resulted from a $_{\sigma}2_a + _{\pi}2_s$ (or $_{\sigma}2_s + _{\pi}2_a$) addition of cyclopropyl bond a (see **15**) across the allyl unit analogous to that observed in nondirected systems.[4a] Thus, the 1,2 shift represents least nuclear motion[13] and therefore should predominate. It is interesting to note that, in this case, the restraints imposed by the principle of least motion are enough to overcome the thermodynamic driving force for release of strain energy. These results have important implications for synthetic applications. In addition to the high stereoselectivity in spiroannelations, 1-lithiocyclopropyl phenyl sulfide fully complements the behavior of diphenylsulfonium cyclopropylide in terms of both stereochemistry of spiroannelation and chemospecificity[14] with conjugated enones.

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(15) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

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Calculation of Steric Effects in Reactions

Sir:

There is increasing interest in reactions which show acceleration due to forced proximity of reacting groups, particularly with respect to possible relationships to enzymatic catalysis.[1–4] Results are often discussed in such terms as preferred reaction trajectories and occasionally with such phrases as "orbital steering." There have, however, been important successes in quantitative calculations of energies of postulated transition states where steric factors have played a considerable role.[5–8] The purpose of this communication is to describe another quantitative procedure for evaluating steric effects which in several cases has given results of comparable accuracy.

We first define a formalism which, like transition state theory, is a thermodynamic model

$$A = B \longrightarrow C \qquad (1)$$

A designates reactants, B some intermediate structure, and C products. Superficially this may appear to be nothing more than a restatement of the transition-state concept, for it is commonly assumed that calculations cannot succeed unless B is a really good model of the transition state.

There are indeed reactions for which B must be the transition state, but the point of the formalism is that this is not at all a general requirement. Suppose that we are comparing examples of a cyclization reaction where there are large rate differences due to remote steric factors. It should be possible to discover many working models for B any one of which could represent reasonably well the relative differences in steric energies between reactants and transition states but none of which was a really accurate model of the transition state. Other examples are to be found among the successes of linear free energy relationships. In these reaction series the structure of B need not even have been clearly defined. Further examples are presented below. It is also possible to state the corollary that we are not justified in assuming that a given model B is a good representation of the transition state just because it gives a good rate correlation.

We do not claim originality for the approach, but we do believe that specific recognition of the basis of this formalism will lead to more fruitful treatment of reaction models. We shall now apply the formalism to the treatment of steric factors, but clearly the formalism is general and applicable to other effects as well.

To implement the formalism for treatment of steric effects, we must define precise structures for the B_i and we must find a way to calculate the free energy change from A_i to B_i. In most cases we cannot hope to find adequate thermodynamic values even for reactants, and the B_i will not generally represent stable molecules. Developments in molecular mechanics and in related parameterized computations hold great promise.[8–14] For the present we propose to use hydrocarbon models for the A_i and B_i in the calculation of relative steric effects. The justification for this approximation is that for many reactions the hydrocarbon part of the molecule is responsible for most of the steric effect. With some caution we can go further and use methyl groups as surrogates for such heteroatoms as oxygen. As in all uses of models their utility will depend on the extent to which they give a reliable account of experiments. If the models prove generally useful, then the approximations are justified. If not, then we must search further.

To calculate steric hindrance in the classical example of ester hydrolysis, eq 2, we shall postulate that the
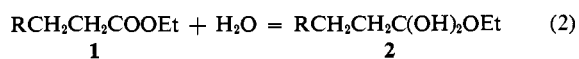
$$RCH_2CH_2COOEt + H_2O = RCH_2CH_2C(OH)_2OEt \qquad (2)$$
$$\mathbf{1} \qquad\qquad\qquad\qquad \mathbf{2}$$

total steric effect will be represented in going from starting ester **1** to tetrahedral intermediate **2**. As hydrocarbon models, we will use the isoalkanes **3** as the

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analogs of the esters and neoalkanes **4** as the analogs of

$$RCH_2CH_2CH(CH_3)_2 + CH_4 = RCH_2CH_2C(CH_3)_3 + H_2 \quad (3)$$
$$\mathbf{3}\mathbf{4}$$
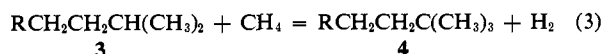
the tetrahedral intermediates **2**. The assignment of tetrahedral intermediate to B is relatively conventional, but the formalism does not require this to be a close representation of the transition state. In this reaction it is reasonable to suppose that the transition state is not much more compressed than B, and that the representation should be quite good.

