, and log G is the regression coefficient. Equation (1) belongs to the most frequently used equations, as it can be seen in a survey by Bell[8] and other publications[22,33-38], nevertheless, its application sometimes encounters various anomalies (non-lineari-ty[39-41], α effect). The relation (2) suggested by Swain and Scott[42] represents a formal analogy of the Hammett equation,

$$\log k = \log k_0 + s \, n \,, \tag{2}$$

where n means a parameter which characterizes only the properties of the nucleo-phile, and s is the regression coefficient characterizing the substrate (and reaction conditions generally). The standard substrate is methyl bromide $(s = 1)$ in water $(n = 0)$. Application examples of Eq. (2) can be found e.g. in refs[33,43-46]. Variation of the standard substrate led to suggestions of other scales analogous to n by Swain and Scott, the best known being the n_{Pt} scale[47,48] and n_{Mel} scale[48].

The two-parameter (with respect to description of nucleophilicity) equation (3) by Edwards[49] is based on a somewhat different basis:

$$\log k = \log k_0 + \alpha \, E_n + \beta \, H \,, \tag{3}$$

where E_n and H are parameters of nucleophilicity, log k_0 represents the absolute term, and α and β are regression coefficients. The E_n parameter is related to the polarizability of nucleophile, and it is defined as the potential of oxidative dimeriza-tion of the nucleophile $+2\cdot60$ (which value represents a standardization for water for which $E_n = 0$). The H parameter expresses the basicity related to the proton, and it is equal to $pK_a + 1\cdot74$ (for water H = 0). As Eq. (3) represents an extended version of Eq. (1), its application can give better or at least equally successful cor-relations as compared with the Brönsted relation. Equation (3) was further modified with application of molar refraction of nucleophile[50], but this version is not much widespread. The basic Eq. (3), too, was used for the nucleophilicity correlations only rarely[51,52].

Jencks[53] suggested the equilibrium constants of nucleophilic additions to aldehydic

carbonyl group as the basis of his parameter scale. The validity of the equation

$$\log K_0 = \Delta\,\gamma + A\,,\tag{4}$$

where γ characterizes the nucleophile (methylamine as the standard), A is the absolute term, and Δ is the regression coefficient, was verified on several examples[54-56]. Drago[57,58] suggested the four-parameter equation (5) describing the donor–acceptor interaction,

$$-\Delta H = E_A E_B + C_A C_B\,,\tag{5}$$

where E_A and E_B are the parameters characterizing the electrostatic (hard) interaction for acid and base, respectively, and C_A and C_B are parameters characterizing the covalent (soft) interaction. This equation can be considered one of the quantitative expressions of the HSAB principle.

One of the most significant empirical equations for the nucleophilicity correlations is that by Ritchie[59]

$$\log k = \log k_0 + N_+\,,\tag{6}$$

where the single parameter N_+ is determined from the difference of logarithms of rate constants of the addition of the nucleophile and water to p-nitromalachite green. The validity range of Eq. (6) is clearly evaluated in two recent papers[11,60]. Some modifications of the original equation were also suggested[61-63].

Beside the correlation equations mentioned, which have already become generally known, several other relations and scales were suggested [64-66]. No attention is paid to the equations for correlations of solvolytic reactions. None of the relations given can be considered universal, since it is not yet known which factors should be included into the parameters characterizing the nucleophile and how many such parameters should be. As the reactivity order of nucleophiles is changed (not only reversed) with a change of substrate or medium, a single parameter will obviously be insufficient. Another problem consists in the way in which the description of properties of the nucleophile itself should be obtained from experimental results without taking into account the reaction conditions. In this context a certain possibility is indicated from the analysis of a representative data set assembled from various reactions at various conditions wherefrom it is possible to obtain quantitative characteristics of nucleophiles by a suitable statistical method. The form of correlation equation is not given unambiguously either, although the well-tried and serviceable linear relation appears to be the most suitable.

The aim of this work is to suggest an empirical correlation equation with the parameters obtained by statistical treatment of selected experimental data and to evaluate the relation suggested in the context of the empirical correlation equations already used.

THEORETICAL AND CALCULATIONS

Our previous investigation[67] carried out with application of the factor analysis showed that the nucleophilicity can be described by a linear relation with two parameters in the form:

$$\hat{y} = a_0 + a_1\, P_1 + a_2\, P_2 , \tag{7}$$

where P_1 and P_2 are the parameters, a_0 is the absolute term, a_1 and a_2 are the regression coefficients. The P_1, P_2 parameters are declared in such way that they reflect only the properties of the nucleophile regardless of the reaction conditions (in the sense of LFER). The parameters for indiviual nucleophiles can then be obtained by applying a suitable mathematical-statistical method (based e.g. on the least squares treatment) to a representative, systematically selected data set. One of the possibilities of obtaining the P_1 and P_2 parameters is the application of the principal component analysis or factor analysis with subsequent rotation for expressing the physical meaning. This procedure does not ensure selection of the optimum parameters giving the minimum residual standard deviation in the regressions, if the calculation starts from an incomplete matrix (almost always) and some regression coefficients are statistically insignificant. A direct optimization of the parameters of Eq. (7) cannot be carried out rationally. A more suitable variant consists in the optimization of the P_1 and P_2 parameters only, and in subsequent calculation of the other parameters by the linear regression. Also in this case it can be expected that the convergence will be slow with respect to the large number of parameters.

