

Bioisosterism: Quantitation of Structure and Property Effects

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Dedicated to the memory of *Nabil El Tayar*, an educator, scientist, colleague, and friend, who called our attention to this important aspect of molecular design.

The powerful concept of bioisosterism is presented as a method for selecting molecular groups for drug design and lead-compound development. Three group-structure characteristics are described for this purpose. The E-State value for an attached atom is used as a measure of electrotopological group impact. The volume of the group is estimated from counts of σ , π , and lone-pair n electrons, as embodied in the valence and simple connectivity δ values for atoms in the group. Polarity is described in terms of the polarity index Q . Specific examples are given for commonly used groups. Parameter spaces encoding these three attributes are presented as examples that may be used to guide bioisostere selection in late-stage drug-design procedures. The method presented here is of practical value in the decision processes of molecular modification.

1. The Bioisosteric Concept. – The concept of bioisosterism is perhaps the oldest source of a chemical-information model for molecular modification in the process of drug design and development. It was intended to provide some answer to the question facing the chemist: ‘what do I synthesize next?’ Bioisosterism is now an integral part of the intuition that the chemist brings to bear on this challenge. The origins of this concept deserve a brief retelling to bring us up to date for the modern applications.

The antecedent of bioisosterism is isosterism, a term introduced by *Langmuir* in 1919 [1]. Isosterism was defined as the relationship between sets of atoms or groups that impart similar properties to them, *e.g.*:

H⁻, He, Li⁺
O²⁻, F⁻, Ne, Na⁺, Mg²⁺, Al³⁺
S²⁻, Cl⁻, Ar, K⁺, Ca²⁺
Cu²⁻, Zn²⁺
N₂, CO, CN⁻
CH₄, NH₄⁺
CO₂, N₂O, N₃⁻, CNO⁻

Later, *Grimm* [2] elaborated on this concept by organizing atoms and fragments on the basis of their valence electrons and the count of electron pairs in bonds from H-atoms. This concept is generally known as *Grimm’s* hydride-displacement law:

C	N	O	F	Ne	Na
	CH	NH	OH	HF	–
		CH ₂	NH ₂	H ₂ O	H ₂ F ⁺
			CH ₃	NH ₃	H ₃ O ⁺
				CH ₄	NH ₄ ⁺

Some success came from these estimates of similarity in molecular design, although this concept remained merely a curiosity until massive efforts at molecular modification arose some three decades ago.

The term *bioisosterism* was introduced by *Friedman* [3], who foresaw the application to biological activity. A recent review has focused on the use of bioisosterism to modify lead compounds in drug-design [4]. These reports emphasize the successes in achieving drug design goals in many specific cases. It must be recognized that, generally, structural variations lead to different biological activities. There is no common theme, where a certain change in structure produces a predictable change in biological profile. A Me group, *e.g.*, inserted into a lead compound A, may produce a biological response quite different from the results of a similar operation with respect to lead compound B. In both cases, the intrinsic characteristics of the Me group are the same, but the overall biological effect is often very different.

What can we learn from examining different scenarios of bioisosterism? It is not possible to generalize the biological effect of each structural change. What we do learn from separate studies are insights into the characteristics of the structures used in the process of molecular modification. However, without understanding the mechanistic details of biological receptors or enzymes at the molecular level, it is not possible to anticipate the effect on biological activity that arises from such modifications. Nevertheless, we can often anticipate the effect of a certain bioisosteric replacement on the physical properties of the molecules involved. What we can understand about a Me group as a bioisostere, is the electronic, the steric, and the hydrophobic influences produced upon change in structure.

The focus of this paper is the structural variation introduced by the interchange of one group for another in the molecular modification process. This structural variation is partitioned into group volume, group polarity, and electronic influence on the attached structure. We will employ several nonempirical structural descriptors to elucidate the effects of changes classified as *bioisosteric replacements*. By defining this structural variation in familiar and important terms, *i.e.*, polarity, volume, and electronic influence, the drug-design scientist can make choices in the important question of how to direct molecular-modification process.

