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Steric effects: the problem of their quantitative assessment and manifestation in the reactivity of hetero-organic compounds

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ABSTRACT. Literature data on the methods of quantitatively assessing steric effects and their manifestation in the reactivity of various hetero-organic compounds is systematised. The authors' own results are considered in the light of a model of frontal steric effects and of a calculated scale of steric constants R_s, the high effectiveness of which has been demonstrated in more than 100 reaction series involving organic and hetero-organic compounds.

The bibliography contains 202 references.

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I. Introduction

Current ideas on the effects of the spatial structure of molecules on their reactivity embrace many diverse phenomena. The overall interaction of substituents with a reaction centre is assumed to be subdivided into inductive, resonance and steric components.

When attempting a quantitative assessment of the steric component investigators have frequently encountered a problem when choosing parameters reflecting the steric effect of substituents. The presence of many steric scales complicates such a choice. The assessment of spatial effects in the chemistry of hetero-organic compounds (HOC) was problematical until recently owing to the uncertainty of its overall theoretical character. Whether steric effects actually influence the reactivity of HOC was still in question.

The present review is devoted to a discussion of studies affecting both aspects of the problem. In addition to an analysis and comparison of the existing methods of calculating steric effects attempts will be made to use these methods for the analysis of the reactivity of HOC. In those cases when the material of the present review partially overlaps reviews published already the appropriate references are given.

II. Quantitative methods of assessing steric effects

1. General concepts of steric effects

a) History of their development

It is considered (see Ref. 1 and literature therein) that the idea of a steric effect was introduced for the first time by Khermann in the mid-nineteenth century to explain the chemical inertness of substituted quinones by the steric effect of *ortho* substituents. Up to the thirties of the present century the concept of a steric effect was widely drawn upon by Hofman, Menshutkin, Holleman, Conant and other authors to explain chemical phenomena. However the development of steric effect theory later went into a decline caused by the predominant attention paid by investigators to the inductive effect of substituents.

Subsequently the reactivation and blossoming of steric effect theory was linked mainly with the precise quantitative investigations carried out by Ingold, Brown and Taft (see Ref. 2 and literature therein).

At present the steric effect shown by a substituent is recognised as steric hindrance or cooperation in the course of a reaction as a result of which there is a change in valence angles and coordination number of the reaction centre during the reaction or on activation.[3] The concept of a substituent shielding a reaction centre is widely used.[4] The drawing together of molecules in space is considered to be the most important factor determining the energy of activation.[5,6] According to contemporary ideas[7–9] steric effects for processes occurring in solution reduce in many cases to the hindrance which a substituent creates for solvation of the reaction centre. Finally, steric effects of substituents may be manifested by the inhibition of resonance structure formation.[4]

These factors of structure and reactivity have been considered in adequate detail for organic compounds in the review literature.[3,10–13] For hetero-organic compounds these aspects have not as yet been generalised in any appreciable manner although there are individual reviews concerning compounds of phosphorus, silicon and nitrogen[9,14–18] and a whole series of individual papers and series of papers on the chemistry of other elements in which some aspects of the spatial effect of substituents are considered. It must be noted that the possibility of the actual manifestation of steric effects in HOC chemistry was discussed comparatively recently,[19] although there are numerous investigations, including some carried out at the quantitative level,[20,21] pointing in favour of the existence of such an effect.

An extremely important factor moderating the study of steric effects until now has been the absence, in spite of many experimental data, of a satisfactory physical model of steric interactions, although the latter are linked in a sense with the spatial structure of

molecules.[3] Taft, for example, considers that the more bulky (or more branched) the interacting group is and the closer it is located to the reaction centre then the stronger these interactions will be. It is assumed that these correspond to repulsive forces.[13,22]

At the present time quantitative methods of calculating the steric effect comprise quantochemical, topological, structural and experimental approaches.

2. Methods of molecular mechanics and quantum chemistry

In the theoretical approach to the study of steric effects it is most important[3] to consider the combination of phenomena united by the term 'spatial effects of substituents' as a part of the more general problem of conformational analysis. Consequently a quantitative calculated–theoretical approach to the study of spatial effects must be based on the achievements of theories of conformational analysis,[4] i.e. on quantochemical calculations of the total energy of a molecule as a function of the angles of rotation, which enable the most stable conformation to be established.

It is accepted (see Ref. 2 and literature therein) that the general theory of spatial effects was first formulated in 1946 by Hill who showed that the energy of any molecule (or activated complex) may be described as the sum of the van der Waals potential energy (for the interaction of non-valently linked atoms) and the energy required for the deformation of bond lengths and valency angles of the molecule.

$$SE=E_r(r)+E_\theta(\theta)+E_\varphi(\varphi)+E_{nb}(d), \quad (1)$$

where SE is the system energy, E_r is the energy for deformation of bond length, E_θ is the energy for deformation of valency angles, E_φ is the torsional energy and E_{nb} the energy of non-bonding interactions.

The energy minimum corresponds to the optimum conformation of the molecule. The mathematical problem therefore reduces to varying the structural parameters in the search for the energy minimum.

The approaches of various authors have differed, as a rule, by ignoring some or other of the components of Eqn. (1) or by including additional terms and by the form of the potential function, the force field and by the mathematics and programs provided.

The method,[23] which has received the name atom–atom potential functions, was first applied to the calculation of the spatial influence of substituents in substitution reactions at a saturated carbon atom.[24] The agreement of calculated and experimental data was fairly satisfactory considering that the calculations were carried out manually. After a twenty-year break the studies were continued using computers (see Ref. 2 and literature therein). Initially the calculation plans were most simple, being stepwise, and were then improved by considering an analysis of the energy differences linked with a change in each coordinate of a mobile atom. The Engler 73 and Allinger 71 force field programs were developed.

The approach modified in this way, called the force-field or molecular-mechanics method, is better than previous methods since the set of structural parameters and deformation values used is appreciably improved, the choice of potential function is easier and the calculation procedure for the user is simplified.

The method of molecular mechanics has been used in various branches of organic chemistry. The results of the previous studies of Ingold on the S_N2 process have been re-examined (see Ref. 2 and literature therein) using more precise models. The method proved to be applicable to explain the processes of solvolysis of carbocations and their rearrangements and for conformational calculations of molecules and certain reactions.

DeTar[25] has proposed assessing steric effects using hydrocarbon models. The method considered afforded an explanation of the results of certain reactions[26] and proof of the steric sense of the experimental Taft constants, E_S.[27]

In a series of studies Kalamov and Kuzmin[28–32] developed and verified an approach to the assessment of the steric factors of reactivity based on calculation of the energy of the various conformations of a substrate and an intermediate within the framework of a force field model. By varying the torsion angle and the distance to a reactant a picture was constructed of the potential surfaces which enabled the reactivity of the compounds investigated to be analysed qualitatively and the stereochemical result of a reaction to be explained.

The steric index of reactivity (SIR) was introduced by these authors[28–32] for the quantitative description of the steric effects. This correlates satisfactorily with the E_S constants of alkyl groups and also with the rate constants for the hydrolysis of various esters. Such an approach also enables the stereochemical result of the reduction of α-substituted β- and γ-ketoesters to be explained.

Another approach[33] to the quantitative assessment of steric effects is based on the analysis of the overlap volumes of van der Waals shells of pairs of reactants. A good agreement of calculated and experimental data was achieved. This and methods similar to it are applied mainly to the correlation of biochemical data and biological activity (see Ref. 2 and literature therein).

Recently *ab initio* quantum methods have been developed for the calculation of potential barriers to internal rotation and of the total energy of a molecule as a function of the angles of internal rotation.

