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CONCEPT OF A STERICALLY ACTIVE ENVIRONMENT IN ALICYCLIC STRUCTURES

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Abstract: *By seeking analogies in behavior between aliphatic and alicyclic carboxylic acids, it is possible to determine the sterically active sites of the latter.*

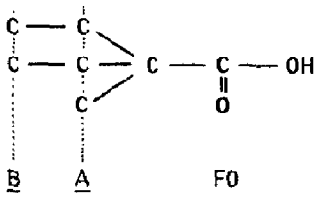
Few of the many works on steric effects[1-3] deal with cyclic groups. Steric parameters generally express group effects, but we recently showed[4] that these latter effects can be analyzed more finely as a function of site effects which, for an alkyl group, have been distinguished as being either sterically active or inactive.

By considering a sterically active environment, either all or part of the topological environment of the carboxyl group, it has been possible to unite the three types of behavior detected for alkyl groups[4b] into a *coherent* non-linear scale of steric parameters, E'_S, based on a single reference reaction (esterification in MeOH at 40°) covering over eight powers of ten.[4] These three types of behavior, related to the degree of substitution of the alkyl radicals, successively correspond to a *"normal" augmentation effect*, a *levelling effect*, and an *inversion effect*. Given that we treat a group as a graph and given the mode of analysis of a sterically active environment, our approach to aliphatic structures can be formally extended to alicyclic structures. We seek to define the steric influence of cyclic sites as a function of their topographic positions in relation to the reaction center, which is usually done qualitatively in conformational analysis. Thus, the relative pK_B value of triethylamine and that of quinuclidine are explained by the difference in steric contribution between the first blocked carbons of quinuclidine and all the mobile carbons of the aliphatic amine.[5] Similarly, we try to identify the active steric sites within the cyclic environment through the location of the experimental cyclic E'_S values in the acyclic E'_S scale for which all the site contributions are well defined.

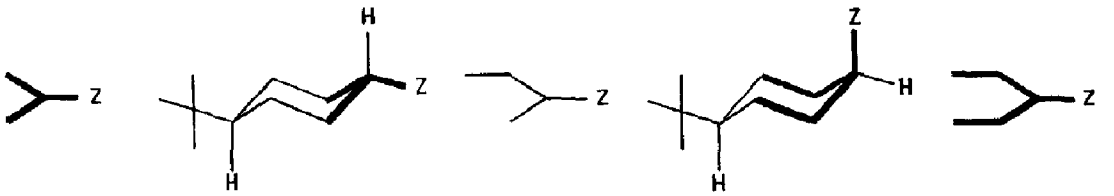
Our experimentally determined steric parameters E'_S for six cyclic groups are first reported here in the given examples and range from -0.73 to -7.01 units. The steric parameters ($E_S \simeq E'_S$) for four of these groups were predicted by Detar and Tenpas[6] using molecular mechanics calculations (MOLMEC and GENLSS programs). Three out of our four experimental E'_S values deviate considerably from the thereby calculated values. We partly ascribe these deviations to an inadequate parametrization in their programs and partly to a non-differentiation between sterically active and inactive sites; however, we believe that their theoretical modelling where an ortho- acid, $RC(OH)_3$, represents the transition state is quite adequate.

Analogies between Cyclic Structures and Isotopologous Aliphatic Structures

In a first approximation the environment of the carbonyl group for an aliphatic carboxylic acid is described by the topology of the alkyl radical and, *if additional information is needed, by its topography.* With acetic acid as reference compound, the substructure -(C-COOH) is designated as the focus, FO, the environment of which is organized in concentric layers (A, B, ...) i.e. which are made up of atoms that are β and γ to the carbonyl group.



It is well known that substituents δ to the carbonyl group play only a minor part in the overall steric effect. Therefore, we compare α,β *relevant sub-graphs* instead of open graphs entirely depicting the cycles under study. But which sub-graphs? In order to identify the active sub-graph of the cyclic graph, the E_S' values of the cyclic systems are at first systematically compared to those of the series of aliphatic graphs, starting with those which are isotopologous at the level of the atoms in layer A and ending with those which are isotopologous in layers A and B. Cis- and trans-4-tert-butylcyclohexane carboxylic acids illustrate this procedure.



$E_S' = -0.48$ $E_S' = -0.73$ $E_S' = -1.00$ $E_S' = -1.91$ $E_S' = -2.00$

One notices that the E_S' of the cis- acid is analogous to that of $-CHEt_2$, whereas that of the trans- acid is near that of $-CHMe_2$. *The different locations of the rank B atom* (γ-carbon) with respect to the carboxyl group *explains this difference in behavior.* A detailed study requires that the conformation of the carboxyl group be determined and that the distance between each rank B atom and the perpendicular to the plane of the carboxyl group[7] passing through the sp^2 carbon be assessed. However, by separating the space using plane P defined by the three rank A sites, it is easy to make a quick assessment of the participation of each atom in the overall steric effect. In a first approximation, the rank B atoms directed towards the carboxyl group appear to be sterically active (the cis- acid), whereas those directed away from it are sterically inactive (the trans- acid).