2. Functional-Group Replacement. – The substitution of an atom or functional group in a molecular skeleton is essentially an isosteric replacement. Two basic reasons dictate the choice of a particular group: *a*) the change of the characteristics of the group relative to those already present in the molecule, and *b*) the influence of the atom or group on some attributes of the whole molecule, which ultimately influence the physical or biological properties. It is possible that both categories of interest are the basis for a replacement, although such a dual expectation may lead to a more complex

outcome. We will consider each of these aspects and reveal the calculated effects of bioisosteric replacement on some sample molecules.

2.1. *Group Attributes.* Adding an atom or a group to a molecule is based on the expectation that the contribution of some characteristics of that group itself will enhance the activity of the molecule. The structure of the group may possess 1) a steric or size attribute, 2) an electronic characteristic, and 3) an influence on surrounding H₂O molecules (solubility, hydrophobic effects, and partitioning between two solvent phases, or between H₂O and a membrane). Any or all of these expectations may lie in the realm of molecular-design objectives. We will consider each in turn.

2.1.1. *Group Size, Shape, or Steric Character.* A group may be added to a molecule for reasons based on its size or steric character in the expectation of producing or relieving a crowding effect at a receptor or an enzyme. The group may also be added for the purpose of crowding some other part of the molecule, e.g., to inhibit a reaction or to alter a conformational preference. These attributes may be estimated from an atom or group radius [5][6], or by a topological index correlating with some estimate of volume, e.g., that of Kier and Hall [7][8]. In the latter study [8], a topological descriptor was defined that produced a close correlation with the *Bondi* group volumes [5]. To derive this descriptor, a hydrogen-suppressed graph of a molecule is written down. Each atom or hydride group is defined by two indices. The first, δ , is the count of neighboring atoms that are σ -bonded to the atom (or hydride group). The second index, δ^v , is defined as the count of valence electrons contributed by the hydrogen-suppressed atom, i.e., the sum of σ , π , and lone-pair n electrons on the atom. The size index, $(\delta + \delta^v)$, was shown to strongly correlate with the *Bondi* atom and/or group volume V (in cm³/mol) [5]:

$$V = 17.03 - 6.36 \cdot (\delta + \delta^v) / N^2 \quad (r^2 = 0.97, s = 0.52, n = 20)$$

in which N is the principal quantum number of the atom. The ability of this descriptor to estimate fragment and group volumes can now be used to characterize and classify bioisosteric fragments for molecular design. In these studies, we have simplified this volume to the volume index $V^b = N^2 / (\delta^v + \delta)$ for each atom or hydride group, with fragment examples shown in *Table 1*.

2.1.2. *Group Electrotological Character.* The electrotopological character of the various atoms or groups that may be employed in bioisosteric replacement can be revealed by calculation of this attribute. The electrotopological state (E-State) of an atom or hydride group in a molecule is an estimate of the electron accessibility at that atom, i.e., electron excess or depletion mitigated by the topological position of that atom. The index is derived from the electronegativity of the atom (or hydride group) and the topological character. The Kier–Hall electronegativity, expressed as $\delta^v - \delta$, has been shown to nicely correlate with the Mulliken–Jaffe electronegativity, and is used in deriving the E-State index [8]. The other ingredient in the derivation is the topological character of an atom, expressed as the δ value. Upon combining these two values and simplifying the expression, an index I , called *intrinsic state* (of an atom), is created. This is the E-State of an 'isolated' atom, not considering the influence of other atoms in the molecule. The other atoms in the molecule do influence a given atom i , and so its I_i value must reflect the sum of perturbations *via* electronegativity equalization. To

Table 1. *Volume Indices ($V^\delta = N^2/(\delta^V + \delta)$) and Reported [5] vs. Calculated (calc.) Volumes for Selected Structural Elements*