The approach proposed by Becker[34–36] is considered to be the most fundamental among this group of methods. Steric effects of substituents are proposed as the manifestation of particular conformational relationships.[34–36] However at the basis of Becker's method there are complex mathematical calculations and parameters which are difficult to determine and which hamper its practical use. It is necessary to mention the work of Bohle[37] on the development of optimisation programs based on Becker's approach in which a satisfactory description of the steric effect of alkyl substituents was achieved with specific assumptions. However it is also unlikely that this modification will be successful in the short term.

Periodically studies have appeared using various methods of disregarding differential overlap in calculations, such as CNDO, CNDO/2, MNDO, CS-INDO.[38–42] However the results of calculations did not always agree with the experimental data.

Various MO methods have been applied with varying success to the calculation of rotational barriers[43,44] and the investigation of various reactions.[45,46]

3. Topological methods

Topological indices have been applied in chemistry comparatively recently and have already acquired a wide reputation (see Refs. 2 and 47 and literature therein).

The development of topological approaches is linked with the application of graph theory. Usually an abstract mathematical structure, the so-called 'molecular graph', is characterised by two matrices, a proximity matrix A and a distance matrix D. The topological indices are quantitative characteristics of such graphs and represent various combinations of the elements of both matrices and reflect some aspect of the structure of the molecule.

The topological index was first introduced by Weiner (see Ref. 2 and literature therein). He introduced the W index denoting the number of edges connecting all pairs of apices to one another and showing the extent of branching of the molecule. Like W the I indices, the Platt index f, and the index N_2 derived from it, depend on the number of linking edges but in a different manner. The Hosoi index Z reflects the distance between all the unconnected apices. The indices of Gutman (M_I), Randic (χ) and Kier–Hall (h_x) are indicators of the extent of substitution at each apex.

A new group of informational indices I_{PC} and $\bar{I}_{PC}$ was introduced by Bonchev. These indices are combinations of indices W, Z and χ.

The group of centric indices of Balaban reflect the structure of a tree-like graph and is also linked with the geometric structure of the molecule.

The topological indices represented above and certain others are considered in a more detailed manner in the review[2] and in the literature cited in it.

Topological indices are intuitively linked with the structural parameters of molecules[2] but there are very few quantitative investigations of them. Recently Balaban[48] has correlated 14 known topological indices with molecular refraction and van der Waals volume. The best correlations were obtained for the indices W, I, χ and the informational indices I_D^W and I_D^E. This enabled a conclusion to be drawn on the similarity of these indices with the experimental constants E_S and v_X. In addition it turned out that all 14 of the indices investigated were linked linearly to one another which prevented the creation of a new superindex of the linear combination of several of the known indices. However in several cases the correlation of experimental data with the indices of Randic[49] and Kier–Hall[50] proved to be successful. A linear connection between the Randic indices and steric constants has also been recorded.[49]

The lack of consideration of the conformation of a molecule is a considerable drawback to the use of the indices mentioned. This drawback is removed when using the DARC system of Dubois (see Ref. 2 and literature therein). However this system is an order of magnitude more complicated than the 'disordered' topological indices.

The topological indices may be and already are being used for the calculation of steric effects, for example in computer synthesis programs. However the absence of a clear physical and geometric meaning and also the lack of consideration of the conformation of molecules restrains their application.

4. Structural and geometric scales

The approaches to the modelling of steric effects using various structural, geometric and physical parameters differ from the previous two by the considerable simplification of the mathematics used, by its more graphic nature and by a clear geometric meaning. As a rule available structural parameters, such as valence angles, atomic, covalent, van der Waals radii of atoms and bond lengths, are used as the initial data.

Attempts to create similar accessible methods for the calculation of steric effects were undertaken long ago and were unsuccessful initially. For example some authors compared distances between chemically unbonded atoms with the sum of their van der Waals radii.[51] Such a comparison was usually uninformative but sometimes this method gave acceptable results.

Intramolecular covalent radii, proposed by Bartell[52] as a measure of steric effects, have also not been widely applied.

Tolman's method of cone angles has proved to be more popular. The plane angle subtended at the apex of a cone tangential to the whole ligand was proposed as a measure of the steric effect of the ligand in transition metal complexes.[14,53] However the precision of the measurements conducted at the scale of the model was not high and the method has not enabled linear relationships to be obtained between the stability of complexes and the steric effect of ligands. It succeeded only in explaining qualitatively the effect of some ligands and in placing them in a series according to the order of increasing steric effect.

$$(CH_3)P < (C_2H_5)_3P < (C_3H_7)_3P < (C_6H_5)_3P < (\text{iso-}C_3H_7)_3P < < (\text{sec-}C_4H_9)_3P < (\text{t-}C_4H_9)_3P < [2,4,6\text{-}(CH_3)_3C_6H_2]_3P.$$

Tolman's cone angle model has been further developed in a series of studies[54–59] which has appeared recently. It is proposed to use the idea of 'coordination space' for the quantitative description of steric effects in the coordination sphere of a metal atom in complexes. This space is set by the Tolman cone angles of the ligand at a fixed (ionic) radius of the metal and the van der Waals radii of the atoms in the ligand. The concept of a packing function characterising the density of packing of ligands was also introduced.

This approach has enabled the molecular structure of several complexes to be explained. Rules have emerged for packing saturation, the geometrical parameters of complexes have been calculated and agree with data of X-ray structural analysis. Based on an analysis of the packing function the course of certain reactions has been successfully explained, such as the disproportionation and ligand insertion reactions.

The Tolman cone angle concept has also been extended to cluster systems.[60]

Tolman cone angles have been recalculated by Imyanutov[61,62] using a simple mathematical device and new values have been obtained. The more recent individual values for the extent of screening Λ_c of a central atom, characterising the part of the sphere occupied by the cone angle, proved to be applicable in coordination and organic chemistry and served (for a while) as a basis for a new scale of Λ_c constants.[63] However this scale does not always correlate well with the experimental E_S scale; the authors confined themselves only to a graphical correlation.

Tolman's approach served as a basis for the creation of the solid angle method. Initially[64,65] the steric hindrance generated by a substituent at a carbon atom was assessed on a semiquantitative basis. The solid angles cast by the atoms of a substituent on the sphere of the central atom was used as a measure of the hindrance. The method was used at the quantitative level more recently[66–69] by applying a computer for the calculations. A good correlation was obtained between the stability of a complex and the total solid angles of the ligand. The method also proved to be suitable for the assessment of the screening of individual atomic fragments (such as an individual chemical bond or individual atoms) of the remaining portion of the molecule.[66–69]

The concept of screening a reaction centre by a substituent has been used in many studies. It is thus considered obvious that any substituent screens a reaction centre but the extent of screening is determined by the area cast by the substituent. Approaches to the actual assessment of this area vary.

It was proposed[51,70] to assess the area of screening by the solid angle describing the substituent. The measure of the steric effect is the sum of the ratios $S_L/4\pi R^2$ where S_L is the area screened and R is the distance from each atom to the reaction centre. The equality

of this sum to unity indicates coordination saturation has been reached.

This approach is close in essence to the frontal steric effect model proposed by us two years previously[71] which is based on kinetic collision theory. In it the procedure for calculating the screened area is simpler. A scale of steric constants R_S is proposed which are linked linearly with the available experimental scales. More detail on this method and the different aspects of its application will be considered below.

An ideology almost identical to the ideology of the frontal steric effect served as a basis for the generation in 1989 of a scale of Ω_S constants.[72] This scale differs from the R_S scale only in the use of more complicated methods of calculation. It also correlates well with the E_S constants, but in contrast to the R_S scale gives distinct relationships for primary, secondary and tertiary alkyls. The Ω_S constants also correlate with certain experimental data.