The parameters in Eq. (7) (but also in any equation of this type) can be obtained relatively simply by a procedure based on the linear regression for which we suggest the name "the method of conjugated deviations". The difference between the calculated and experimental values of the dependent random variable is given, inter alia, by the values of independent non-random variables whose change can improve the correlation. The magnitude and sense of the change of non-random variable can be derived from those of the deviation of the dependent variable from the regression line. Hence, both the deviations are mutually conjugated. The practically well-tried expression for the correction ΔP_{ijk} reads as follows:

$$\Delta P_{ijk} = a_i(y_{kj} - a_0 - a_1\, P_{1j} - a_2\, P_{2j})/(|a_1| + |a_2|) , \tag{8}$$

where the index i denotes the first or the second parameter of Eq. (7), the index j denotes the corresponding nucleophile in k-th data set, a_0 is the absolute term, a_1 and a_2 are statistically significant (according to the t-test) regression coefficients calculated by double linear regression, and y_{kj} means the value of the dependent variable for the j-th nucleophile. Before the calculation of the regression, the values of dependent variable were standardized to zero average and unit spread. Thereby it is ensured

that also the corrections ΔP_{ijk} are comparable for all experimental determining equations, and their summation (inclusive of their sign) for a given nucleophile leads to the corresponding correction. Magnitude of the correction can be changed — in order to ensure the convergence — by means of a suitable term α according to the equation

$$P_{ij} = P_{ij}^0 + \alpha \sum_{k=1}^{m} \Delta P_{ijk} , \qquad (9)$$

where m means number of experimental equations used for the calculation. If the whole procedure is repeated with corrected parameter values, then with a suitable choice of the α term the calculation converges to give the optimum set of parameters. If necessary, the parameters can be standardized to the interval $\langle 0; 1 \rangle$ in every iteration step. The starting estimates of parameters can be obtained e.g. by means of the PCA or FA methods. The advantages of the procedure described include the respecting of statistical significance of the regression coefficients, insensitivity to the missing data, easy algoritmization, and small demands with respect to the computer time and memory.

The above-described method of conjugated deviations was implemented in the FORTRAN language on an EC 1033 computer.

RESULTS AND DISCUSSION

The above-described method of conjugated deviations was applied to a set of 28 nucleophiles (Table I) whose manifestations were described for 47 physical and chemical processes (Table II). The P_1 and P_2 nucleophilicity parameters were optimized in two variants: without explicit description of the charge — in the form

$$\log k = \log k_0 + a_1 P_1 + a_2 P_2 \qquad (10)$$

and with explicitely considering the charge — in the form

$$\log k = \log k_0 + a_1 P_1 + a_2 P_2 + a_3 Z . \qquad (11)$$

In both cases the initial estimates were taken from the method of principal components, the choice of the damping term of Eq. (9) was $\alpha = 1$. The values of nucleophilicity parameters standardized to the interval $\langle 0; 1 \rangle$ and obtained for Eqs (10) and (11) are summarized in Table I. The difference between the values of parameters from the two variants is small, which is also documented by the correlation coefficients for P_1 (r 0·996) and P_2 (r 0·991) Hence, in most cases the charge participates in the nucleophilicity less than the other factors do. The quality of parameters can, inter alia, be judged on the basis of the deviation calculated from the ΔP_{ijk} correc-

TABLE I

The $P_1 = ND$, $P_2 = PD$ parameters of nucleophiles determined by the method of conjugated deviations according to Eqs (*10*) and (*11*), the parameter deviations s determined from Eq. (*12*) on m determining equations

No. Nucleophile	(10)				(11)			
	P_1 (s)	m	P_2 (s)	m	P_1 (s)	m	P_2 (s)	m
1 Water	0·000 (0·006)	15	0·000 (0·005)	8	0·000 (0·006)	16	0·000 (0·004)	6
2 Methanol	0·084 (0·006)	12	0·103 (0·003)	5	0·096 (0·006)	12	0·084 (0·002)	3
3 Hydroxide	0·546 (0·009)	15	0·827 (0·009)	10	0·582 (0·003)	16	0·824 (0·005)	10
4 Methoxide	0·723 (0·008)	13	0·995 (0·006)	6	0·711 (0·011)	13	0·985 (0·002)	6
5 Phenoxide	0·685 (0·010)	12	0·740 (0·014)	9	0·691 (0·010)	12	0·721 (0·010)	9
6 Peroxidate	0·824 (0·010)	10	1·000 (0·008)	8	0·819 (0·009)	11	1·000 (0·006)	8
7 Acetate	0·403 (0·009)	21	0·357 (0·011)	15	0·435 (0·009)	19	0·374 (0·007)	15
8 Nitrate	0·263 (0·011)	7	0·117 (0·003)	3	0·278 (0·011)	7	0·128 (0·002)	3
9 Nitrite	0·606 (0·015)	13	0·471 (0·010)	13	0·610 (0·017)	11	0·475 (0·006)	14
10 Ammonia	0·533 (0·008)	12	0·676 (0·002)	6	0·535 (0·008)	12	0·656 (0·001)	5
11 Piperidine	0·780 (0·010)	13	0·848 (0·005)	11	0·772 (0·012)	14	0·810 (0·005)	10
12 Morpholine	0·746 (0·007)	6	0·747 (0·009)	8	0·747 (0·007)	6	0·714 (0·005)	9
13 Aniline	0·639 (0·012)	16	0·535 (0·006)	13	0·647 (0·013)	14	0·539 (0·005)	14
14 Imidazole	0·561 (0·012)	8	0·588 (0·011)	9	0·500 (0·004)	7	0·574 (0·007)	9
15 Pyridine	0·551 (0·007)	15	0·551 (0·010)	13	0·545 (0·004)	14	0·534 (0·005)	13
16 Hydroxylamine	0·674 (0·006)	8	0·734 (0·009)	10	0·647 (0·004)	9	0·675 (0·005)	8

TABLE I

(*Continued*)