Atom, Group	V^δ	V [cm ³ /mol]	
		lit. [5]	calc.
> C <	0.50	3.33	4.31
> CH –	0.67	6.78	7.49
–CH ₂ –	1.00	10.23	10.67
–Me	2.00	13.67	13.85
=CH ₂	1.33	11.94	12.26
–C≡, =C=	0.67	7.50	7.49
≡CH	1.00	11.55	10.67
=CH–	0.80	8.47	9.08
–O–	0.50	4.45	4.31
–OH	0.67	8.04	7.49
–NH ₂	1.00	10.54	10.67
–NH–	0.67	8.08	7.49
> N–	0.50	4.33	4.31
≡N	0.67	7.90	7.49
=C <	0.57	5.54	5.90
=O	0.57	6.79	5.90
=NH	0.80	9.50	9.08
=N–	0.57	6.06	5.90
–F	0.50	5.72	4.31
–Cl	1.14	11.38	11.62
–Br	2.00	13.85	14.40
–SH	1.50	12.79	14.80
–S–	1.14	10.80	11.62

estimate this effect, one computes the perturbation on I_i from all other atoms j as the intrinsic state differences between atom i and all other atoms j , and modifies this with the path difference expressed as the count of atoms in each separating path, r :

$$\Delta I = (I_i - I_j) / r^2$$

Applying the total perturbation to the intrinsic state of any atom i , we arrive at the E-State, S_i , for that atom (or hydride group) within the context of a particular molecule:

$$S_i = I_i + \sum_j \Delta I_{ij}$$

A list of employed atoms and groups used in bioisosteric replacement is shown in Table 2, along with the calculated E-States. The groups are located on a cyclohexyl ring to model them as substituents. The group values S are computed as the E-State value for the C-atom to which the group is bonded.

2.1.3. Group Hydrophobic Effect. The influence of a molecule on the surrounding H₂O is referred to as *hydrophobic effect*. The extent to which the solvent is affected largely depends on the relative polarity of an atom or group. The effect can be approximated from the sum of contributions of the fragments of a molecule.

Table 2. *E-State and Hydrophobicity Values (S and Q_v , resp.) of Selected Groups and/or Atoms (R) attached to a Cyclohexyl Ring.* The positions α and β refer to the non-H-atoms of the substituent, α -atoms being directly attached to the ring.

R	$S(\alpha)$	$S(\beta)$	$Q_v^a)$
F	11.91		1.372
Cl	5.54		2.132
Br	3.31		2.554
OH	8.63		1.619
NH ₂	5.36		1.713
Me	2.08		2.678
SH	4.08		2.395
H			3.240
OMe	4.91	1.66	2.678
NHMe	3.03	1.91	3.020
NMe ₂	2.08	2.04 ^{b)}	3.677
Et	1.14	2.16	3.431
i-Pr	0.66	2.20 ^{b)}	3.971
<i>t</i> -Bu	0.29	2.23 ^{c)}	4.495
NO ₂	−0.42	10.01 ^{b)}	1.499
C≡N	2.03	8.29	1.940
COOH	−0.88	10.20/8.39 ^{d)}	1.655
CF ₃	−4.21	11.79 ^{c)}	1.180

^{a)} Whole molecule. ^{b)} Two identical β -positions. ^{c)} Three identical β -positions. ^{d)} =O and OH groups of COOH, resp.

Accordingly, the influence of an atom or group used in a bioisosteric replacement may be quantified in a number of ways. The recently introduced Q_v polarity index [9] may be used to encode the desired information. This index is derived from the intrinsic state values (I) for an atom or hydride group, as described above. These I values are summed over the atoms in a fragment or molecule to give a value ΣI_i . This value is compared to the minimum value ($\Sigma I_{\min}$) possible when all atoms in that molecule are sp³ C-atoms, and when all atoms have the maximum possible I values ($\Sigma I_{\max}$). Such an algorithm produces a relative value of the polarity of that atom or group called Q_v :

$$Q_v = \frac{\Sigma I_{\min} \cdot \Sigma I_{\max}}{(\Sigma I_i)^2}$$

The larger the Q_v value, the greater the hydrophobic character of the molecule or fragment. In Table 2, the Q_v values for several groups are listed.

