worked up as above. The calculations were based on the middle methylene in the propyl group.

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Registry No.—1, 69897-69-4; 2, 3010-81-9; 3, 69897-70-7; 4, 69897-71-8; 6, 49757-42-8; *p*-bromoanisole, 104-92-7; methyl *p*-anisate, 121-98-2; ethyl mercaptan, 75-08-1; sodium ethoxide, 141-52-6; *n*-propanethiol, 107-03-9.

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Multiparameter Optimization Procedure for the Analysis of Reaction Mechanistic Schemes. Solvolyses of Cyclopentyl *p*-Bromobenzenesulfonate

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Through the use of steady-state equations, the isotope rate effects and product yields for the solvolysis of cyclopentyl *p*-bromobenzenesulfonate and its α-*d*, cis-β-*d*, trans-β-*d*, and β-d_4 analogues in eight different ethanol–water, trifluoroethanol–water, and hexafluoroisopropyl alcohol–water solvents have been quantitatively fitted to a reaction mechanistic scheme involving two ion-pair intermediates. The number of adjustable mechanistic parameters is reduced by the assumption that the isotope effects on the various single steps of the mechanism are solvent independent and by the assumption that isotope effects on certain of the steps are identical. The simplex method was used to select the best values for the ion-pair partitioning ratios in each solvent and the best values for the isotope effects on the various steps of the mechanism. In general, the calculated results fit the experimental observations well within the expected experimental error. The single step isotope effects seem well-determined ("rugged") and are close to the values previously determined from observations on other secondary sulfonates. The secondary β-*d* effects on proton elimination from the tight ion pair suggest a twisted-envelope transition state structure. The mechanism will not fit satisfactorily unless significant fractions of ion-pair return are allowed in most of the solvents. The mechanism fits the results without the necessity of postulating nucleophilic solvation of the ion-pair intermediate. We believe that the approach used to fit the experimental observations to the reaction mechanistic scheme is novel and of general utility.

In earlier papers, α- and β-deuterium rate effects, product distributions, and the stereochemistry of elimination and substitution in the solvolysis of cyclopentyl *p*-bromobenzenesulfonate (I) in a series of solvents of varying nucleophilicity and polarity have been reported.[1] These results have been interpreted *qualitatively* and *semiquantitatively* in terms of a common mechanism involving two ion-pair intermediates. The influences of solvent changes on the isotope effects and product yields were rationalized on the basis of reasonable shifts in the relative rates of the various steps in the common mechanism, it being assumed that the isotope effects on the individual mechanistic steps were approximately solvent independent. In this paper, we apply a newly developed, versatile technique, which we believe is of general utility, to the *quantitative* fitting of all of these data to the proposed mechanism.

The general problem in the quantitative fitting of a reaction to a branched mechanistic scheme, such as that given below, is that in any solvent there are more unknowns than there are observable results which can be used to define them. With a given set of results, one then seeks to alter the system in some way which provides more information, for example, by a change in the solvent or by modification of the reactant with a substituent. However, since substituent and solvent changes perturb the free energies of reactants, intermediates, and transition states in a variety of ways that are difficult to account for, the relative rates of all of the single step processes of the reaction scheme change; in principle, the problem is not simplified, although linear free energy relationships can be used to give, for example, rate–product correlations.[2] However, isotopes constitute a class of substituents with properties uniquely favorable for the study of reaction mechanisms both from a theoretical and an operational standpoint.[3a]

Experience indicates that α- and β-deuterium rate effects in solvolytic reactions do not strongly depend on solvent change except when the change causes a shift in mechanism

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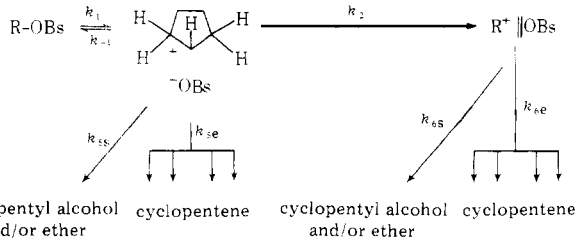
that in turn changes the extent of carbonium ion orbital vacancy in the transition state.[3] Thus, if (1) the isotope effects on the individual steps of the reaction scheme can be assumed to be the same in each solvent and if (2) the number of branches needed to specify the reaction scheme are fewer than the number of independent kinetic isotope effects and product yields which can be observed, then the number of known parameters in the problem can be increased faster than the number of unknown parameters by examining the reaction in additional solvents. The multi-solvent study also has the advantage of providing additional information about the mechanistic parameters through the use of linear free-energy correlations.