No. Nucleophile	(10)				(11)			
	P_1 (s)	m	P_2 (s)	m	P_1 (s)	m	P_2 (s)	m
17 Hydrazine	0·741 (0·009)	13	0·768 (0·006)	10	0·729 (0·009)	14	0·718 (0·003)	9
18 Azide	0·650 (0·012)	21	0·525 (0·016)	13	0·682 (0·011)	19	0·483 (0·013)	14
19 Rhodanide	0·694 (0·006)	16	0·252 (0·004)	8	0·708 (0·007)	16	0·273 (0·005)	6
20 Thiourea	0·733 (0·009)	7	0·272 (0·008)	3	0·765 (0·013)	7	0·381 (0·001)	2
21 Thiophenoxide	1·000 (0·008)	14	0·771 (0·002)	7	1·000 (0·008)	14	0·804 (0·002)	7
22 Thiosulfate	0·914 (0·005)	12	0·501 (0·011)	8	0·929 (0·005)	11	0·606 (0·008)	8
23 Sulfite	0·842 (0·007)	9	0·669 (0·004)	5	0·844 (0·007)	9	0·718 (0·003)	5
24 Cyanide	0·637 (0·021)	17	0·703 (0·007)	8	0·649 (0·007)	17	0·762 (0·017)	8
25 Fluoride	0·221 (0·010)	20	0·400 (0·010)	14	0·241 (0·010)	19	0·416 (0·008)	13
26 Chloride	0·461 (0·004)	18	0·142 (0·004)	8	0·480 (0·004)	18	0·153 (0·004)	6
27 Bromide	0·586 (0·003)	17	0·069 (0·002)	8	0·605 (0·004)	17	0·091 (0·002)	6
28 Iodide	0·760 (0·005)	17	0·038 (0·006)	7	0·780 (0·004)	17	0·052 (0·005)	6

tions (Eq. (8)) for the optimum parameters according to the relation

$$s_{ij} = [(\sum_{k=1}^{m} \Delta P_{ijk}^2)/(m - 1)]^{1/2} . \qquad (12)$$

The s_{ij} deviations given in Table I indicate differences in behaviour of nucleophiles. Whereas e.g. the nucleophilicity of bromide anion is very little affected by reaction conditions, the opposite is true of cyanide, azide, or nitrite anions. The ambient

TABLE II

Description of the properties and processes used to adjusting and testing of the nucleophilicity parameters, numbers n of experimental points, and values of regression coefficients a_1, a_2, a_3 in the correlations according to Eq. (11)

No.	Property of nucleophile, nucleophilic process	n	Ref.	a_1	a_2	a_3
1	pK_a, water, 25°C	28	48, 68	−12·0	26·0	—
2	E_n, potential of oxidative dimerization +2·60	22	49	3·3	—	—
3	E_0^{ox}, one-electron oxidation potential, water, 25°C	23	69	−29·0	—	—
4	E_0, oxidation-reduction potential of $Nu^·/Nu^-$ system from thermochemical data	13	70	−34·0	—	—
5	IP, vertical ionization potential	15	71	−90·0	—	—
6	ΔG_5^0, the Gibbs energy of one-electron oxidation	11	72	−69·0	—	—
7	n, sensitivity of nucleophile to the transfer between solvents related to chloride anion.	7	73	−1·9	—	—
8	N_+, log k, A_N, 4-nitromalachite green	20	59	8·3	—	—
9	log k, A_N, 3,4-dehydrotoluene, water	9	74	2·9	—	—
10	log K, A_N, aldehyde carbonyl	6	53	—	—	21·0
11	log K, S_N of ligand, *trans*-bis(pyridine)-dichloroplatinum(II) complex	22	48	7·5	—	—
12	log K, S_N of ligand, methylhydrargyrium cation	15	75, 48	14·0	—	—
13	log k, S_N ($C sp^3$), pentamethylene-iodonium hexafluoroantimonate(V)	8	76	6·8	—	0·92
14	log k, S_N($C sp^3$), oxirane, water	10	77	5·2	—	—
15	−log k, S_N($C sp^3$), chloromethane, water	9	78	7·1	1·8	1·2
16	n, log k, S_N($C sp^3$), bromoethane	22	42	6·6	—	—
17	−ΔG^0, the standard Gibbs energy of exchange, S_N($C sp^3$), iodomethane, water	20	69	—	36·0	—
18	log k, S_N($C sp^3$), iodomethane, methanol	24	48	10·0	—	—
19	log k, S_N($C sp^3$), iodomethane, dimethylformamide, 0°C	6	12	—	3·3	—

TABLE II

(*Continued*)

No.	Property of nucleophile, nucleophilic process	n	Ref.	a_1	a_2	a_3
20	log k, $S_N(C\,sp^3)$, N,N-bis(2-chloro-ethyl)aniline, 50% aqueous ethanol, 51°C	9	79	—	—	1·3
21	log k_1, $S_N(C\,sp^3)$, 1-(4-nitrophenyl)--2-bromopropane, 50% aqueous trifluoromethanol, 75°C	10	46	4·2	—	—
22	log k, $S_N(C\,sp^3)$, 1-(4-nitrophenyl)--2-iodopropane, 50% aqueous trifluoromethanol, 75°C	8	46	5·7	—	—
23	log k, $S_N(C\,sp^3)$, 2-(1-(4-nitrophenyl)-propyl)4-methylbenzenesulfonate, 50% aqueous trifluoromethanol, 75°C	11	46	3·1	—	—
24	log k, $S_N(C\,sp^3)$, methyl 4-methyl-benzenesulfonate, methanol	8	80	6·4	1·0	—
25	log k, $S_N(C\,sp^3)$, 3-(methoxysulfonyl)--N-methylpyridinium perchlorate	10	81	6·8	3·0	—
26	N_+ — log k_{-x}, acetates, correction for the leaving group	12	82	—	20·0	—
27	log k, $S_N(C\,sp^2)$, 4-nitrophenyl hydrogen ethanedioate	8	83	11·0	—	3·9
28	log k, $S_N(C\,sp^2)$, 4-nitrophenyl ethanoate	13	51	—4·2	16·0	0·94
29	log k, $S_N(C\,sp^2)$, 2,4-dinitrophenyl ethanoate	18	68	—	10·0	9·6
30	log k, $S_N(C\,sp^2)$, 2,4-dinitrophenyl ethanoate, 52% aqueous methanol	13	67	—	1·7	0·15
31	log k, $S_N(SO_2)$, sultone of 2-hydroxy--5-nitrotoluene-α-sulfonic acid	11	84	—	16·0	—1·5
32	log k, $S_N(SO_2)$, phenyl thiobenzene-sulfonate, 60% aqueous dioxane	10	85	—	11·0	—3·1
33	log k, $S_N(SO_2)$, diphenyl sulfone, 60% aqueous dioxane, 25°C	12	86	—	7·8	—
34	log k, $S_N(C\,sp^2)$, acetyl chloride, water	8	36	8·6	—	—
35	log k, $S_N(SO_2)$, benzenesulfonyl chloride, water, 25°C	10	87	—	7·3	—
36	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, water, 25°C	9	63	—	8·5	—