Another direction for assessing steric effects is in essence close to the use of topological indices. Here the number of α-, β-, γ-, etc. carbon atoms is used to characterise the shape of the molecule.[73,74] This is less convenient since it requires several numbers for the description of a substituent[73] and it does not have such a clear geometric and physical sense as is possessed by scales based on the screening of a reaction centre by a substituent. For the same reason it is inconvenient to use parameters characterising the geometric shape of the molecule, such as the length and width in various directions proposed independently by Balaban[75] and by Verloop (see Ref. 2 and literature therein).

The number of carbon atoms in the sixth position in relation to the reaction centre in reactions of addition to an unsaturated system known as the 'six-number' of Newman[76] is used fairly widely (see Ref. 2 and literature therein) and is linked with the E'_S constants of Dubois.[77]

Steric effects are also characterised by parameters reflecting the size and shape of a molecule such as molecular weight or van der Waals volume. However these methods have not had particular success.

Structural methods, as a rule, describe fairly precisely the steric effect of a substituent. Their drawbacks are considered to be that they calculate for only one conformation, they have a static character and they ignore the second reactant. For the usual investigational purposes this is frequently not necessary. Special problems linked with a dynamic change in conformation may occasionally be resolved within the framework of these methods but requires other approaches. The solution of some of these problems will be considered below using the frontal steric effect model.

5. Experimental methods

Experimental methods of determining the steric effect developed completely by another independent route have been applied widely. These methods, proposed by Ingold and Taft,[3,13,78] are based on the principle of the linearity of free energies (LFE). This has been carried out for an enormous number of chemical processes and among them it is possible to pick out those in which the influence of one of the effects predominates. Taft[13,22] proposed that in aliphatic compounds there are powerful steric effects of substituents which must be separated from the electronic. He proposed assessing steric effects using the hydrolysis of carboxylic acid esters.[79] The inductive constants of aliphatic substituents were assessed at the same time.

$$\sigma^* = \frac{1}{2.48}[\lg (k/k_0)_B - \lg (k/k_0)_A],$$

$$E_S = \lg (k/k_0)_A,$$

where σ^* is the constant for a substituent depending exclusively on the overall polar effect of the substituent (corresponding rate constant k), k_0 is the rate constant for a standard compound with substituent CH_3, E_S is the constant of the substituent reflecting its steric effect, the indices A and B refer to the reaction of alkaline and acidic hydrolysis of carboxylic acid esters identical in all other respects. The factor 2.48 is a constant introduced with the aim of making the polar scale of σ^* within the limits of the same scale as applied by Hammett.

The E_S constants have been and still are widely applied in contemporary chemistry in reactions of nucleophilic substitution and fission at a saturated carbon atom (their use is possible both in reaction series analogues to the standard and in very different series) and in unsaturated systems, in catalysis and polymerisation processes, in the chemistry of free radicals, in processes of association in solution and in the gas phase and in spectroscopy. Periodically refined values of constants appear for certain substituents.[80] Correlations of E_S have been obtained with steric energy (ΔSE) calculated by the method of molecular mechanics[27] which, in the authors' opinion,[27] neatly proves the steric nature of the E_S constants.

The Taft E_S scale has been modified by Hancock[81] using a value of $h = 0.306$, calculated by MO methods, for the reaction series of ester hydrolysis, with the aim of calculating the contribution of the hyperconjugation of C–H bonds. The corrected values of the steric constants E_S^c, obtained in this way are linked with the Taft E_S values by the following expression:

$$E_S^c = E_S + 0.306(n-3),$$

where n is the number of hydrogen atoms on the first carbon atom of the substituent being considered and 3 is the same figure for the standard substituent CH_3.

The values of E_S^c lead in several cases to a marked improvement in correlations[82–84] compared with results obtained using E_S constants.

Pal'm has proposed taking into consideration the hyperconjugation of C–C bonds as well.[85]

$$E_S^0 = E_S - 0.33(3-n_H) + 0.13n_C.$$

Several scales similar to E_S have also been introduced. One of them (E_N) is based on the principle of isostericity for substituents at a nitrogen atom,[86] a second on the approach of DeTar[87] and a third on the E_S(Si) constants of Cartiedge.[88] Particular mention must be made of the E'_S scale (MacPhee, Panaye and Dubois[89–91]) determined from the acid esterification of carboxylic acids.

$$RCOOH + CH_3OH \xrightarrow{H^+,\ 40^\circ C} RCOOCH_3.$$

The E'_S scale is similar to the E_S scale for all substituents, except for the very bulky.

An E_S^* scale of constants, similar to the E'_S scale, has been introduced for reactions the transition state of which is analogous to that in hydroboration reactions.[92]

The scale of v_X constants, proposed by Charton,[93] is based on several other principles. The Charton scale may be described as semiempirical since v_x constants may be calculated fairly simply from

the following equation for monoatomic and for highly symmetrical substituents of the A_3B type.

$$v_X = r_{v_X} - r_{v_H} = r_{v_X} - 1.20,$$

where r_{v_X} and r_{v_H} are the van der Waals radii of the groups X and atom H. In addition an equation has been obtained within the framework of the standard reaction series of hydrolysis of carboxylic acid esters

$$\lg k_X = \varphi v_X + h,$$

permitting an empirical route for determining v_X constants for complex unsymmetrical substituents. Charton gave values for 61 v_X constants and also carried out an analysis of the correlation ratios between the experimental data and v_X, E_S, E_S^c and E_S^0 constants for data on 22 reactions of esterification and acidic hydrolysis. It turned out that v_X constants gave the best correlation.

The insignificance of electronic effects of substituents was shown[94] in a continuation of the study of alkaline hydrolysis of esters. Correlation with v_X constants again gave excellent results.

In reactions occurring by an S_N2 mechanism,[95] the use of v_X constants did not lead to a very good result since in this case the type of reaction centre, and consequently the structure of the activated complex, is changed. Introduction of a v' scale of constants for substituents at a sp^2-hybridised reaction centre enabled successful application of correlation analysis to these systems. It transpired that the sizes of the steric effects in S_N2 reactions are greater than in esterification reactions.

Finally v_X constants have been used in the study of the kinetics of $E1$ and $E2$ processes, of internal rotational barriers, the hydrolysis of amides and the racemisation of chiral biphenyls (see Ref. 73 and literature therein).

The v_X constants have been shown to be additive.[96] In addition they proved to be applicable to the study of reactions with substituents present on atoms of oxygen, nitrogen, sulphur and phosphorus (see Ref. 97 and literature therein).

The investigation of the effect of branching in a substituent on the value of v_X constants is a logical completion of the studies on v_X constants.[73] The steric v_X parameters of alkyl, alkoxyl, thioalkyl and dialkylamino groups and also values of v' for alkyl groups have been described using Eqn. (2) with a good correlation.

$$v_X(v') = an_\alpha + bn_\beta + cn_\gamma + dn_\delta + i. \qquad (2)$$

Here the parameters n_α, n_β, n_γ and n_δ reflect the number of α-, β-, γ- and δ-carbon atoms. The correlation Eqn. (2) enables assessment of values of the v_X constants of a very large number of groups. In this scheme the E_S^c constants of Hancock and the E_S^0 constants of Pal'm are simpler steric parameters correlating only with the value of n_α, the coefficients a in which are different from those for v_X.

In spite of the wide and fairly successful application of the empirical scales they are constantly subjected to critical analysis and are occasionally disputed. The main attention of critics is paid to the E_S scale of Taft and the scales derived from it.