As we will show in detail below, the pooling of all of the data for solvolysis of cyclopentyl *p*-bromobenzenesulfonate from eight different solvents provides, under the assumption of the solvent independence of isotope effects on individual reaction steps, a sufficient number of experimentally observed quantities so as to *more than determine* the mechanistic parameters needed to describe all of the reactions. Thus, the problem is to select a set of mechanistic parameters which will, through the application of steady state and other pertinent equations, allow the best fit of calculated reaction results to those actually observed.

Procedure and Methods

Our previously published qualitative interpretation indicates that the simplest reaction scheme which should apply for all of the solvolyses of the subject compound so far examined is as follows:[1]



The tight ion pair is the key intermediate for reaction in all solvents, 70, 80, 90, 96, and 100 vol % ethanol–water (70E–100E), 70 and 97 wt % trifluoroethanol–water (70T, 97T), and 90 wt % hexafluoroisopropyl alcohol–water (90H); it is partitioned among return (via k_{-1}), substitution (via k_{5s}), elimination (via k_{5e}) and formation of the solvent separated ion pair (via k_2). Elimination is divided into anti and syn components, k_{5et} and k_{5ec}, respectively, each of which may involve either one of two protons. Products are also derived from the solvent separated ion pair if k_2 is significantly large, but return from the solvent separated ion pair is not allowed in this scheme. In each solvent, the mechanism for the H compound may be quantitatively specified by six reaction rate ratios which define the partitioning of the two ion pairs. The notation for this is indicated in part A.1 of Table I. The mechanism for the α-deuterium-substituted reactant can be specified for each solvent in terms of the six partitioning ratios for the hydrogen compound and six isotope effects on the individual steps, according to the notation given in part A.2a of Table I. For the cis- and trans-2-*d* reactants, 12 isotope effects for each must be specified; four of these are analogous to the four for the α-*d* compound, but four more are needed to specify the primary and three for the secondary effects involved in each of the two eliminations (via k_{5e} and k_{6e}).

Thus, the total number of relevant mechanistic parameters needed to define the mechanism for eight solvents is:

(6 partitioning ratios) 8 + 30 single step isotope effects = 78

This number can be effectively and drastically reduced by making three assumptions about the isotope effects in addition to their assumed solvent independence. The first additional assumption is that the analogous isotope effects for attack on the solvent separated ion pair and on the tight ion

Table I. Notations

A. Mechanistic Parameters[a]

1. Partitioning factors, one set for each solvent (defined for the undeuterated compound)
   $f_2 = k_2/(k_2 + k_{5s} + k_{5e})$; $f_{5s} = k_{5s}/(k_2 + k_{5s} + k_{5e})$
   $f_{5e} = k_{5e}/(k_2 + k_{5s} + k_{5e})$
   thus, $f_2 + f_{5s} + f_{5e} = 1$
   $f_{-1} = k_{-1}/(k_2 + k_{5s} + k_{5e})$
   $f_{6e} = k_{6e}/(k_{6s} + k_{6e})$
   $y_5 = k_{5et}/k_{5ec}$ (the ratio of rates for anti to syn elimination)
   $y_6 = k_{6et}/k_{6ec}$ (the ratio of rates for anti to syn elimination)
2. Single-step isotope effects (generally assumed to be solvent independent)[b]
   a. alpha deuteration
      $r_1^{\alpha} = k_1^{H}/k_1^{\alpha d}\cdot k_2^{\alpha\text{-}d}/k_2^{H}$
      $r_{-1}^{\alpha} = k_{-1}^{H}/k_{-1}^{\alpha d}\cdot k_2^{\alpha\text{-}d}/k_2^{H}$
      $r_{5s}^{\alpha} = k_{-1}^{H}/k_{-1}^{\alpha d}\cdot k_2^{\alpha\text{-}d}/k_2^{H}$
      $r_{5e}^{\alpha} = k_{5e}^{H}/k_{5e}^{\alpha d}\cdot k_2^{\alpha\text{-}d}/k_2^{H}$
      $r_{6s}^{\alpha} = k_{6s}^{H}/k_{6s}^{\alpha d}$
      $r_{6e}^{\alpha} = k_{6e}^{H}/k_{6e}^{\alpha d}$
   b. cis β-deuteration and trans β-deuteration
      defined by analogy with those for α-deuteration
      $r_1^{c}, r_{-1}^{c}, r_{5s}^{c}, r_{6s}^{c}; r_1^{t}, r_{-1}^{t}, r_{5s}^{t}, r_{6s}^{t}$
      defined for the elimination step
      a_5^{c} = isotope effect on k_{5e} (relative to the effect on k_2) when the deuterium is being eliminated
      b_5^{c} = isotope effect on k_{5e} (relative to the effect on k_2) when the hydrogen geminal to the deuterium is being eliminated
      c_5^{c} = isotope effect on k_{5e} (relative to the effect on k_2) when the hydrogen being eliminated is situated at the opposite β position, trans to the deuterium
      d_5^{c} = isotope effect on k_{5e} (relative to k_2) when the hydrogen being eliminated is situated at the opposite β position cis to the deuterium.
      $a_6^{c}, b_6^{c}, c_6^{c}, d_6^{c}, a_5^{t}, b_5^{t}, c_5^{t}, d_5^{t}, a_6^{t}, b_6^{t}, c_6^{t}, d_6^{t}$ are defined analogously