TABLE II
(*Continued*)

No.	Property of nucleophile, nucleophilic process	*n*	Ref.	a_1	a_2	a_3
37	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous methanol	8	63	--	5·1	—
38	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous ethanol	7	63	—	8·8	—0·51
39	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous 1-propanol	5	63		8·8	—0·61
40	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous 2-methoxy-ethanol	5	63	--	--	--
41	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous acetonitrile	6	63	---	--	---
42	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous acetone	6	63	·	---	—
43	log k, $S_N(SO_2)$, 2-thiolanesulfonyl chloride, 90% aqueous dioxane	9	63	—	8·7	—
44	log k, $S_N(C\ sp)$, cyanogen chloride, water, 25°C	7	88	13·0	---	—1·2
45	log k, $S_N(C_{arom.})$, 2,4-dinitrochloro-benzene, dioxane–water 3 : 2	8	89	8·1	--	---
46	log k, $S_N(C_{arom.})$, 2,4-dinitrofluoro-benzene, water, 25°C	8	90	23·0	--	---
47	log k, $S_N(C_{arom.})$, 2,4-dinitrofluoro-benzene, 52% aqueous methanol	14	67	1·6	0·66	—

character of some nucleophiles also plays a role which cannot be neglected. Generally the deviations s_{ij} are lower in the variant with explicitly expressed charges.

Special attention should be paid to the physical meaning of the parameters found. An advantage of the method used lies in the stability of solution with respect to the number of determining equations involved (Table I). Hence the final set obtained has a certain, although unknown, physical meaning in contrast to e.g. the factor analysis where the physical meaning can be ascribed to the parameters only after their transformation. The analysis of parameter magnitude in Table I (irrespective of the type of the optimization variant) indicates that the first parameter is related

to softness, polarizability, i.e. nucleophilicity in a narrower sense, which is typical of sulfur nucleophiles and iodide ion. The second parameter rather characterizes hardness and is relatively closely related to the basicity expressed by pK_a (r 0·915). The whole situation is made more clear by plotting the parameter values of the individual nucleophiles against each other. From Fig. 1 it is seen that there is no significant intercorrelation between the two parameters (r 0·584). Moreover, the set of nucleophiles is divided quite clearly into separated groups involving sulfur, nitrogen, and halogenide nucleophiles. The oxygen nucleophiles lie in a region with roughly the same values of the two parameters which penetrates the groups of halogenide and nitrogen nucleophiles. From the dislocation of nucleophiles in the parameters space the following conclusions can be made. First of all the nucleophilicity is determined by the atom type in the reaction centre, its environment having the lowest and the highest effects on the reactivities of nitrogen and oxygen nucleophiles, respectively. The dislocation of individual groups indicates a direct dependence between nucleophilicity (i.e. C-basicity) and basicity (i.e. H-basicity) for the nucleophiles having the same atom in the reaction centre. Halogens form an exception, the dependence having the reversed character. The dislocation of groups in Fig. 1 expresses the order of ability to react well with substrates having a soft reaction centre, viz. from sulfur through nitrogen to oxygen nucleophiles and from iodide to fluoride anion. The comparisons of hydroxide (No. 3) with peroxide (No. 6) anion, ammonia (No. 10) with hydroxylamine (No. 16) and hydrazine (No. 17) indicate the reactivity increase due to the α effect, the first parameter being affected more than the second parameter. No conclusions can be made from the data given about carbon nucleophiles.
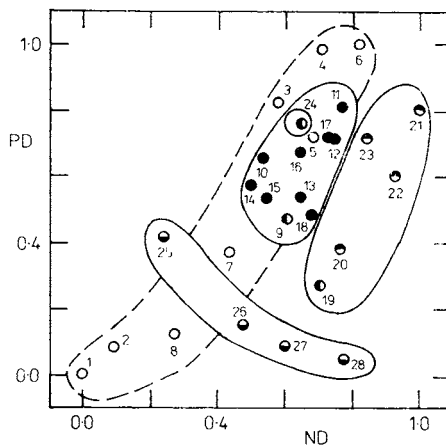

FIG. 1

The dislocation of the nucleophiles from Table I in the space of ND and PD parameters determined by the method of conjugated deviations according to Eq. (11). The denotation corresponds to the reaction centre with nitrogen ●, sulphur ◓, halogenide ion ◓, and oxygen ˋ; ◒ means the ambident nucleophiles

For the further analysis it is appropriate to introduce a new denotation of the nucleophilicity parameters so as to have relation to the property described by the parameter. The first parameter will be denoted as ND (donor ability towards a general nucleus, the activity control towards a general nucleus) and the second parameter as PD (donor ability to the proton, the activity control to the proton).

The application of the nucleophilicity parameters suggested along with Eq. (11) (P_1 = ND, P_2 = PD) to the properties and processes of Table II gave the regression coefficients which are summarized in Table II, the respective residual standard deviations and correlation coefficients being given in Table III. As both the nucleophilicity parameters are standardized, the magnitude of the respective regression coefficients represents a measure of contribution of the corresponding property. The pK_a value (No. 1) correlates relatively well with both the parameters, the PD parameter being more significant; the signs agree with the previous discussion. The physical quantities (Nos 2 and 6) are unambiguously related to the first parameter ND, the relation being not very close. As the quantities in question are related to the HOMO energy, the ND parameter also reflects the ability of a nucleophile to donate its electrons into the LUMO of the electrophile. A not very close relation exists also for the n parameter (No. 7) derived from the solvation energies in S_N2 reactions, the ND parameter only being significant. The nucleophilic additions (Nos 8, 9) also are functions of the ND parameter only, the insignificance of charge in the correlation of the N_+ parameter by Ritchie being surprising. The correlations are not close, the same being true of the nucleophilic addition to carbonyl group (No. 10). In this case − contrary to expectation − the charge of nucleophiles represents the only substantial property. It is possible that in this case some other factor (which is not involved in our scale) makes itself felt. The substitution of ligands in complex compounds (Nos 11, 12) shows a not very close dependence on the ND parameter.