In particular it has been shown[98] that the observed rate constant for the standard ester hydrolysis reaction is an effective (but not a simple) constant. The dissecting out of the rate constant for the primary bimolecular stage enabled E_S^b constants to be determined based on it, the values of which are different from the values of the Taft E_S constants. A dependence was also detected for the E_S constants on σ* constants having the form of several straight lines with the same slope for each individual number of α-hydrogen atoms.[99] This led investigators to the concept of the non-electronic nature of σ* constants, although σ* constants work successfully in many cases.[100] On analysis of the experimental data on the hydrolysis of carboxylic acid amides it was proposed[101] that the Taft σ* constants for alkyl groups do not reflect the electronic effect of alkyl groups. More recently Charton[102] discovered that the Taft constants correlate well with the degree of branching of the alkyl group at the α and β positions. From this it was concluded that the σ* constants reflect principally the steric effect of substituents.

Other authors have arrived at the same conclusion. When investigating σ*, σ_I and E_S constants DeTar[103] drew the following notable conclusions. The σ* constants of alkyl groups are inaccurate values which comprise a residual steric effect and experimental error. The use of any other nonsteric values for alkyl groups is also erroneous. References to the nonsteric effects of alkyl groups are based on incorrect data. The alternative scales, such as E_S^c and v_X have no special merit and should be rejected.

One of the main errors of Taft when determining the E_S scale has been considered[90] to be the *a priori* assumption that the various reaction series (acidic and alkaline hydrolysis) used for calculations have identical sensitivities to steric effects.

The lack of consideration of the conformational state of a substituent is described[2] as an appreciable drawback of the E_S scale although the importance of the influence of conformation on the steric effect of a substituent has been recognised by many authors.[73,104–106]

Much attention has been paid to the problem of the additivity of E_S constants. Taft himself recorded[13] that E_S constants were nonadditive but show a telescoping effect (the change of a constant in relation to the position of the substituent at the reaction centre). However certain authors[107,108] use ΣE_S in correlation analysis.

There is another possible approach to the consideration of the additivity of the constants. The following equation has been proposed.[107]

$$E_S(C_{XYZ}) = aE_S(X) + bE_S(Y) + cE_S(Z),$$

which enables various conformations of substituents to be taken into account and the E_S constants of any complex group to be calculated.

Much work has been devoted to a study of the physical significance of the E_S scale. Numerous attempts have been made to find the interconnection between the E_S constants and the various geometric and structural parameters of a molecule. For example, a linear relationship was discovered between E_S constants and the φ_{R_1} scale,[109] reflecting the contribution of the spatial stress built up by α, β and γ C–H bonds. Attempts to link the E_S values directly with the number of α, β and γ carbon atoms were not particularly successful[73] since a correlation was detected only with the number of α carbon atoms. Inherent geometric parameters of a substituent such as its length or width in two orthogonal directions proved to be completely unconnected with the E_S scale.[75]

Taking the results of all these investigations into account and also the recent work of Kramer[110,111] on the nature and additivity of E_S constants, it may be regarded as established that the E_S scale has on the whole a steric nature, its successful use in correlations is well founded in principle but it does not have a clear physical and geometric sense. It is not known which of the aspects or what proportions of steric effects it reflects. Certain actual values of the E_S constants need refinement, such as the E_S constants for the

t-BuMe$_2$C and t-Bu(t-BuCH$_2$)MeC substituents.[90] Recent achievements in solvation theory enable consideration of the appreciable contribution of solvation effects to the size of E_S constants. Thus the conclusion of Motoc and Balaban[75] on the need to create a new scale of spatial constants with a clearer physical, geometric or topological meaning is entirely well founded.

The E_S^c and E_S^0 scales, being derived from the E_S scale, have absorbed all of its drawbacks and virtues. In addition they proved to have their own specific defects. It has been made clear[90] that the size of the hyperconjugation coefficient h on both scales depends appreciably on the choice of reaction series and solvent which significantly reduces their universal nature. Pal'm[3] was guided by these same considerations when justifyng the need for the correction of the E_S^c constants. However it has been considered[90] that the E_S^0 scale is not completely free from the indicated drawbacks.

Even in the early studies of Charton doubt was expressed on the expediency of estimating the hyperconjugation components in the E_S^c and E_S^0 scales.[112,113] More recently these doubts became stronger[93] and then grew in confidence.[114] It was shown that all the results previously explainable by hyperconjugation may be interpreted by drawing on electronic, steric and polarisation effects alone and there is no need to use the E_S^c and E_S^0 scales. Istomin and Baranskii arrived at the same conclusion almost simultaneously.[115]

The ν_X scale being semiempirical has nonetheless acquired the drawbacks of the experimental scales, namely a dependence on the conditions and precision of the experiment. In its calculated portion it is also not completely reliable for large and unsymmetrical substituents.[90] Charton himself acknowledged that the values of ν_X for such groups may have not one but at least two values, a minimum and a maximum.[112] It turned out that neither correlates with the value of log k determined experimentally or with the experimental ν_X constants.

In conclusion it must be noted that in spite of a proposal to give up the use of experimental scales,[116] they still remain a common and useful instrument in correlation analysis and are a good basis for creating, testing and developing a new generation of steric constants.

III. Steric effects in the chemistry of hetero-organic compounds

Historically organic chemistry was the first area where the theory of steric effects was applied. There are examples demonstrating the influence of steric effects on the course of the nucleophilic substitution reaction.[117,118] The majority of the existing methods for the quantitative estimation of steric effects are based on the data of organic chemistry. The literature data on this theme are contained in numerous reviews.[3,10–12] Some of these studies have been referred to by us above so we will not consider them in more detail.

There is also the question of estimating steric effects in hetero-organic chemistry. For a long time it was considered[19,119] that steric effects were insignificant in the chemistry of phosphorus and the majority of other elements in view of the large size of the atoms of these elements. Information on steric effects was vague, sketchy and only at the qualitative level.[120,121]

However the experimental results accumulated up to the present indicate that the role of steric effects in the reactivity of HOC is far more substantial than was supposed previously. It is sufficient to note the opinion which is now established in the literature[17,94] that alkyl substituents in general do not exert any effect other than steric.

Numerous studies have appeared (see for example Refs. 15, 16, 53) in which there is a description of a steric effect at the qualitative level in the chemistry of boron, silicon, phosphorus and other elements.

It is recorded[4] that steric effects play a more varied role in HOC chemistry than in carbon chemistry. Spatial effects have an influence in three areas, viz. reactivity, complex-forming ability and conjugation. The majority of the existing steric scales of substituents are applicable only to the first area. Consequently it is probable that the literature data concerning the chemistry of various elements describe mainly the effect of substituents on the acid–base properties of HOC and on their reactivity in reactions of various types. On varying the nature of the reaction centre the problem inevitably arises of the possibility of applying the carbon scales of steric constants. Opinions are divided concerning this. On the one hand it is considered[3] that the carbon experimental scales of the E_S type are inapplicable for describing steric effects in HOC chemistry and the introduction of special scales is required. On the other hand Charton (see Ref. 97 and literature therein), when obtaining scales of ν_X constants for nitrogen, oxygen, sulphur and phosphorus, discovered their linear interrelation and concluded that special calculations were unnecessary and that the carbon steric ν_X constants for substituents may be used to describe the reactivity of any HOC (see Ref. 73 and literature therein). The E_S constants have proved to be applicable in phosphorus chemistry.[20]

Steric Λ_C constants have been calculated for more than 20 atoms[122] and an empirical link has been discovered between the scales obtained, which is characterised by discrete parameters unconnected with dimensions or with any characteristics of reaction centres.

On the whole the situation remains unclear and the same variety of scales of steric constants are applied for the estimation of steric effects in HOC chemistry. The main bulk of data relates to the description of steric effects in the chemistry of nitrogen, sulphur, phosphorus and arsenic.

1. Steric effects of substituents at a nitrogen atom

When studying steric effects in nitrogen chemistry two predominant directions of investigation stand out, viz. effects on the basicity of amines and effects on the reactivity of amines, amides and related compounds in various reactions.