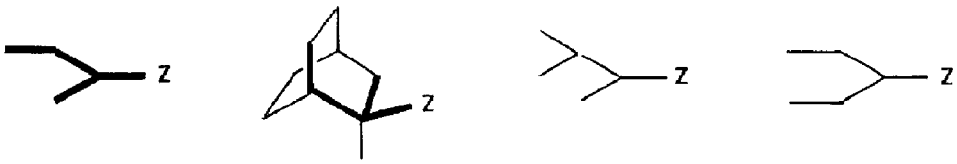
Light Sterically Active Cyclic Environment

This analogy between acyclic and alicyclic structures is but a first approximation. In cyclic structures, some conformations are blocked (fixed location), whereas in slightly or fairly hindered acyclic structures, the probable conformations authorize free rotations (statistical location). Identification of the *sterically active cyclic environment* must take into account the difference between the set location of a site in a cyclic environment and the statistical location of this site in an acyclic structure. For example, the value of the E'_S parameter for the adamantyl radical is very far from that for $-CEt_3$ and slightly higher than that of -tBu. There is a logical explanation for this since the three rank B carbons, like in the quinuclidine example, are directed away from the carbonyl group.

$E'_S = -1.43$ $E'_S = -1.64$ $E'_S = -2.28$ $E'_S = -5.29$

Nevertheless, the $-CMe_2Et$ radical could also have been a candidate structure, because in its most stable conformation, the rank B carbon of the sub-group Et is also directed away from the carbonyl group. Such a conformation corresponds to that of adamantyl; however, in $-CMe_2Et$, free rotations are possible and the intermittent probability of a rank B carbon in the cone of preferred approach[7] of the carbonyl group explains a certain influence on both the E'_S value of this group and the augmented value of the adamantyl group versus the -tBu one.

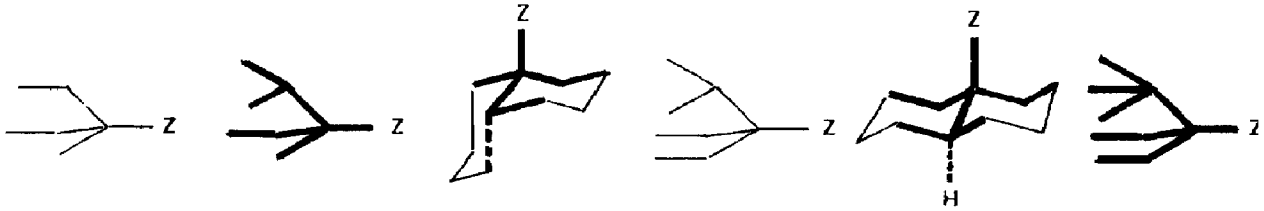
Likewise, for 2-bicyclo[2.2.2]octanecarboxylic acid, only one rank B atom is directed towards the carbonyl group and comparison with the acyclic structures indicates that only one rank B carbon atom is sterically active.



$E'_S = -1.00$ $E'_S = -1.24$ $E'_S = -1.92$ $E'_S = -2.00$

Heavy Sterically Active Cyclic Environment

In the cis-decalin system, looking from the Z group, all three rank A atoms - but only two of the rank B atoms - of the active environment are visible. It should be noted that the rank B atom seen in the sub-group $-CH(CH_2)_2$ actually contributes as much as the two rotating methyls of the aliphatic sub-group. The dotted bond in the sub-graph of the cis-decalin system serves here to express, in graph form, the weight of the frozen rank B site of the isopropyl group; so with this *pseudo-equivalent sub-graph* the comparison with the E'_S scale tool remains consistent. The effect of the sterically active environment of cis-decalin ($E'_S = -5.77$) is slightly stronger than the overall effect of the corresponding alkyl group MeEtiPrC-.



E'_S = -3.63 (cal) E'_S = -5.21 (cal) E'_S = -5.57 E'_S = -6.20 E'_S = -7.01 E'_S = -7.21

It should be noted that all rank B sites are visible from Z and are active in the trans-decalin system which also lies beyond its normal isotopologous aliphatic homologue because, in this blocked conformation, the cone of preferred approach of the carbonyl group is statistically occupied to a greater extent by the rank B sites of the sub-group $-CH(CH_2)_2$ than by the corresponding rank B sites of the isotopologous $-CH(CH_3)_2$. This apparent exaltation (E'_S = -7.01 for E'_S = -6.20) can be accounted for if it is noticed that the probability of presence of these rank B atoms of the isopropyl group is comparable to the B occurrence of a $-C(CH_3)_3$ sub-group, as shown in the last sub-graph (E'_S = -7.21).

In conclusion, our method of inserting sterically active sub-graphs into the E'_S scale makes possible a satisfactory assessment of the steric effects of the cycles studied. The comparisons between sterically active alicyclic and aliphatic sub-graphs are based on the probabilities of presence of some associated sites in certain locations of the reaction space. These locations are dependent on the privileged conformations of the reference sub-graphs in the E'_S scale. For the least-substituted aliphatic compounds the conformations are most often eclipsed, whereas for the highly substituted ones they tend to be bissected.[4b]

So steric hindrance in crowded cyclic compounds can well be estimated as the corresponding aliphatic compounds have blocked conformations. For strained cycles, complementary energy considerations are needed, but the active cyclic environment concept proves to be fruitful. The DARC-PELCO topological correlations[4b] that we have derived thus far to unify steric interpretation for acyclic compounds can be extended to cyclic compounds with some statistical factors to express the second order effects shown in this note.

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