B. Reaction Results (One Set for Each Solvent)

1. Product yields
   $F_e^{H}, F_e^{\alpha}, F_e^{c}, F_e^{t}, F_e^{d_4}$: the fractions of elimination for the hydrogen, α-*d*, cis-2-*d*, trans-2-*d*, and β-d_4 compounds, respectively
2. Isotope rate effects
   $k_H/k_{\alpha\text{-}d}$, $k_H/k_{c\text{-}d}$, $k_H/k_{t\text{-}d}$, k_H/k_{d_4}: isotope effects on solvolysis rates for the α-*d*, cis-2-*d*, trans-2-*d*, and β-d_4 compounds, respectively
3. Label yields in cyclopentene
   d_0^{c}, 1-d^{c}, 3-d^{c}: the fractions of the total cyclopentene yield from the cis-2-deuterated cyclopentyl *p*-bromobenzenesulfonate which are undeuterated, 1-deuterated, and 3-deuterated, respectively.
   d_0^{t}, 1-d^{t}, 3-d^{t}: the corresponding fractions from the trans-2-deuterated reactant.

[a] *f* generally refers to "fraction" in one branch relative to the total *forward* reaction (note that f_{-1} can be greater than one); subscripts refer to the reaction step; *r* indicates isotope effects; and superscripts refer to the position of deuteration in the reactant: α for α-*d*, c for *cis*-β-*d*, t for *trans*-β-*d*, d_4 for the β-d_4 compound; *y*'s are anti/syn ratios for elimination. [b] The effects on the reactions from each of the two ion pairs are only significant *relative* to one another. Those for the tight ion pair reactions (k_{-1}, k_2, k_{5s}, k_{5e}) are defined relative to the effect on k_2. It seems likely that the effects on k_2 are unity and that the quoted effects on the other reactions apply in the absolute sense, at least approximately. The effects on k_{6s} and k_{6e} are only significant as their ratio affects the product yields because there is no provision in the present scheme for return from the solvent-separated ion-pair stage.

pair are the same, e.g., $r_{6s} = r_{5s}$, etc.; this reduces the number of parameters by 12. The second assumption is that the analogous isotope effects are the same for the cis-β-d as for the trans-β-d compound; this further reduces the number of parameters by seven. Third, because similar transition state structures would be involved, it is expected that isotope effects on return and those on the other nucleophilic attacks on the carbonium ion fragment are of very similar size. Thus, r_{-1}^{α} is expected to be similar to r_{5s}^{α} and r_{-1}^{c} to r_{5s}^{c}, so that the number of different isotope effects required can be reduced by two more to nine.