The study of the basicity of amines was begun in the forties with the work of Brown and co-workers. The results of these studies have been published in a review,[1] consequently we will not analyse these results, we mention only that they led mainly to the determination of basicity constants and the discovery of the anomalous order of the change in basicity of the methylamines.

$$NH_3 < CH_3NH_2 < (CH_3)_2NH > (CH_3)_3N.$$

It has been recorded (see Ref. 9 and literature therein) that the changes in basicity of various classes of amines in all solvents are governed by the same rules and are linked with structural changes and special features of the molecule. This is caused mainly by the electronic effects of substituents and the effects of the medium, actual steric effects only apply to branched residues.

However there are examples of successful correlations of pK_B with σ^* and E_S constants (see Ref. 9 and literature therein). A scale of steric constants for alkyl substituents has even been developed[123] and differs from the Taft scale.

According to a contemporary concept[124] the mechanism of the steric influence on the basicity of amines is included in the steric hindrance of solvation. However for a complete solution of the problem of steric influence (including anomalous changes in basicity) it is necessary to think of the change in the configuration of the atomic orbitals of nitrogen, and in the state of the unshared electron pair responsible for basicity, being connected with the change in nature and number of alkyl groups and the symmetry of the alkylamine.[9]

The influence of the structure of amines on their reactivity was even recorded by Menshutkin[125] but attempts to assess steric effects quantitatively were undertaken relatively recently. Carbon scales were also used and new scales of steric constants have been introduced.

However the latter are, as a rule, only modifications or extensions of scales known already. Examples are the constants of Charton $\nu_X(NR^1R^2)$ which correlate well with various experimental data.[126]

A new standard reaction series has been proposed[127] for determining the steric influence in iodo-lactonisation of (*R*)-*N*-allylaminoacetic acids but no new scale was built up based on this series.

The best known is the scale of E_N constants,[86] which were obtained using the isostericity principle and are the constants of the corresponding carbon analogue. The E_N constants are applied widely to describe the various reactions of amines with alkyl halides,[128–132] such as the Menshutkin reaction,[133,134] and also nucleophilic addition reactions[135–140] and in the study of catalytic activity.[141]

At the same time the equation generally used

$$\lg k = \lg k_0 + \rho\Sigma\sigma^* + \delta\Sigma E_N,$$

does not enable the reactivity of all amines to be described. The deviations observed are taken[142] to be explained by two reasons, viz. by the imperfections of the principle of isostericity and by the presence of specific non-steric interactions of certain substituents with the reaction centre (by the formation of an intramolecular hydrogen bond for example).

It has been proposed[142] that a third and most important reason may be an incorrect allowance for electronic effects. In view of the combined opinion[87,103] on equating the inductive effects of all alkyl groups to that of a methyl group it was proposed[142] to take only the steric effect into consideration. In this case

$$\lg k = \lg k_0 + \delta E_S' + \rho_H^* n_H \sigma_H^*,$$

where n_H is the number of hydrogen atoms on the nitrogen, $\sigma_H^* = 0.49$ the inductive constant for the H atom, ρ_H^* is a coefficient showing the sensitivity of the reaction centre to substitution of a hydrogen by an alkyl group, E_S' is the modified MacPhee scale,[90] differing from the E_S scale by the larger range of substituents and better self-consistency.

The classical E_S constants have been used for calculations of steric effects in some correlations[143–146] and the E_S^0 constants in a further study.[147]

2. Steric effects in the chemistry of organosilicon compounds

The influence of steric effects of substituents on the reactivity of the most varied organosilicon compounds at the qualitative level has been discussed very widely in the literature. One of the first investigators who attempted a quantitative description of steric effects was Sommer[148] when recording the combined influence of steric and electronic effects in solvolysis and chlorination reactions in compounds containing the R_3Si fragment. The E_S constants for the alkyl substituents on the silicon atom were calculated on the basis of literature and the authors' own kinetic data. Sizes of the deviation from the dependence of log k on σ^* for various reactions taken from the E_S constants were not mutually consistent and had no particular practical importance.

The conclusion has been drawn (see Ref. 149 and literature therein) on the basis of a comprehensive analysis of literature data that the manifestation of steric effects of substituents was important in many reactions of compounds of the R_3SiX and even R_2SiX_2 types (R is an organic substituent and X a functional group). In all cases steric effects were suitable for describing compounds with three alkyl substituents on silicon. Occasionally such an approach is also applied for substituents having iso-structures. In certain reaction series the reaction kinetics were interpreted successfully only using the steric constants E_S^c and E_S^0, for example in the hydrolysis of R_3SiH, the methanolysis of siloxanes, the ozonolysis of silanes and in the hydrosilylation reactions of 1-hexyne.

It has been emphasised[149] that the absence of a direct correlation of reactivity with steric constants does not imply that the steric effect makes an unimportant contribution since in these cases, as a rule, substituents are used which differ little in their steric characteristics.

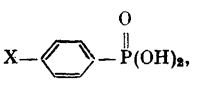
The use of scales based on the degree of branching of substituents[150] and the E_S(Si) steric scale of Cartiedge[88] must also be noted. A series of acid hydrolyses was used as the model.

$$R_3SiOR + H_2O \xrightarrow[-ROH]{EtOH,\ HCl,\ 25^\circ C} R_3SiOH.$$

The E_S(Si) constants obtained correlated best of all with the Charton ν_X constants and possessed the property of additivity. However these scales are not used widely and in several cases (see Ref. 151 for example) correlation with E_S constants was significantly better than with E_S(Si).

3. Steric effects in the chemistry of organophosphorus compounds

Study of the quantitative interrelation between the structure of organophosphorus compounds (OPC) and their reactivity began around 1953. The first studies[152–154] showed that the Hammett equation was applicable to the ionisation of phosphonic acids of the form



where X is the substituent being varied. The Hammett constants and the Taft σ^* constants were used to characterise the influence of the substituent X. With the purpose of building up a scale of similar constants for radicals joined to phosphorus (σ^P), Kabachnik[119] subjected the literature data on the pK_a values of the phosphorus acids $RPO(OH)_2$, $R^1R^2P(S)OH$, $R^1R^2PO_2H$ to quantitative treatment using the Hammett equation in the form

$$pK_a = pK_a' - \rho\Sigma\sigma^P.$$

It must be noted that in all cases only the electronic effects of substituents were taken into account. It was proposed[19,119] that steric effects were insignificant in view of the large size of the phosphorus (or other element) atom.

This opinion has been held for a fairly long time.[120,121] However with the subsequent accumulation of new experimental data the σ^P scale has been subjected to careful analysis and its relation to steric effects has been reconsidered.

It has been shown[115] that the σ^P constants of alkyl groups and electronegative substituents having no α,β multiple bonds or unshared electron pairs on the α atom are combined values and contain inductive and steric components. The inductive and steric components are described adequately by the scales accepted in correlation analysis for the corresponding types of interactions using the σ^* and E_S scales, i.e. the phosphorus atom does not require any special scales.

Consideration of the standard reaction series used as a basis of the σ^P scale also showed[156] that the experimental values are described adequately by a single correlation equation using the σ^* and E_S scales. It was noted that the principal difficulty when considering such broad sets of data obtained by different authors was the lack of self-consistency.[157]

In a review[20] of the results of a correlation analysis of organic derivatives of pentavalent four-coordinate phosphorus it was shown that the σ^P constants widely used in the chemistry of OPC are complex and include contributions from the inductive, steric and resonance interactions of substituents with the reaction centre. The σ^P scale is applicable to those cases when the proportions of the various contributions to the overall effect of a substituent and the structure of the reaction centre in the series of compounds being studied are the same as or close to the values on which these constants are based in the standard reaction series. In other cases a different approach must be sought.