2.2. Group Influence on the Whole Molecule. The other role that bioisosteric replacement plays is the influence an atom or group may have on the rest of the molecule. This effect adds to the intrinsic contribution of the group itself, as described above. The desired effect can be a specific target that may govern the choice of groups. This change in the molecule is primarily an electronic one, coupled with some proximal influence on topology. A useful quantitation of this effect can be made with the E-State indices. Table 3 illustrates the influence of several atoms and groups on an isobutyl fragment. This systematic analysis serves as a guide in the selection of bioisosteres that

Table 3. Group Influence on the *E*-State Values (*S*) of 1-Substituted 2-Methylpropane ($R-CH_2-CHMe_2$)

R	<i>S</i> (–CH ₂)	<i>S</i> (–CH<)	<i>S</i> (–Me)
F	– 0.19	0.22	1.85
OH	0.31	0.44	1.97
Cl	0.78	0.65	2.09
NH ₂	0.81	0.66	2.10
Br	1.11	0.80	2.17
Me	1.31	0.88	2.22

are intended to evoke a desired molecular change. This information must be blended with the intrinsic attribute of any atom or group, as described above, to obtain a complete profile of the role of a specific atom or group in bioisosteric replacement.

3. Group Attribute Space. – Each of these three intrinsic attributes of atoms or groups, described above, must be considered in the selection of an atom or group bioisosteric replacement. If the selection is based on only one attribute, it is inescapable that the other two are still in operation, and some knowledge of their role must be at hand. One way to consolidate this information is to consider each category of intrinsic attributes as a dimension in structure-parameter space. This concept is illustrated in Figs. 1–3 (see also Table 4), where the steric, electronic, and hydrophobic intrinsic attributes of several atoms and groups are shown as two-dimensional plots. The consequences of the use of a group for a specific goal can now be assessed with this information. It is notable that the quantitation of these attributes is based on nonempirical indices of structure rather than physical properties. Further, these attributes are rapidly calculated from precise algorithms.

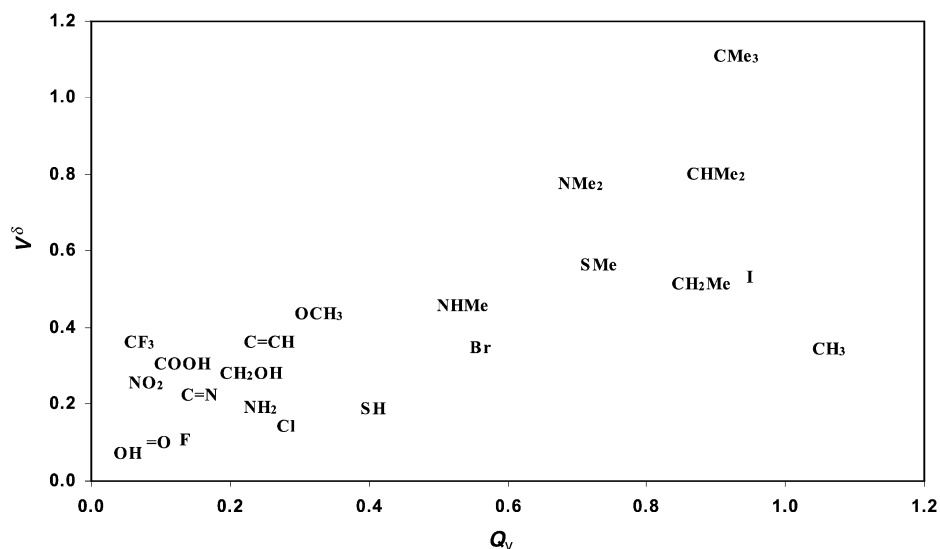


Fig. 1. Plot of the volume (V^3) vs. polarity (Q_v) indices calculated for a cyclohexane C-atom attached to a given functional group. For numerical data, see Table 4.