A large group is formed by nucleophilic substitutions at the sp^3-hybridized carbon. Excellent interpretation is obtained for the substitution of pentamethyleneiodonium cation (No. 13), the charge decreasing the raction rate. The salt effect is quite obvious in this case. An average correlation is observed for the ring opening reactions of oxirane (No. 14), the nucleophilicity expressed by the ND parameter being predominant. As compared with the previous two cases, the nucleophilic substitution of chloromethane (No. 15) appears to be quite complex, the correlation being very close. The ND parameter makes itself felt more markedly, the salt effect probably has a negative influence. Less close but with greater statistical weight are the correlations of the data obtained for nucleophilic substitutions of bromomethane (No. 16), the ND parameter only being significant. Somewhat contradictory results are obtained from the application of Eq. (11) to the nucleophilic substitutions of iodomethane (Nos 17−19). The correlations can be denoted as average, the activity of nucleophiles being predominantly described by the PD parameters in water and dimethylformamide and by ND in methanol. If solvation decreases the hardness

TABLE III

The residual standard deviations (s), correlation coefficients (r) (Eqs (2), (6), (1)), and coefficients of multiple correlation (R) (Eqs (10), (11), (3)) obtained by application of correlation equations to the processes from Table II

No.	(10)	(11)	(2)	(2)^a	(2)^b	(6)	(1)	(3)
1	2·57	2·33	----	--		13·7	0·000	0·000
	(0·971)	(0·974)	----	----		(0·504)	(1·000)	(1·000)
2	0·111	0·113	0·134	0·107	0·190	0·504		0·000
	(0·930)	(0·929)	(0·921)	(0·929)	(0·869)	(0·661)		(1·000)
3	0·279	0·284	0·416	0·431	---	0·620	--	0·446
	(0·801)	(0·797)	(−0·709)	(−0·617)		(−0·583)		(0·681)
4	0·141	0·153	0·195	0·268		—		0·224
	(0·888)	(0·879)	(−0·847)	(−0·797)				(0·816)
5	166	149	300	224		267		336
	(0·874)	(0·888)	(−0·775)	(−0·760)		(−0·822)		(0·778)
6	130	134	227	—		225	--	—
	(0·853)	(0·849)	(−0·781)	—		(-·0·728)		—
7	0·0288	0·0332	0·0136	0·0269	0·0402	0·0016	—	0·0564
	(0·915)	(0·902)	(−0·961)	(−0·921)	(−0·989)	(−1·000)		(0·826)
8	1·34	1·25	2·52	1·47	··	0·000	3·51	3·26
	(0·846)	(0·857)	(0·743)	(0·784)	----	(1·000)	(0·504)	(0·661)
9	0·0789	0·0708	0·0985	0·0438	0·0753	0·0693		0·103
	(0·921)	(0·929)	(0·913)	(0·957)	(0·935)	(0·957)		(0·910)
10	··	1·81	—	--	0·610			
	—	(0·819)	—	—	(0·956)			—
11	1·34	1·49	1·90	1·21	0·000		----	1·20
	(0·826)	(0·793)	(0·700)	(0·835)	(1·000)			(0·869)
12	6·45	6·60	3·50	5·48	6·71	----	---	4·66
	(0·772)	(0·766)	(0·825)	(0·811)	(0·762)	--		(0·842)
13	0·0735	0·0245	0·162	0·279	0·294			0·148
	(0·988)	(0·997)	(0·973)	(0·945)	(0·942)			(0·975)
14	0·368	0·389	0·140	0·161	—	0·742	1·19	0·516
	(0·926)	(0·922)	(0·963)	(0·969)	----	(0·677)	(0·735)	(0·881)
15	0·173	0·0860	0·139	0·307	0·0985	--	—	0·441
	(0·980)	(0·992)	(−0·981)	(--0·937)	(−0·980)	---	--	(0·939)
16	0·282	0·298	0·000	0·199	0·892	1·36	--	0·484
	(0·949)	(0·946)	(1·000)	(0·957)	(0·700)	(0·743)		(0·921)
17	22·8	18·5	108	97·6	---	70·4	47·8	13·5
	(0·929)	(0·943)	(0·634)	(0·573)	--	(0·704)	(0·845)	(0·960)

TABLE III
(*Continued*)