The $\nu_X(P)$ scale of Charton obtained for substituents at a phosphorus atom may serve as one of such approaches to the assessment of spatial effects.[97] The successful use of the carbon ν_X scale in OPC chemistry is also possible. There are also data on the successful application of E_S constants in correlations with pK_b values of alkyldiphenylphosphines.[158]

Relying on data of recent years[101,159] regarding the electrical neutrality of alkyl groups an approach has been suggested[17,21] involving the separation of the σ^P constants into inductive (σ_i^P), resonance (σ_r^Φ) and steric (σ_s^Φ) components. The σ_s^Φ scale was then used successfully to correlate the chemical and biological activity of OPC[160–164] and evidently the approach must be acknowledged to be totally fruitful.

At the same time when separating the σ^P constant into its primary components the authors[17] used certain assumptions which from our point of view were not completely argued through. For example the E_s^0 constants of alkoxyl groups were estimated on the basis of isostericity (from the E_s^0 constants of the isosteric alkyls) and these values were then included in the overall correlation with alkyl substituents virtually giving the isosteric constant the significance of the true constants. In a way this may be one of the reasons for the low quality of the correlation (r = 0.92) in the overall reaction series including alkyl and alkoxyl residues.[17]

Various approaches and combinations of scales are used when describing the influence of steric effects on the reactivity of OPC. The carbon scales are frequently used which is quite understandable because of the discovered similarity of the influence of substituents on the reactivity of compounds of phosphorus and carbon[165] and of phosphorus and silicon.[166]

The stability of complexes of $(RO)_3P$ with R_FI, as has been shown,[167] correlates poorly with the value of σ^P, particularly for branched substituents, the reason for which[167] is the lack of consideration of steric effects. A satisfactory correlation was achieved with the joint use of E_s and $\Sigma(\sigma_i^P + \sigma_r^P)$ constants. At the same time the acid–base properties of R_3PO with alkyl and alkoxyl substituents correlate quite successfully with the σ^P constants.[168] Consequently the σ^P scale works well in some cases[169,170] but must be replaced by different scales in others.[171]

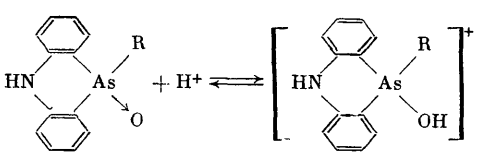
Occasionally it has been proposed in discussion to discard the apparatus of correlation in general and to replace it by methods of linear algebra.[172] However it is doubtful whether this suggestion meets with wide response.

In general the variety of quantitative approaches and the unpredictability of the importance of one or other parameter in the various correlations is extremely inconvenient in practice. A search is needed for a universal scale enabling description as far as possible of all cases of steric interactions in OPC chemistry.

As will be shown below the use of the calculated R_s scale, proposed on the basis of a model of the frontal steric effect,[71] gives good results when describing the very varied reaction series involving OPC.

4. Steric effects in the chemistry of organoarsenic compounds

Steric effects have not been considered in the few quantitative studies of the properties (mainly acid–base) or organoarsenic compounds up to the present time. The available data on the acidity of certain alkyl- and arylphosphonic acids and on arsinic acids in water[173] and in DMF[174] and data on the basicity of tertiary arsine oxides[175] correlated either with the σ^* constants or with σ^P constants. Correlation was better with the Taft inductive constants (σ^*). Analysis of the basicity of 10-alkyl-5,10-dihydrophenarsazines showed a very unusual dependence of pK_b on the σ^* constants.[176]



The values of pK_b for the alkyl-containing compounds in the series R = CH_3, C_2H_5, iso-C_3H_7, t-C_4H_9, $CH_2{=}CH{-}CH_2$, Ph, Ph–C≡C, OH lie on a separate straight line with a positive ρ coefficient although when the inductive influence predominates the value of ρ must be negative. A link was also detected between pK_b and parameters characterising the branching of a substituent. It was concluded[176] that another effect, which requires clarification, exerts an influence.

In our opinion, allowing for all the above-mentioned it may be deduced that the effect in question has a steric nature, although confirmation of this must finally be obtained experimentally. Regrettably there are still very few investigations of that type.

A Japanese study[158] is devoted to the examination of the nucleophilicity of a wide range of alkyldiphenylphosphines and -arsines (reaction with methyl iodide for example). A linear correlation was established between the nucleophility of phosphines and arsines expressed by the equation

$$\lg k_{As} = 0.49 \lg k_P - 3.14.$$

Phosphines are three orders of magnitude more nucleophilic than arsines. The nucleophilicity of both types of compound is described by a two-parameter Taft equation using σ^* and E_S constants.

Similar compounds of arsenic were investigated previously by Soviet authors.[177,178] It was shown that the nucleophilicity of arsines correlates with σ^* constants but does not correlate with σ^P, which the authors link with the possible manifestation of steric effects.

5. Steric effects in the chemistry of organosulphur compounds

The influence of steric effects on the reactivity of sulphur compounds was considered by Charton[97] who showed that the AlkS group possessed a constant electronic effect. The ν_x(SR) parameter for SR substituents was determined using the hydrolysis of alkylthioacetates in 40% aqueous dioxan as the reaction series. The ν_X parameters obtained were used in the analysis of 24 sets of acidic and alkaline hydrolysis. This enabled the conclusion that the effect of alkyl groups joined to sulphur was fairly large and had a predominantly steric nature.

The constants obtained have been used by other authors, for example in the investigation of the catalytic activity of thiols.[179]

The E_S scale is also widely applied in addition to the ν_X parameters. Processes successfully described with it are the oxidation of alkyl aryl sulphides,[180] the electron donating properties of sulphides,[181] the chemoselectivity of alkanesulphonates[182] and the catalytic sulphonylation of phenol with a sterically hindered sulphonyl chloride.[183]

$$RC_6H_4SO_2Cl + HOC_6H_5 \xrightarrow[-HCl]{(C_2H_5)_3N,\ C_6H_6,\ 40^\circ C} RC_6H_4SO_2OC_6H_5,$$

$$R = 2\text{-}CH_3,\ 2\text{-}C_2H_5,\ 4\text{-t-}C_4H_9,\ 2,4,6\text{-}(C_2H_5)_3,\ 2,4,6\text{-(iso-}C_3H_7)_3.$$

In the latter case, in fact, the E_S^0 constants were used.

Regrettably the limited amount of experimental data enabled a conclusion to be drawn only on the appreciable influence of steric effects in the chemistry of organic sulphur compounds but did not enable a comparative analysis to be carried out with compounds of other elements.

6. Steric effects in the chemistry of organometallic compounds

Literally a single study is devoted to steric effects in the chemistry of organometallic compounds (the chemistry of complex compounds is not considered here). Pal'm[3] has drawn attention to the reaction of alkylmagnesium bromide with pinacolin.[184]

$$RMgBr + CH_3\overset{\overset{O}{\|}}{C}C_4H_9\text{-t} \xrightarrow{\text{ether}} \begin{matrix} & CH_3 & & OMgBr \\ & \diagdown & \diagup & \\ & & C & \\ & \diagup & \diagdown & \\ R & & & C_4H_9\text{-t} \end{matrix},$$

which, in his opinion, might be used for obtaining a new scale of 'pure' steric constants. However this was not sustained.[184,185] Of the three parallel processes, viz. reduction, addition and enolisation, taking place in the reaction of pinacolin with RMgBr only the last two are linked with steric effects. The addition reaction is linked predominantly only with the steric effects of alkyl substituents and correlates with the E_S^0 constants. The rate of the uncatalysed reaction of $R_3SnOCOC_2H_5$ with phenyl glycidyl ether[186] and the rate of electroreduction of titanium and zirconium bis-(cyclopentadienyl) chlorides[187] are linked linearly with the same constants.