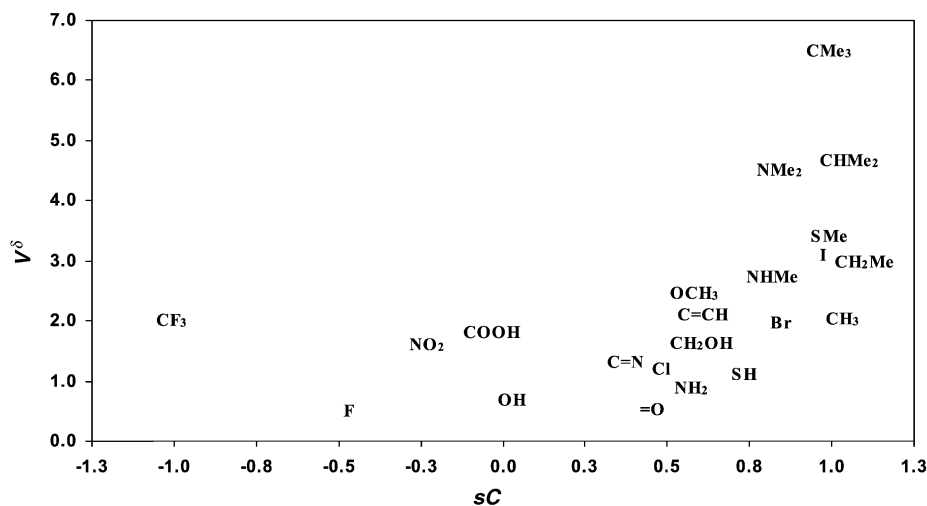


Fig. 2. Plot of the volume (V^δ) vs. E-State (sC) indices calculated for a cyclohexane C-atom attached to a given functional group. For numerical data, see Table 4.

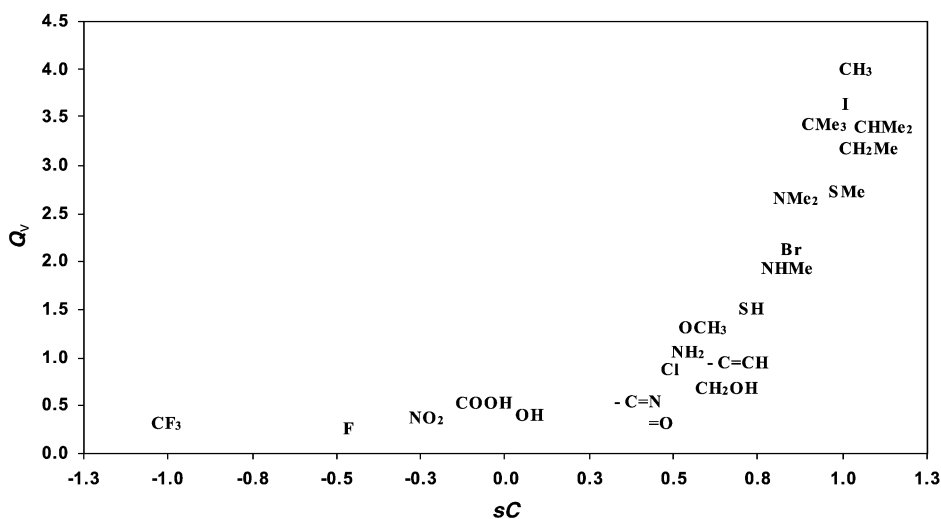


Fig. 3. Plot of the polarity (Q_v) vs. E-State (sC) indices calculated for a cyclohexane C-atom attached to a given functional group. For numerical data, see Table 4.

Several examples of the use of group-attribute space are illuminating. In Fig. 1, the CF₃, COOH, NO₂ and CH₂OH groups are clustered, which indicates that they are isosteric in V^δ and Q_v space. They can be interchanged if these properties are relevant to the goals of the molecular modification. If, however, the electronic influence on the rest of the molecule is important in a particular study, then these four groups are not isosterically related, as shown by their scattered relationship in Fig. 2. Similarly, the F,

Table 4. Topological Group Values Encoding Volume (V^{δ}), Polarity (Q_v), and E-State (sC) Influences, resp., of Selected Structural Elements. See Figs. 1–3 for the corresponding plots.