No.	(10)	(11)	(2)	(2)[a]	(2)[b]	(6)	(1)	(3)
18	0·277	0·209	0·395	0·000	1·40	1·13	—	0·814
	(0·977)	(0·979)	(0·957)	(1·000)	(0·835)	(0·784)	—	(0·929)
19	0·162	0·108	--	—	—	—	0·120	0·120
	(0·943)	(0·962)	...	—	—	—	(0·958)	(0·958)
20	--	0·586	---	--	0·329	—	—	0·0829
	—	(0·742)	—	—	(0·885)	—	—	(0·960)
21	0·300	0·267	0·550	0·383	0·742	0·368	—	0·862
	(0·926)	(0·935)	(0·857)	(0·846)	(0·670)	(0·945)	—	(0·770)
22	0·0836	0·140	0·261	0·320	0·617	—	—	0·627
	(0·988)	(0·975)	(0·956)	(0·909)	(0·815)	—	—	(0·885)
23	0·223	0·205	0·395	0·304	—	0·212	—	0·556
	(0·896)	(0·905)	(0·797)	(0·781)	--	(0·946)	—	(0·712)
24	0·0422	0·0455	0·224	0·205	1·57	---	—	0·0905
	(0·996)	(0·996)	(0·995)	(0·976)	(0·800)	—	—	(0·991)
25	0·206	0·166	0·421	0·168	0·419	—	--	0·372
	(0·975)	(0·980)	(0·941)	(0·976)	(0·926)	—	—	(0·955)
26	1·18	1·20	1·56	5·36	4·45	—	2·18	1·06
	(0·938)	(0·937)	(0·910)	(0·706)	(0·707)	—	(0·882)	(0·949)
27	5·07	3·37	--	—	0·760	—	—	—
	(0·793)	(0·891)	—	—	(0·947)	—	—	—
28	0·349	0·536	—	—	—	2·39	2·27	0·720
	(0·986)	(0·980)	—	—	—	(0·893)	(0·894)	(0·957)
29	0·430	0·520	2·82	2·51	—	2·27	2·02	1·67
	(0·949)	(0·942)	(0·641)	(0·621)	—	(0·688)	(0·729)	(0·773)
30	0·0101	0·0172	--	—	—	0·0501	0·0231	0·0200
	(0·945)	(0·914)	—	—	—	(0·584)	(0·870)	(0·825)
31	1·40	0·783	—	2·28	—	3·68	2·07	1·09
	(0·873)	(0·939)	—	(0·779)	—	(0·613)	(0·806)	(0·940)
32	—	2·27	—	--	-	—	—	--
	—	(0·893)	—	—	—	—	—	—
33	0·417	0·555	—	0·948	--	1·18	1·34	—
	(0·927)	(0·901)	—	(0·709)	—	(0·775)	(0·740)	...
34	0·207	0·131	—	0·185	0·366	0·269	--	—
	(0·927)	(0·954)	--	(0·933)	(0·863)	(0·903)	--	...

TABLE III
(Continued)

No.	(10)	(11)	(2)	(2)[a]	(2)[b]	(6)	(1)	(3)
35	0·240	0·317	1·62	·--	—	1·42	1·37	1·57
	(0·959)	(0·945)	(0·761)	---	—	(0·759)	(0·732)	(0·726)
36	0·192	0·0700	1·48	–	—	1·21	1·34	1·34
	(0·966)	(0·988)	(0·744)	—	—	(0·767)	(0·729)	(0·729)
37	0·0778	0·0307	0·0416	0·0755	0·0634	·	—	0·0930
	(0·798)	(0·926)	(0·926)	(0·805)	(0·839)	–	—	(0·776)
38	0·0314	0·0081	---	—	0·0383	·	—	—
	(0·928)	(0·986)	—	—	(0·911)	·	—	---
39	0·0352	0·0060	---	0·0288	0·0187	·--	—	---
	(0·912)	(0·990)	···	(0·929)	(0·954)	—	—	··
40		···	··	····	·-	--·	···	----
		··	··	··	·-	··	··	-
41		···	···	··	··	···	--·	---
		···	---	·	—	···	—	---
42		·	···	·	··	··	--·	—
		··	··	·	---	---	---	---
43	0·658	0·499	···	··	—	··	0·701	—
	(0·833)	(0·877)	····	··	--·	—	(0·821)	—
44	0·391	0·107	3·74	·--	····	1·52	5·83	—[c]
	(0·989)	(0·998)	(0·910)	···	-	(0·956)	(0·817)	—[c]
45	0·732	0·768	0·986	··	--	1·05	—	····
	(0·827)	(0·817)	(0·803)	--·	--·	(0·738)	—	··
46	0·294	0·321	---	·	···	—	—	·-·
	(0·942)	(0·937)	—	---	···	—	—	—
47	0·0112	0·0104	0·0264	0·0380	---·	0·0294	0·0592	0·0330
	(0·939)	(0·943)	(0·836)	(0·781)	--·	(0·813)	(0·562)	(0·878)

[a] n_{MeI}; [b] n_{Pt}; [c] insufficient number of data.

of nucleophiles, the result can be well understood in the cases of Nos 18 and 19 but not in the case of No. 17. No dependence is observed (practically) with the reaction No. 20: in this case the substitution is probably accompanied by elimination, and the ratio of the two reactions depends on the nucleophile. The substitutions Nos 21 − 23 represent examples of the effect of leaving groups. The better is the leaving group, the closer is the correlation and the higher is the regression coefficient in the ND

parameter. In the nucleophilic substitutions with sulfonates (Nos 24, 25) the hardness of nucleophiles partially makes itself felt as a result of the character of the reaction centre. The correlation is very good.

Nucleophilic substitutions at the sp^2-hybridized carbon atom mostly refer to esters. The parameter modified by Ritchie (No. 26) for these substrates shows an only average correlation with the ND parameter. Also not very close are the correlations for the ester substrates Nos 27 − 30. In all the cases the charge of nucleophiles exhibits a negative influence, the salt effect − inter alia − being obviously also significant. The hardness of nucleophiles (described by the PD parameter) makes itself felt to a greater extent. The same is also true of the substitutions of sulfonate esters (Nos 31, 32) taking place at the sulfur atom: in this case the charged nucleophiles are more reactive, the salt effect being not easily evaluated. The nucleophilic decomposition of disulfone (No. 33) shows a not very close correlation with the PD parameter.

Another important group is formed by nucleophilic substitutions of chlorine in acyl chlorides. Whereas the substitution in acetyl chloride (No. 34) is surprisingly interpreted by the ND parameter (an average correlation), those in sulfonyl chlorides (Nos 35 − 43) are described by the PD parameter, of course, if any correlation exists at all. The reactions Nos 36 − 43 represent a good example of solvent effect. When going from water and methanol to ethanol and 1-propanol we can observe a positive influence of the charge, the correlations being good in some cases. In methoxy-ethanol and aprotic solvents (except dioxane) the correlation is statistically insignificant, which is surprising. The nucleophilic substitution at the sp-hybridized carbon atom of cyanogen chloride (No. 44) is excellently interpreted by the ND parameter, the influence of charge being positive. The nucleophilic aromatic substitutions of activated halogenobenzenes (Nos 45 − 47) show bad to average correlations with the ND parameter; on going from water (No. 46) to a methanol–water mixture (No. 47) we also observe a manifestation of the hardness of nucleophiles (expressed by the PD parameter).