IV. A model of the frontal steric effect and its application to the analysis of the reactivity of organic and hetero-organic compounds

The numerous approaches to the assessment of the steric effect to describe the reactivity of organic and hetero-organic compounds indicates the need to search for a universal scale of steric constants ready for use in any region of organic and hetero-organic chemistry. Such a scale must probably be based on calculated structural methods such as the experimental scales linked to actual conditions and to the precision of an experiment. It must also consider the conformational state of a substituent. It is necessary, when changing the conformation of a substituent, to obtain refined values of the steric constants fairly simply. Finally, the universal nature of this scale must be subject to broad experimental verification. It is necessary that such a scale should describe, as far as possible, the maximum amount of experimental data correlated by other scales, while retaining a high degree of correlation.

We have attempted to create such a scale and verify it in a large number of different reaction series, including hetero-organic compounds.

1. A model of frontal steric effects and the R_S scale

A model of frontal steric effects and its mathematics have been presented in a fairly detailed manner[71,188] consequently a short description only will be given here. The basis of the model is the concept of the frontal character of the steric effect, i.e. simple mechanical shielding of the reaction centre by a substituent (Fig. 1). This model enables the steric effect of any substituent at any reaction centre to be described, proceeding only from its structure and conformation. Parameters describing the structure of a molecule, i.e. bond lengths and valence angles, are used as the initial data.

It is easy to show, within the framework of kinetic collision theory and a simple mathematical procedure, that the steric effect of a substituent is proportional to the area which it occupies on the sphere separating it from a reaction centre. The final expression for the reaction rate constant of a compound with a particular substituent has the following form:

$$k_R = \left(1 - \sum_{i=1}^{n} r_i^2/4R_i^2\right) Z \exp(-E/RT),$$

where r_i is the radius of each actual atom in a multiatomic substituent, R_i is the distance of this atom from the reaction centre, Z is the frequency of twin collisions and E the activation energy.

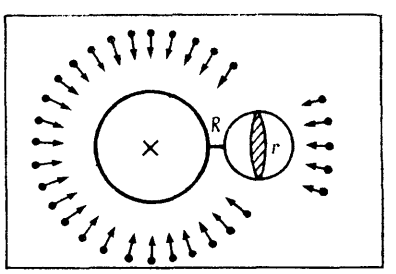


Figure 1. Attack at a substituted reaction centre.

The correctness of the model proposed was verified[71] by comparing values of the steric effect for substituents (first for alkyl and then others), calculated theoretically on its basis, with the existing steric scales E_S, E_S^0 and ν_X, which are based on hundreds of reaction series with steric control. An excellent correlation ($r \approx 0.99$) was obtained in every case covering the whole possible range of variation of steric effects (from +1.24 to −4.0 on the E_S scale), which indicates that proposed model describes steric effects in an adequately correct manner. In order to solve problems insoluble or soluble with difficulty within the framework of the existing experimental scales, a purely calculated steric R_S scale has been proposed which, for the reasons detailed,[71] has been introduced as

$$R_S = 30 \lg \left(1 - \sum_{i=1}^{n} r_i^2/4R_i^2\right).$$

This scale correlates well with the empirical scales and describes adequately the steric effect of the most varied substituents. For example the majority of halogen, hydroxy, alkylthio and alkoxy substituents are described satisfactorily by the relationship of R_S and E_S which applies to alkyl substituents.[71]

$$R_S = (-1.702 \pm 0.032) + (0.730 \pm 0.022) E_S, \quad n=35, \quad r=0.9854, \quad S_0=0.141. \qquad (3)$$

At the same time it must be emphasised that a strict physical interpretation cannot be conferred on such a limitingly simplified steric model.[71,188] In spite of the fact that the better quality of correlation as in (3) would justify assumptions to be made, the steric effects of a substituent undoubtedly cannot lead only to screening of a reaction centre, ignoring completely the energy contributions of other types of steric interactions. The screening effect must be considered as only one component of the steric effect which for some reason (possibly simply formal) is linked linearly with the total effect.

The proposed model is therefore more formal rather than physical. At the same time it represents a fairly successful means for the correct calculation of the steric effects of various substituents and may be extremely useful in solving the most varied problems. This will be illustrated below with some examples.

2. The principle of isostericity

The standard reaction series forming the basis of the empirical scales impose some serious limitations on the possibility of determining the steric constants of substituents. In the E_S scale, and the E_S^c and E_S^0 scales derived from it, the standard reaction series, viz. the hydrolysis of esters, does not permit determination of the steric constants of hetero-atomic substituents such as OR, SR, NR_2, etc.

In practice the isostericity principle is used in these cases, which means that the steric effect of any heteroatomic substituent is equated to the effect of the corresponding (isosteric) alkyl substituent.[3]

Since the model considered above enables direct calculation of the steric effect of any hetero-atomic substituent there is the possibility of verifying to what extent the indicated principle remains within this framework and what are the limits of its applicability. This was carried out[71] using as example a set of alkoxyl and thioalkyl substituents by comparing the R_S constants calculated for them with those for the isosteric hydrocarbon analogues.

It turned out that in each series excellent linear relationships were satisfied.

$$R_S(\mathrm{OR}) = (0.812 \pm 0.115) + (1.256 \pm 0.053) R_S(\mathrm{CH_2R}), \quad n=8, \quad r=0.9954, \quad S_0=0.058;$$

$$R_S(\mathrm{SR}) = (-0.459 \pm 0.039) + (0.976 \pm 0.018) R_S(\mathrm{CH_2R}), \quad n=8, \quad r=0.9991, \quad S_0=0.019.$$

It follows from the correlation equations obtained that the steric constants for OR and SR substituents are linearly related to the constants of the CH_2R group but are not equal to them. Hence it is evident that the isostericity principle must work well in sets of substituents of the same type (for example, only OR or only SR) but will not be effective in mixed sets.

Within the framework of the present model the application of the isostericity principle has a mathematical foundation but at the same time its limitations are clearly evident. However since it is possible to calculate directly the R_S constants for any heteroatomic substituent, the principle of isostericity in general loses its value in this scale.

3. The steric effect of substituents at non-carbon atoms

As was indicated above more data have appeared in the literature recently which indicate the appreciable contribution of steric effects in the reactivity of many hetero-organic compounds. In some studies the presence of a linear relationship between the steric effect of substituents at a heteroatom and at carbon has been suggested.

The R_S constants for 25 substituents at phosphorus, sulphur, arsenic and antimony have been compared with the constants for the same substituents as carbon with the aim of clarifying the sensitivity of various atoms to steric effects and detecting the presence or absence of linear relationships between the steric effects of substituents at these atoms and of the same substituents at a carbon atom.[189] This series has been extended more recently to 43 substituents at 20 elements (from hydrogen to lead).

It has been established[189] that the steric effect of a substituent is reduced uniformly with an increase in the size of the central atom. At the same time there was a strict linear relationship ($r > 0.99$) between the steric effects of substituents at each heteroatom studied and the steric effects of the substituents at a carbon atom.

$$R_S(\mathrm{E}) = A_0 + A_1 R_S(\mathrm{C}),$$

where $R_S(\mathrm{E})$ are the steric constants for substituents at any element and $R_S(\mathrm{C})$ are the steric constants for the same substituents at a carbon atom.

The results obtained are completely in agreement with the literature data mentioned above according to which the steric effects of substituents at various heteroatoms (particularly at atoms of phosphorus, sulphur, oxygen, nitrogen and silicon) are described well by correlation equations using the constants for carbon.

The linear dependence established between the steric effects of substituents at various atoms and at a carbon atom removes the problem of determining the steric constants for substituents for each individual element since it is possible, when analysing the reactivity of hetero-organic compounds, to use the steric constants for substituents at a carbon atom with equal success.