Free energies of formation of the necessary hydrocarbon models are available in standard tables.[15] Results are presented in Table I as double differences using

Table I. Hydrocarbon Models of Steric Effects in Ester Hydrolysis

R^a	$-\Delta\Delta G_{298}{}^b$	$\log k_{rel}{}^c$ calcd	$\log k_{rel}{}^d$ obsd
H–	$(1.7)^e$	$(1.0)^e$	1.24
	α-Series		
CH_3–	0	0	0
CH_3CH_2	0.11	0.07	−0.07
$(CH_3)_2CH$–	−0.65	−0.39	−0.47
$(CH_3)_3C$–	−2.89	−1.72	−1.54
	β-Series		
CH_3CH_2	0.11	0.07	−0.07
$CH_3CH_2CH_2$	0.13	0.08	−0.36
$(CH_3)_2CHCH_2$–	−1.18	−0.70	−0.93
$(CH_3)_3CCH_2$–	−3.51	−2.08	−1.63

^{a} $RCOOEt$, $RCH(CH_3)_2$. ^{b} From ref 15. ^{c} $-\Delta\Delta G/2.3RT$ with $t = 70°$. ^{d} Reference 16. ^{e} From molecular mechanics V_s steric values (2(isobutane)–propane–neopentane).

ethyl acetate (isobutane to neopentane) as the reference compound. The $\Delta\Delta G$ values have been converted to relative rates at 70° to give calculated $\log k_{rel}$ in column 3 and these are intended to reproduce the observed values in column 4,[16] which they do to within a factor of 2.2 out of 40, excluding the formic ester. We regard this agreement as good as can be expected until more detailed computations can be made, and it certainly is suitable for many purposes.

Several comments are in order. It turns out that roughly the same results are obtained from $\Delta\Delta H_{298}$ or from $\Delta\Delta G_{400}$. Hence entropy effects largely cancel. Actually the free energy values pertain to the gas phase, but it is to be expected that free energies of solution will almost exactly cancel in the double difference. And finally, the reason why the tables cannot be used for formic esters is that the free energy change computed in eq 3 involves bond hybridization and other factors as well as steric factors. As long as all formal changes are identical, these other factors will largely cancel. But the model for the formic acid base converts propane to isobutane where a secondary hydrogen is replaced by methyl while in all other cases a tertiary hydrogen is replaced by methyl. We give an approximate value in parentheses based on a molecular mechanics computation using the Allinger 1971 "force field."[11] Since this represents a $\Delta\Delta H$ term, it is actually not exactly comparable.

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Quantitative Predictions of Steric Acceleration

Sir:

We have proposed a thermodynamic formalism which serves as a guide to devising models for calculating effects of structure on reaction rates.[1] We have successfully used hydrocarbon models in calculating steric retardation of ester formation. This same approach gives a good account of steric accelerations in cyclizations to lactones without invoking special reaction trajectories or "orbital steering."[2,3] Koshland's group has provided interesting kinetic data for cyclizations covering a rate range of more than 10,000. We have computed the magnitudes of steric effects in these reactions.

In the present study we have used two hydrocarbon model systems, eq 2 and 3, for lactone formation, eq 1.
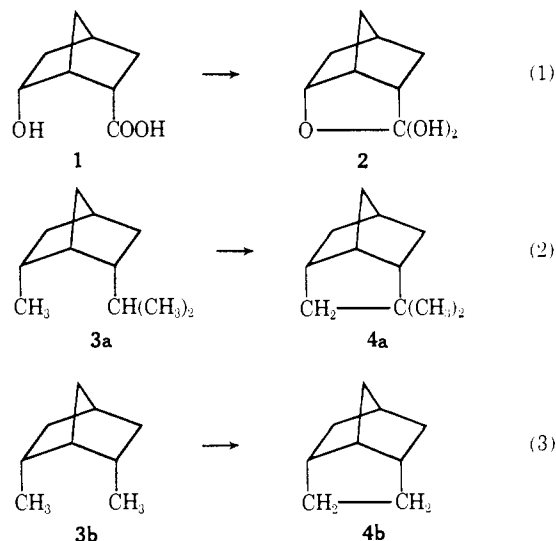
As for ester hydrolysis we have taken the tetrahedral intermediate **2** as the model for B in the formalism.[1] Hydrocarbon models **3** are used to represent the hydroxy acid **1** and hydrocarbon models **4** represent **2**. It is our hope that the steric energy difference **3a** → **4a** and **3b** → **4b** will reflect quantitatively most of the steric energy differences of **1** → **2** and that the latter will account for the observed relative rates.

Since thermodynamic data are not available for all of the hydrocarbon models, we have calculated steric en-

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