Atom, Group	V^{δ}	Q_v	sC^a
<i>t</i> -Bu	6.50	3.48	1.001
<i>i</i> -Pr	4.67	3.37	1.054
Et	3.00	3.29	1.087
Me	2.00	4.00	1.036
C $\equiv$ CH	2.13	0.95	0.615
OMe	2.50	1.33	0.587
=O	0.57	0.33	0.464
OH	0.67	0.44	0.036
COOH	1.81	0.45	– 0.029
CF ₃	2.00	0.29	– 1.000
CH ₂ OH	1.66	0.72	0.640
NH ₂	1.00	1.00	0.536
NHMe	2.67	1.99	0.837
NMe ₂	4.50	2.67	0.888
C $\equiv$ N	1.33	0.56	0.392
NO ₂	1.64	0.38	– 0.223
F	0.50	0.25	– 0.464
Cl	1.13	0.95	0.508
Br	2.00	2.12	0.848
I	3.13	3.56	1.006
SH	1.13	1.54	0.730
SMe	3.33	2.74	1.003

^a) E-State value of a cyclohexane C-atom bonded to the atom or group.

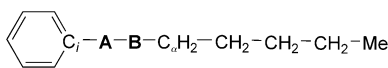
OH, and NH₂ groups are roughly comparable in volume and polarity space (*Fig. 1*), but much less comparable in volume- and E-State influence space (*Fig. 2*).

Another observation is interesting. The MeS group, Me group, and I-atom display comparable values of volume and E-State influences (*Fig. 2*). An inspection of *Fig. 1*, encoding volume and polarity, reveals a dispersed placement of these groups and, thus, a wider variation in their polarity values. If this is an important aspect of the replacement decision, then these groups are not good candidates for interchange. If volume and E-State influence are the only considerations in bioisosteric selection, then the Me group, Br-atom, and ethyne group are comparable (*Fig. 2*). They are, however, not comparable if polarity is a factor, as shown by their scattered relationship in *Fig. 3*. In contrast, the CN, Cl, SH, and NH₂ groups or atoms are comparable in their volume, polarity, and E-State attributes (*Figs. 1, 2, and 3*), hence they are possible candidates for bioisosteric replacement under some circumstances.

4. Linking Groups. – A second broad class of bioisosteres links two major fragments of a molecule. The use of linking fragments in a molecule is made with the expectation that the adjacent molecular features will retain a major part of their original role, but will also be improved by bioisosteric replacement. The goals of bioisosteric replacement in these cases may include: 1) a modest alteration in the steric relationship of the parts; 2) a change in molecular hydrophobicity; 3) a change in one or both linked fragments in terms of electronic structure; and 4) the insertion of a fragment with some

new, desirable intrinsic attributes. These influences can be predicted for a set of linking fragments joining two molecular features. To illustrate the influences on two different molecular features, an aromatic ring and an alkyl chain have been chosen. The E-States of the linking atoms, an estimate of their linear dimension, and the E-State values of proximal atoms on the linked fragments are shown in *Table 5*.

Table 5. Effect of Single (**A**) vs. Double Links (**A–B**) between a Phenyl Ring and a Pentyl Substituent on the E-State Values (*S*) of Selected Atoms or Groups



	S_A	S_B	S_{C_i}	$S_{C_nH_2}$	S_{Me}	$(\delta^v + \delta)_A$	$(\delta^v + \delta)_B$	D^a
<i>Single Link</i>								
A								
O	5.51	–	0.98	0.85	2.20	8	–	2.06
NH	3.78	–	1.23	1.10	2.23	6	–	2.39
S	1.96	–	1.40	1.26	2.24	4.67	–	2.62
CH ₂	1.25	–	1.48	1.35	2.25	4	–	2.73
<i>Double Link</i>								
A–B								
N=N	4.10	4.10	0.94	0.85	2.19	7	7	4.45
C≡C	3.15	3.19	1.12	1.03	2.21	6	6	4.78
NH–NH	3.15	3.19	1.12	1.03	2.21	6	6	4.78
O–CH ₂	5.55	0.85	0.99	1.17	2.22	8	4	4.78
CH ₂ –O	0.76	5.52	1.26	0.89	2.21	4	8	4.78
N=CH	4.35	2.02	1.06	1.10	2.22	7	5	4.78
CH=N	1.95	4.35	1.19	0.96	2.21	5	7	4.78
CH=CH	2.20	2.27	1.31	1.21	2.24	5	5	5.12
NH–CH ₂	3.40	1.10	1.24	1.28	2.24	6	4	5.12
CH ₂ –NH	1.01	3.44	1.27	1.14	2.23	4	6	5.12
CH ₂ –CH ₂	1.26	1.35	1.49	1.39	2.26	4	4	5.46
CH ₂ –S	1.17	2.05	1.45	1.31	2.25	4	4.67	5.35
S–CH ₂	1.97	1.27	1.40	1.36	2.26	4.67	4	5.35

^a) Linear dimension [$\text{\AA}$] of the **A** or **A–B** linkage.