4. Steric effects and the conformation of a substituent

It is evident that the steric effect of any substituent within the framework of the model being considered is linked directly and in an extremely effective manner with its conformation. In particular the parameter R_i in the expression $\sum_{i=1}^{n} r_i^2/4R_i^2$, which corresponds to the distance from each of the atoms contained in the substituent to the reaction centre, is sensitive to conformation. On the one hand this points in favour of the adequacy of the model since the dependence of steric effects on conformation actually occurs.[2,73,104–106] On the other hand such a conformational sensitivity may seem to be an undesirable factor because the conformation may not be known precisely for each substituent. For the majority of substituents the problem of conformational uncertainty is either completely absent or one of several possible conformations is known to be obviously in existence. In such a case it is possible to go over to the reverse procedure, i.e. to determine which conformation exists in those substituents in which the proportion of conformational uncertainty is large. For this it is sufficient to compare the theoretical values of R_S for each of the possible conformations (as a rule there are no more than two) with the experimental parameter log k and to select that which is best described in coordinates of log k and R_S for the general series (a reaction series composed of conformationally unequivocal substituents).

An actual example of such an unusual conformational analysis has been described[71] for the substituents CH_2OCH_3 and CH_2SCH_3. Two of the possible types of orientation of these substituents relative to the reaction centre were examined, viz. the transoid and the conformation with free rotation about the CH_2-E bond. Comparison of the theoretically calculated values of R_S for each orientation with the values calculated according to the correlation Eqn. (3) from the experimental values of E_S showed that the methylthiomethyl substituent has a clearly expressed transoid orientation while it is impossible to exclude free rotation or the existence of a *gauche* form for the methoxymethyl substituent.

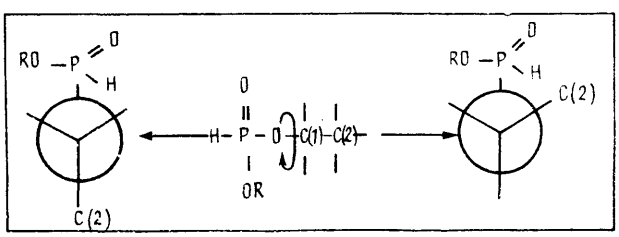


Figure 2. Conformations of alkoxy substituents in the Pudovik and Abramov reactions.

The dynamic stereochemistry of dialkyl phosphorus acids and their anions have been investigated in an analogous manner in the Pudovik and Abramov reactions.[190,191] It was shown that the reactivity and acid properties of the free dialkyl phosphites were well described by a choice of R_S constant corresponding to the least sterically hindered *trans* orientation of the P–O and C(1)–C(2) bonds in both alkoxyl groups on the phosphorus atom. At the same time the best correlation for the dialkyl phosphite anion was observed on proposing a *gauche* orientation for the P–O and C(1)–C(2) bonds in one of the alkoxyl substituents (Fig. 2). It is possible to explain such an orientation for the substituent by the electrostatic interaction of the anion and the alkyl group polarised by it.

Conformational sensitivity is therefore not a drawback of the proposed model but on the contrary makes it more flexible and more useful in a practical sense.

Table 1. Some types of reaction series described using R_S steric constants.

Series number	Type of reaction series	Q	N_{av}	R_{av}	Refs.
1	Existing scales of steric constants E_s, E_s^0, v_x	3	35	>0.98	[71]
2	Reactions of organic compounds of nitrogen	19	6	~0.99	[192]
3	Reactions of organic compounds of oxygen	8	5	~0.96	[192]
4	Reactions of organosilicon compounds	5	7	~0.98	[192]
5	Reactions of organophosphorus compounds	22	5	~0.99	[192]
6	Reactions of organic compounds of sulphur	4	5	~0.98	[192]
7	Reactions of organic compounds of arsenic	4	4	~0.98	[192]
8	Reactions of organomagnesium compounds	1	5	0.958	[192]
9	Dissociation of phosphoric, phosphonic and phosphinic acids in water and in aqueous alcoholic media	9	9	>0.99	[193]
10	Dissociation of dialkyl phosphites in absolute isopropanol	1	5	0.966	[190]
11	Addition of dialkyl phosphites to an unsaturated compound (Pudovik and Abramov reactions)	10	8	>0.98	[190, 191, 194, 195]
12	Complex formation of nickel and cobalt ions with cyclic and acyclic dithio acids of phosphorus	8	7	~0.97	[196]
13	Reactions of cyclic and acyclic isocyanatophosphites with diphenylcarbodiimide	2	4	>0.99	[197, 198]
14	1,3-Dipolar cycloaddition reactions to a phosphorylated allene and an acetylene	2	6	>0.98	[199]
15	Reaction of dithio acids of phosphorus with cumene hydroperoxide	4	66	>0.97	[200]
16	Williamson reaction in the chloromethylphosphine oxide series	2	24	~0.99	[201]
17	Reaction of gelatine with aldehydes	1	6	0.989	[202]
18	*cis-trans*-Isomerism of ethylenes	2	6	>0.97	[188]

Footnote. Symbols used: Q is the number of reaction series, N_{av} the average number of points in the correlation and R_{av} the mean correlation coefficient.

5. Analysis of the reactivity of organic and hetero-organic compounds

Since the proposed model enables steric effects to be calculated fairly simply for any substituent at any reaction centre it is natural that the largest area for its application is the analysis of steric interactions in the reaction series varying most widely and firstly

where the steric effects of substituents are not expressed adequately by the existing scales. This applies primarily to hetero-organic compounds although recently more data have appeared on purely organic reaction series containing complex branched or heteroatomic substituents, the steric effect of which may not be described in the empirical scales. In this case the theoretical calculation of the steric effect remains the only possibility for an effective analysis and prediction of reactivity.

Attempts to apply the proposed approach indicate its high effectiveness in describing the most varied reaction series both under purely steric control and with a mixed influence of electronic and steric factors within the framework of a multiparameter regression analysis.

Certain types of organic and hetero-organic reaction series which are described successfully using R_S constants are shown in Table 1.

The first 8 types of reaction series in Table 1 are literature data which have been processed previously using other steric scales. Comparative analysis of the quality of the correlations shows that the R_S scale describes the given reaction series in every case no worse than the various scales [E_S, E_S^0, ν_X, $\nu_X(NR^1R^2)$, $\nu_X(P)$, $\nu_X(SR)$, $E_S(Si)$, etc.] which were used in the original correlations. Experimental investigation of the remaining reaction series (series 9–18) were carried out by us either independently or in collaboration which is reflected in the corresponding literature references. It follows from Table 1 that the R_S scale gives good results when describing the reactivity of the most varied HOC in different types of reaction, from acid–base properties to processes of complex formation. In this way regularities often became apparent which could not be detected within the framework of the existing experimental scales. For example, on repeating the experimental study of the dissociation of various types of phosphorus acids (phosphoric, phosphonic and phosphinic)[193] not only were the pK_α values of certain acids successfully refined but it was also discovered that there were distinct relationships between pK_a and R_S for these types of acid, i.e. a given reaction series selected as a standard in HOC chemistry was not a single reaction series. This conclusion was also confirmed by studying the Brønsted relationships.

The approach proposed therefore turned out to be extremely effective in the analysis of the most varied chemical processes and also in solving theoretical problems connected with steric effects. Although simple it provides a fairly correct description of the steric interactions developing to a certain extent and of their nature. Using simple and available mathematics it enables calculation of the steric effects of any substituent at any reaction centre, starting from its structure and conformation, and may be useful in understanding and predicting interrelationships between the structure and reactivity of organic and hetero-organic compounds.

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