Both the advantages and drawbacks of the parameter scale suggested become more distinct in comparison with the most significant scales used so far, some of which, however, being used outside their validity range. Table III summarizes the statistical characteristics obtained by application of Eqs (2) (using the n scale[42]; n_{MeI} scale[48]; n_{Pt} scale[47,48]), (6), (1), and (3). If the successfulness of the equations mentioned is compared with that of Eqs (10) and (11) on the basis of the value of residual standard deviation, the following average order of the equations is obtained: (11) 2·05, (10) 2·63, (2) (n_{MeI} scale) 4·59, (3) 4·59, (2) 4·80, (6) 5·14, (2) (n_{Pt} scale) 5·61, (1) 5·95. The differences in the sequence are inasmuch distinct, that the good quality of the parameters suggested can be ascribed a more general validity. The failure of the n_{Pt} and pK_a scales is due to their specialized nature. The n_{Pt} scale describes (almost exclusively) the orbital interaction, which is similar to E_n in the Eq. (3) by Edwards as it was shown by the factor analysis[67]. pK_a represents the other

extreme, since it predominantly reflects the charge interaction at a hard centre. The relatively large difference between the successfulness of Eqs *(10)* and *(11)* stresses the importance of the charge in nucleophiles which makes itself felt by salt effects in most cases. The analysis of results in the table allows no general conclusions to be made about the applicability of the correlation equations published to certain substrates or reaction conditions. The kinetic measurements (Nos 40 − 42), where all the correlation equations fail, are probably loaded with experimental imperfectness.

REFERENCES

1. Edwards J. O., Pearson R. G.: J. Am. Chem. Soc. *84*, 16 (1962).
2. Bunnett J. F.: Annu. Rev. Phys. Chem. *14*, 271 (1963).
3. Gompper R.: Angew. Chem., Int. Ed. *3*, 560 (1964).
4. Alexander R., Ko E. C. F., Parker A. J., Broxton T. J.: J. Am. Chem. Soc. *90*, 5049 (1968).
5. Parker A. J.: Chem. Rev. *69*, 1 (1969).
6. Pearson R. G. in: *Advances in LFER* (N. B. Chapman and J. Shorter, Eds), p. 281. Plenum, London 1972.
7. Grekov A. P., Veselov V. Ya.: Usp. Khim. *47*, 1200 (1978).
8. Bell R. P. in: *Correlation Analysis in Chemistry. Recent Advances* (N. B. Chapman and J. Shorter, Eds), Chap. 2. Plenum, New York 1978.
9. Duboc V. in: *Correlation Analysis in Chemistry. Recent Advances* (N. B. Chapman and J. Shorter, Eds), p. 313. Plenum, New York 1978.
10. Modena G., Paradisi C., Scorrano G.: Stud. Org. Chem. *19*, 568 (1985).
11. Ritchie C. D.: Can. J. Chem. *64*, 2239 (1986).
12. Streitwieser A.: Proc. Natl. Acad. Sci. U.S.A. *82*, 8288 (1985).
13. Skrebets T. E., Komarov E. V.: Zh. Obshch. Khim. *56*, 451 (1986).
14. Heaton M. M.: J. Am. Chem. Soc. *100*, 2004 (1978).
15. Buncel E., Hoz S.: Tetrahedron Lett. *24*, 4777 (1983).
16. De Puy C. H., Della E. W., Filley J.: J. Am. Chem. Soc. *105*, 2481 (1983).
17. Laloi-Diard M., Verchene J. F., Gosselin P., Terrier F.: Tetrahedron Lett. *25*, 1267 (1984).
18. Shustov G. V.: Dokl. Akad. Nauk SSSR *280*, 1378 (1985).
19. Buncel E., Um I. H.: J. Chem. Soc., Chem. Commun. *1986*, 595.
20. Stirling C. J. M.: J. Am. Chem. Soc. *101*, 198 (1979).
21. Creary X.: J. Org. Chem. *50*, 5080 (1985).
22. Castro E. A., Borquez M. T., Parada P. M.: J. Org. Chem. *51*, 5072 (1986).
23. Klopman G.: *Chemical Reactivity and Reaction Paths*. Wiley, New York 1974.
24. Fleming I.: *Frontier Orbitals and Organic Chemical Reactions*. Wiley, Chichester 1976.
25. Pearson R. G.: Proc. Natl. Acad. Sci. U.S.A. *83*, 8440 (1986).
26. Peterson P. E., Waller F. J.: J. Am. Chem. Soc. *94*, 991 (1972).
27. Schadt F. L., Bentley T. W., Schleyer P.: J. Am. Chem. Soc. *98*, 7667 (1976).
28. Dvorko G. F., Evtushenko N. Yu., Ponomareva E. A.: Org. Reactiv. *22*, 449 (1985).
29. Kevill D. N., Rissman T. J.: J. Org. Chem. *50*, 3062 (1985).
30. Kevill D. N., Anderson S. W.: J. Am. Chem. Soc. *108*, 1579 (1986).
31. Litvinenko L. M., Oleinik N. M.: *Mekhanizmy Deistviya Organicheskikh Katalizatorov*. Naukova Dumka, Kiev 1984.
32. Smith G. F.: J. Chem. Soc. *1943*, 521.
33. Jencks W. P.: J. Am. Chem. Soc. *102*, 6789 (1980).