To recount, the 30 isotope effects on the individual steps can be reduced to nine different numerical values as follows:

1, $r_{1\alpha}$; 2, $r_{-1}^{\alpha} \equiv r_{5s}^{\alpha} \equiv r_{6s}^{\alpha}$; 3, $r_{5e}^{\alpha} \equiv r_{6e}^{\alpha}$; 4, $r_1^{c} \equiv r_1^{t}$; 5, $r_{-1}^{c} \equiv r_{-1}^{t} \equiv r_{5s}^{c} \equiv r_{6s}^{c} \equiv r_{5s}^{t} \equiv r_{6s}^{t}$; 6, $a_5^{c} \equiv a_5^{t} \equiv a_6^{c} \equiv a_6^{t}$; 7, $b_5^{c} \equiv b_5^{t} \equiv b_6^{c} \equiv b_6^{t}$; 8, $c_5^{c} \equiv c_5^{t} \equiv c_6^{c} \equiv c_6^{t}$; and 9, $d_5^{c} \equiv d_5^{t} \equiv d_6^{c} \equiv d_6^{t}$.

The partitioning ratios can also be reduced by certain reasonable assumptions. These are (a) that the anti/syn elimination ratio for the solvent-separated ion pair, y_6, is solvent independent and (b) that the anti/syn ratio y_5 has one value for all ethanol–water mixtures, another value for the two trifluoroethanol–water mixtures, and a third value for the HFIP–water mixtures.[1b,e] This reduces the total number of partitioning fractions by 11, so that the total number of different numerical values for the parameters needed to specify all results is 37 partitioning ratios plus 9 single-step isotope effects or 46. This would appear to be near the minimum number of different parameters that could reasonably be expected to give an approximate fit. As will be seen below, our method of fitting allows one, in response to the quality of the overall fit, to increase or reduce the number of independent parameters determined.

The number of observed reaction results includes, in principle, for each solvent: the fraction of elimination for the hydrogen and for the α-d, cis-2-d, trans-2-d, and β-d_4 compounds (the fraction of substitution is considered to be a complementary *dependent* variable); the isotope rate effect for each of the four deuterium compounds; and for the cis-2-d and trans-2-d reactants, two independent ratios giving the fractions of cyclopentene-*1*-d and cyclopentene-*3*-d of the total cyclopentene yield (the fraction of cyclopentene-d_0 is considered to be a complementary dependent variable). Thus, for each solvent there are potentially 13 observable results for an eight-solvent total of 104. Since not all observations were made in all solvents (see Table II), the actual number used is 88. This number can be increased by 7 to 95 if one assumes that the *ionization* rate (k_1) of cyclopentyl p-bromobenzenesulfonate should have the same *logarithmic* dependence on solvent as does the *reaction* rate of pinacolyl p-bromobenzenesulfonate. This is closely analogous to an m–Y correlation[4] but uses pinacolyl p-bromobenzenesulfonate as the reference reactant rather than *tert*-butyl chloride. Thus, the system which requires 46 parametric values to fit 95 experimental observations would appear to be adequately overdetermined to allow not only the calculation of the parameters but some internal checks on their reliability.

In order to select the values of the parameters, 15 equations are needed to calculate the 15 independently observable quantities in each of the eight solvents. For calculating the four isotope effects, we use equations derived from the steady state assumption[5] (see Supplementary Material for examples). For calculating yields, we use equations analogous to those of the steady state method, while the solvolysis rate correlation uses the familiar logarithmic relationship[4] (see Supplementary Material).

In order to optimize the fit of the 46 parameters to the 95 experimental observations, one first needs a measure of the quality of the fit; for this we use the sums of the squares of the differences between the observed and calculated values ("residuals") for the reaction results. Except for the rate ratios calculated from the linear free-energy relationships, we do not use differential weights for the residuals, because the other observed reaction results are all isotope effects or reaction yield fractions which have expected errors in the range of 0.01 to 0.02. For the log k_1(solvent)/k_1(80E) values, the residuals (the differences between the *logarithms* of the calculated and observed rate ratios) are squared, multiplied by 0.1, and added to the grand sum of the squares of the residuals (ΣR^2). The 46 reaction parameters were first selected by inspection, transfer, or trial and error and then optimized by the simplex method.

The simplex method of optimization as introduced by Spendley et al.[6] and later modified by Nelder and Mead[7] has been demonstrated to be a powerful tool for fitting parameters related to a variety of kinds of experiments.[8] To our knowledge, this is the first application of the method in the correlation of rates, product distributions, and effect of isotopic substitution on both rates and product distributions.