5. Ring Replacement. – The effects of the replacement of one ring for another transcends the influential effect of a small functional group on the attached molecular fragment. A ring, typically composed of ten or more atoms, imparts a significant role in its own right due to its intrinsic structure and surface area, which influence lipophilicity and polarity. These characteristics alter the binding of the molecule, and, thus, its role at a receptor. Evidence for the dominance of the intrinsic character rather than its influence on the rest of the molecule is revealed in an E-State analysis of several rings that are frequent candidates for bioisosteric replacement.

In *Table 6*, the effect of various rings on an attached Et group is demonstrated by means of the E-State value *S* of the attached CH₂ C-atom. The intrinsic character of the ring itself is represented by the polarity index Q_v , calculated from the total E-State

Table 6. *Ring Bioisosteres and Calculated Structural Attributes (E-State and polarity indices) for Fragments of the Type R–CH₂–CH₃*

R	Name	$S(\text{CH}_2)$	Q_v
	Phenyl	1.140	3.43
	Pyridin-4-yl	1.100	3.02
	Pyridin-3-yl	1.077	3.02
	Furan-2-yl	0.993	2.47
	Furan-3-yl	1.066	2.47
	Thiophen-2-yl	1.178	3.14
	Thiophen-3-yl	1.170	3.14
	Pyrrol-2-yl	1.104	2.84
	Pyrrol-3-yl	1.128	2.84
	Cyclohexyl	1.417	5.19
	Tetrahydropyridin-3-yl	1.354	4.44
	N-Morpholino	1.170	3.51

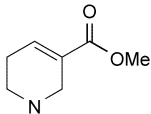
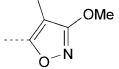
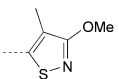
intrinsic values. Among the aromatic rings, there is a very small difference in $S(\text{CH}_2)$. Among rings that are not aromatic, the influence is somewhat greater, but not too different within this subset. In contrast, the intrinsic character of the rings vary widely, depending on the structure. Among the aromatic rings, the polarity index Q_v is usually smaller than that of the Ph ring, which indicates higher polarity. Among rings that are not aromatic, the polarity indices are higher, and these rings are, thus, less polar. From this analysis, it is possible to anticipate, at least in a general way, the structural contribution to the molecule with a bioisosteric replacement of rings.

6. Ring Formation. – 6.1. *Arecoline Modifications.* One broad approach to molecular modification sometimes included in the bioisosteric replacement category

is the conversion of a fragment of a molecule into a cyclic structure [4]. The cholinergic agent arecoline has been modified in this manner to achieve some improvement in potency. Of interest to us in a broad analysis of bioisosteric modification are the structural and property changes that follow this kind of bioisosteric change. Several such modifications have been reported and are summarized in *Table 7*. The ester group on the tetrahydropyridyl ring has been contorted into a second ring, retaining the same inter-ring linkage. We have examined two structural consequences of these changes, the electronic influence (S_N) on the basic pyridyl N-atom, and the polarity (Q_v) of the new ring, as estimated by means of E-State calculations. The E-State for the pyridyl N-atom in each molecule can be taken as a measure of the intermolecular accessibility of that atom.

The ring modifications in general lead to a higher E-State value for the pyridyl N-atom, suggesting a higher relative basicity and accessibility. The new rings all have a

Table 7. *Effect of Isosteric Replacement of the Arecoline Ester Group by Various Heterocyclic Rings (R)*. The calculated E-State values (S_N) at the tetrahydropyridine N-atom are listed together with the polarity-lipophilicity values Q_v of the five-membered heterocycles introduced.