34. Bordwell F. G., Hughes D. L.: J. Org. Chem. *46*, 3570 (1981).
35. Bordwell F. G., Hughes D. L.: J. Org. Chem. *47*, 169 (1982).
36. Palling D. J., Jencks W. P.: J. Am. Chem. Soc. *106*, 4869 (1984).
37. Skoog M. T., Jencks W. P.: J. Am. Chem. Soc. *106*, 7597 (1984).
38. Jencks W. P., Haber M. T., Herschlag D., Nazaretian K. L.: J. Am. Chem. Soc. *108*, 479 (1986).
39. Hupe D. J., Jencks W. P.: J. Am. Chem. Soc. *99*, 451 (1977).
40. Hupe D. J., Wu D., Shepperd P.: J. Am. Chem. Soc. *99*, 7659 (1977).
41. Castro E. A., Santander C. L.: J. Am. Chem. Soc. *50*, 3595 (1985).
42. Swain C. G., Scott C. B.: J. Am. Chem. Soc. *75*, 141 (1953).
43. Biggs I. D., Williams D. L. H.: J. Chem. Soc., Perkin Trans. 2, *1975*, 107.
44. Craze G. A., Kirby A. J., Osborne R.: J. Chem. Soc., Perkin Trans. 2, *1978*, 357.
45. Ogata Y., Yansuchi Y.: Bull. Chem. Soc. Jpn. *52*, 2171 (1979).
46. Dietze P. E., Jencks W. P.: J. Am. Chem. Soc. *108*, 4549 (1986).
47. Belluco U., Cattalini L., Basolo F., Pearson R. G., Turco A.: J. Am. Chem. Soc. *87*, 241 (1965).
48. Pearson R. G., Sobel H., Songstad J.: J. Am. Chem. Soc. *90*, 319 (1968).
49. Edvards J. O.: J. Am. Chem. Soc. *76*, 1540 (1954).
50. Edwards J. O.: J. Am. Chem. Soc. *78*, 1819 (1956).
51. Jencks W. P., Carriuolo J.: J. Am. Chem. Soc. *82*, 1778 (1960).
52. Davis R. E.: Tetrahedron Lett. *1966*, 5021.
53. Sander E. G., Jencks W. P.: J. Am. Chem. Soc. *90*, 6154 (1968).
54. Cho M. J., Pitman I. H.: J. Am. Chem. Soc. *96*, 1843 (1974).
55. Guthrie J. P.: Can. J. Chem. *52*, 2037 (1974).
56. Fischer G., Kullertz G., Schellenberg A.: Tetrahedron *32*, 1503 (1976).
57. Drago R. S., Wayland B. B.: J. Am. Chem. Soc. *87*, 3571 (1965).
58. Drago R. S.: Struct. Bond. *15*, 73 (1973).
59. Ritchie C. D., Virtanen P. O. I.: J. Am. Chem. Soc. *94*, 4966 (1972).
60. Sinev V. V.: Vopr. Fiz. Org. Khim. *2*, 77 (1984).
61. Ritchie C. D.: J. Am. Chem. Soc. *97*, 1170 (1975).
62. Hillier K., Scott J. M. W. Barnes D. J., Steele F. J. P.: Can. J. Chem. *54*, 3312 (1976).
63. Arcoria A., Ballisteri F. B., Tomaselli G. A.: Tetrahedron *34*, 2545 (1978).
64. Finiels A., Geneste P.: J. Org. Chem. *44*, 1577 1979).
65. Parr R. G., Pearson R. G.: J. Am. Chem. Soc. (*105*, 7512 (1983).
66. Lee I., Sohn S. C.: Bull. Korean Chem. Soc. *1986*, 321.
67. Zima V., Pytela O., Večeřa M.: Collect. Czech. Chem. Commun. *53*, 814 (1988).
68. Jencks W. P., Gilchrist M.: J. Am. Chem. Soc. *90*, 2622 (1968).
69. Pearson R. G.: J. Org. Chem. *52*, 2131 (1987).
70. Eberson L.: Acta Chem. Scand., B *38*, 439 (1984).
71. Shaik S. S.: J. Org. Chem. *52*, 1563 (1987).
72. Ritchie C. D.: J. Am. Chem. Soc. *105*, 7313 (1983).
73. Parker A. J., Mayer V., Schmid R., Gutmann V.: J. Org. Chem. *43*, 843 (1978).
74. Zoratti M., Bunnett J. F.: J. Org. Chem. *45*, 1776 (1980).
75. Schwarzenbach G., Schellenberg M.: Helv. Chim. Acta *48*, 28 (1965).
76. Peterson P. E., Vidrine D. W., Waller F. J., Henrichs P. M.: J. Am. Chem. Soc. *99*, 7968 (1977).
77. Virtanen P. O. I., Korhonen R.: Acta Chem. Scand. *27*, 2650 (1973).
78. Scott J. M. W.: Can. J. Chem. *48*, 3807 (1970).
79. Yaguzhinskii L. S., Chinaeva A. D.: Zh. Obshch. Khim. *39*, 2581 (1969).

80. Pearson R. G., Songstad J.: J. Org. Chem. *32*, 2899 (1967).
81. Ash A. B., Blumbergs P., Stevens C. L., Michel H. O., Hackley B. E., Epstein J.: J. Org. Chem. *34*, 4070 (1969).
82. Ritchie C. D., Wright D. J., Huang D. H., Kamego A. A.: J. Am. Chem. Soc. *97*, 1163 (1975).
83. Bruice T. C., Holmquist B.: J. Am. Chem. Soc. *89*, 4028 (1977).
84. Deacon T., Steltner A., Williams A.: J. Chem. Soc., Perkin Trans. 2, *1975*, 1778.
85. Kice J. L., Lin C. A.: J. Org. Chem. *44*, 1918 (1979).
86. Kice J. L., Legan E.: J. Am. Chem. Soc. *95*, 3912 (1973).
87. Rogue O.: J. Chem. Soc., B *1970*, 1056.
88. Edwards J. O., Erstfeld T. E., Ibne-Rasa K. M., Levey G., Moyer M.: Int. J. Chem. Kinet. *18*, 165 (1986).
89. Pietra F., Biggi G.: J. Chem. Soc., B *1971*, 44.
90. Ritchie C. D., Sawada M.: J. Am. Chem. Soc. *99*, 3754 (1977).

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