The simplex optimization method derives its general utility from its lack of constraints on the definition of the response. Thus, it is not necessary to derive complex analytical expressions as are required in the various gradient techniques of optimization.[9] The definition of the response can be quite flexible. For instance, changes in a particular model, or insertions of additional experimental observations, or additional constraints on the problem such as linear free-energy relationships can be incorporated simply by adding additional equations to the set defining the response. It is also possible to study the effects of fixing certain of the input parameters while allowing the rest to vary. Thus, one is free to choose as many or as few response evaluating parameters or input parameters as are necessary to define the system.

The reaction scheme which we use here represents a subset of mechanisms within the larger set represented by the more general scheme we have discussed earlier.[3] This subset is further restricted by the assumptions we have made about the approximate equalities among various single-step isotope effects. A particular mechanism within this restricted subset is specified by a given set of partitioning ratios for the two intermediates. When the simplex optimization procedure is applied, the first question to be answered is whether or not the scheme adequately describes the reactions. We will conclude that it does if we find a reasonable set of parameters that allow the equations to predict the results within experimental error, bearing in mind also that the assumptions about relationships among the single step isotope effects are approximations.

If a satisfactory fit is achieved, two additional questions arise. First, has the exact minimum in the response surface been achieved? With such a large simplex as ours, this question may be difficult to answer, but it is not of much mechanistic significance if the fit obtained is well within experimental error. Second, and more significant, we wish to know how well the various parameters are determined by the experiments. This is, in the first place, an involved question simply because there are 46 different parameters. One can get a "feel" for this by running simplex calculations with different starting values to see how closely the parameters are reproduced. For any *particular* parameter of interest, such as the return ratio, one can assign a series of fixed values, allow the simplex process to optimize the other parametric values, and determine the resulting quality of fit. The scheme can, of course, be further tested by requiring it to fit additional experimental results as these are obtained. Experiments involving reactions with partitioning ratios significantly different from those already used would be of particular significance.

If the restricted scheme does not produce a satisfactory fit of the experimental results, one should consider first whether

Table II. Reaction Parameters which Give the Best Fit with Different Assumed Restrictions