Arecoline  ≡ 		
R	S_N	Q_v
	2.103	3.054
	2.312	5.223
	2.245	4.598
	2.352	5.661
	2.339	5.661
	2.313	5.363
	2.224	4.060
	2.311	4.849

higher Q_v value, corresponding to a lower relative polarity. This index has been shown to bear an approximate relationship to lipophilicity, thus we infer that the ‘cyclizations’ enhance this property.

6.2. GABA Modifications. The neurotransmitter, γ -aminobutyric acid (GABA) has two fragments constituting the pharmacophore, the COOH and the NH₂ termini. Extensive efforts have been made to modify this molecule to improve its activity and pharmacodynamic characteristics. One approach has been to cyclize the COOH fragment, the NH₂ fragment, or both [4]. Several indices have been calculated with the intent to reveal some of the possibly important attributes of these modifications (Table 8). The E-State index for the relatively acidic OH group (a residual of the carboxy OH group in the parent GABA) is an approximate measure of both the acidity and the H-donor/acceptor quality of this feature. In GABA, the E-State of the OH group, $s(\text{OH})$, should be reckoned as the average of the E-States of the =O and the OH groups due to tautomerism.

The $s(\text{OH})$ values of the cyclic structures, with just the OH group remaining (Entries 2–7, and 10–14 in Table 8), are generally higher than the average value for GABA (Entry 1). Noncyclized COOH groups (Entries 8 and 9) have $s(\text{OH})$ values about the same as GABA. The volume of the groups is reflected in the V^δ values; the larger this value, the larger the volume of the group.

7. Conclusions. – The analyses presented in this article are not intended to solve specific problems of bioisosteric replacement, since these are highly dependent on the nature of each study. We cannot recount every pattern of biological influence resulting from every set of bioisostere replacements. What we can do is to sensitize drug-design scientists for the structural changes invoked when a bioisostere is selected. The influences demonstrated here are derived from a general procedure that can be employed in a drug-design project, when the research effort has reached the molecular-modification stage. Procedures are shown for the estimation of the influence of an additional group, a replacement group, a linking fragment, or a cyclic modification in a lead compound. Other modification analyses can be inferred from these examples. As an excellent example, in a recent paper by Sheridan [10], a number of molecular fragments have been identified as useful bioisosteres. Our analysis could be very useful in selecting the optimum influences on a scaffold structure and help to define those influences in semiquantitative terms.

The procedure shown here is based on the estimation of three attributes of atom, group, or fragment bioisosteres. These attributes are 1) the steric or size effect; 2) the electrotopological state, and 3) the polarity or hydrophobic state. These estimates are based on calculated molecular-connectivity δ values, intrinsic states, and electrotopological state indices. We presented three types of plots of these attributes to illustrate how the information can be displayed and used in decision making. These attributes can be calculated for bioisosteric-replacement groups and for their influence on the rest of the molecule. The ease with which these attributes may be calculated is important in drug design processes. Furthermore, the clear interpretability of these indices suggests that this approach is valuable in the refinement stages of molecular design.

Table 8. Calculated *E*-State Values ($s(\text{OH})$) and Volume Indices (V^0) for a Series of Cyclic GABA (γ -aminobutyric acid; see Entry 1) Agonists Modified at the C-Terminus. The $s(\text{OH})$ values refer either to the carboxy OH groups (Entries 1, 8, and 9) or to the corresponding free OH groups at the heterocyclic five-membered rings (Entries 2–7 and 10–14) obtained by ‘cyclization’ and modification of the four parent structures (Entries 1–4).

Entry	Structure	Description	$s(\text{OH})$	V^0 [cm^3/mol]
1		GABA	8.00	5.81
2		Muscimol	8.60	6.08
3		Thiomuscimol	8.70	6.72
4		Isomuscimol	8.50	5.68
5		a)	9.06	7.12
6		b)	9.17	7.76
7		c)	9.04	7.12
8		d)	8.44	6.85
9		d)	8.51	6.49
10		d)	8.96	9.69
11		d)	9.07	10.33
12		d)	8.94	9.69
13		d)	8.94	8.72
14		d)	9.04	9.36

a) Muscimol analog. b) Thiomuscimol analog. c) Isomuscimol analog. d) GABA analog.

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