parameters[a]	calcd values[b] for the following calcn no.						
	1	2	3	4	5	6	7
r_{-1}^{a}	1.137	1.132	1.135	1.129	1.153	1.136	1.122
r_1^{a}	0.916	0.898	0.911	0.894	0.870	0.86	0.890
r_{5e}^{a}	0.996	0.985	0.992	0.981	0.930	0.93	0.980
r_1^{c}	1.11	1.112	1.10	1.093	1.132	1.121	1.099
r_1^{t}	*c*	*c*	1.128	1.139	*c*	*c*	*c*
r_{-1}^{c}	0.92	0.899	0.91	0.905	0.907	0.892	0.889
r_{-1}^{t}	*d*	*d*	0.92	0.923	*d*	*d*	*d*
a_5	1.86	1.78	1.857	1.840	1.82	1.77	1.77
b_5	0.88	0.85	0.870	0.859	0.85	0.832	0.85
c_5	1.04	1.03	1.036	1.005	0.99	0.982	0.984
d_5	0.87	0.83	0.869	0.866	0.86	0.832	0.856
y_5, E[e]	1.327	1.31	1.308	1.307	1.34	1.33	1.35
y_5, T[e]	0.314	0.306	0.304	0.323	0.352	0.316	0.332
y_5, H[e]	0.232	0.204	0.212	0.200	0.264	0.213	0.247
y_6[f]	1.216	1.16	1.183	1.401	1.77	1.14	1.14
m_1[g]	0.739	0.852	0.711	0.936[i]	0.651	0.852	0.878
corr coeff[h]	0.835	0.999	0.839	0.999[i]	0.997	0.991	1.000
f_1 70E	51.05	2.85	50.35	5.54	0.201	1.40	11.93
80E	21.56	2.22	18.16	3.91	0.100	1.000	10.00
90E	2.31	1.53	2.50	2.27	0.124	0.553	7.19
96E	0.968	1.00	1.22	1.91	0.045	0.301	5.46
100E	1.077	0.750	1.34	1.08	0.076	0.144	4.82
70T	13.50	14.67	11.42	12.10	1.85	7.61	52.3
97T	6.08	35.6	6.20	48.45	5.95	20.8	132
90H	37.64	68.1	38.28	144.07	10.05	37.5	250
f_2 70E	0.224	0.345	0.212	0.339	0.970	0.358	0.319
80E	0.018	0.154	0.038	0.139	0.248	0.162	0.155
90E	0.022	0.094	0.021	0.051	0.064	0.091	0.087
96E	0.043	0.106	0.017	0.034	0.240	0.083	0.097
100E	0.031	0.023	0.010	0.015	0.040	0.022	0.041
70T	0.856	0.579	0.858	0.701	0.831	0.541	0.592
97T	0.090	0.052	0.097	0.052	0.052	0.068	0.099
90H	0.220	0.233	0.240	0.222	0.219	0.241	0.244
f_{5e} 70E	0.212	0.186	0.218	0.197	0.183	0.186	0.192
80E	0.273	0.261	0.271	0.264	0.261	0.261	0.258
90E	0.228	0.221	0.228	0.228	0.222	0.220	0.218
96E	0.177	0.161	0.181	0.170	0.160	0.165	0.165
100E	0.129	0.133	0.131	0.135	0.135	0.125	0.130
70T	0.141	0.255	0.132	0.225	0.178	0.244	0.246
97T	0.754	0.753	0.751	0.757	0.750	0.744	0.743
90H	0.782	0.785	0.767	0.797	0.787	0.781	0.781
f_{6e} 70E	0.038	0.101	0.019	0.077	0.031	0.084	0.102
80E	0.053	0.044	0.020	0.030	0.015	0.048	0.057
90E	0.030	0.025	0.016	0.072	0.110	0.019	0.038
96E	0.032	0.086	0.006	0.146	0.045	0.098	0.102
100E	0.038	0.068	0.014	0.097	0.128	0.062	0.076
70T	0.309	0.255	0.323	0.257	0.265	0.291	0.259
97T	0.115	0.120	0.120	0.058	0.104	0.107	0.117
90H	0.136	0.067	0.142	0.067	0.172	0.063	0.062
ΣR^{2}[j]	0.0157	0.0162	0.0135	0.0166	0.0363	0.0167	0.0184
no. of errors[k]							
≥0.02	11	11	6	11	24	13	16
≥0.03	3	2	3	1	7	3	3
≥0.04	0	0	0	0	3	0	0

[a] Most symbols are defined in Table I; exceptions are footnoted. [b] Calculation 1: No LFER required for k_1. Separate values for r_1^t and r_{-1}^t are not allowed. Other isotope effects are related as given in the text. Calculation 2: Same restrictions as calculation 1 except that an LFER of k_1's with solvolysis rates for pinacolyl *p*-bromobenzenesulfonate of selected slope m_1 was required to be fit. Calculation 3: Same restrictions as calculation 1 except that r_1^t and r_1^c were allowed to have different values as were r_{-1}^t and r_{-1}^c. Calculation 4: Same restrictions as for calculation 3 except that k_1 and k_1f_2/f_{-1} were *each* separately required to fit the LFER (described for calculation 2 above) for the ethanol–water solvents only. Calculations 5, 6, 7: The same restrictions as for calculation 2 except that return factors f_{-1} for 80E were required to be 0.1, 1.00, and 10.00 respectively. [c] Fixed to have the same value as r_1^c. [d] Fixed to have the same value as r_{-1}^c. [e] Ratio of anti/syn elimination from the tight ion pair in ethanol solvents (E), trifluoroethanol solvents (T), or 90% hexafluoroisopropyl alcohol (H). [f] Ratio of anti/syn elimination from the solvent-separated ion pair. [g] Slope of the correlation line in the plot of log k_1's vs. log of solvolysis rate constants for pinacolyl *p*-bromobenzenesulfonate. [h] Correlation coefficient for the plot described in *g* above. [i] Value for LFER for E–W solvents only; m_1 and the correlation coefficient for all solvents are 0.884 and 0.994; m_2 and the correlation coefficients are 1.261 and 0.998 for the E solvents and 0.656 and 0.794 for all solvents. [j] Sums of the squares of the differences between calculated and observed experimental results. [k] The number of experimental results differing from the calculated value by the amount indicated.

to relax some of the assumptions about the equalities among single step isotope effects and second whether the scheme should be further generalized by the inclusion of additional mechanistic pathways such as the S_N2 reaction or return from the solvent-separated ion pair. These latter variations would, of course, require that the steady-state rate and product equations be reformulated.

Results

Table II lists the parameters and ΣR^2 responses obtained for a series of simplex calculations based on slightly differing sets of constraints. Also included at the bottom of each column are the number of reaction results which are calculated with differences of ≥ 0.02, ≥ 0.03, and ≥ 0.04 from the experimentally determined values. Column 1 gives the parameters obtained from a calculation in which all parameters (except m_1) were allowed to vary. Column 2 gives the results obtained when a linear free-energy relationship of variable slope, m_1, for the ionization rate, k_1 [which is equal to the observed first-order rate constant multiplied by $(f_{-1} + 1)$], relative to the solvolysis rates for pinacolyl *p*-bromobenzenesulfonate is included as an additional restraint. The responses for the two calculations are not very different. The $k_{obsd}(f_{-1} + 1)$ values calculated from the column 1 results fit the linear free-energy relationship with an m_1 value of 0.739 and a relatively poor correlation coefficient of 0.835; on the other hand, the column 2 results give an m_1 value of 0.852 and a correlation coefficient of 0.999. The linear free-energy relationship imposes constraints on the various return factors, f_{-1}. The isotope effects are not particularly sensitive to the magnitude of return so long as moderate but varying amounts are allowed in the ethanol–water solvents and larger amounts are allowed in the fluorinated alcohol solvents. Thus, the return factors are not very precisely determined by the isotope effects alone.

For the column 1 calculations, six of the eleven calculated values which differ from the observed results by 0.02 or more are isotope effects for the cis-β-*d* and trans-β-*d* compounds. We therefore carried out the calculations of column 3 wherein r_1^c and r_1^t were allowed to have *different* values as were r_{-1}^c and r_{-1}^t. The best fit parameters are very nearly the same for the two calculations; the ΣR^2 was reduced from 0.0157 (column 1) to 0.0135 (column 3) and the number of results in error by 0.02 or greater was reduced by five including three of those six which involved isotope rate effects for *cis*-β-*d*-I or *trans*-β-*d*-I. The r_1^c and r_1^t values which were both 1.11 in the first calculation assumed values of 1.10 and 1.128 in calculation 3 while r_{-1}^c and r_{-1}^t changed from 0.92 to 0.91 and 0.92. Thus, the extra degrees of freedom for the calculation gave parametric values only a little different but with a significantly improved fit. The LFER correlation was about the same as for column 1. In another calculation, not shown, the same restrictions as in column 3 were used, except that the primary isotope effect a_5 was allowed to have one value for ethanol–water solvents and a different value for TFE–W and HFIP–W solvents, because different bases are presumably involved in proton abstraction in these two different sets of solvents, and one might well expect this to cause different primary effects. However, the a_5 value of 1.857 for column 3 was only changed to 1.81 and 1.89 for the two sets of solvents, ΣR^2 was reduced from 0.0135 to 0.0127, and the number of results with errors ≥ 0.03 was reduced from three to one. The improvement seemed marginal. For calculation 4, we used the same restrictions as for calculation 3 but required a linear free-energy relationship fit for *both* k_1 (the ionization rate) and k_1f_2/f_{-1} (the overall rate of reaction via the solvent-separated ion pair) for the reactions in 70E to 100E only, since the well-known phenomenon of "dispersion" generally prevents correlations of this type from being as precise if solvents of widely differing acidities are used. In the E–W solvents good correlations were achieved for both k_1 and k_2k_1/k_{-1} processes with slopes $m_1 = 0.936$ and $m_2 = 1.26$ indicating a greater sensitivity to solvent polarity in the second step than in the first step. The correlations for all solvents (even though the simplex was not required to fit the values for the fluorinated alcohol solvents) were reasonably good for k_1 (m_1, 0.884, correlation coefficient 0.994) but not for k_2k_1/k_{-1} (m_2, 0.655, correlation coefficient 0.794). A plot of the log k_1f_2/f_{-1} values vs. log k_{obsd} for pinacolyl *p*-bromobenzenesulfonate shows that 70T and the E–W solvents fit very well but that the values for 97T and 90H fall significantly below the line.

Columns 5, 6, and 7 give results calculated on a basis similar to those for column 2 except that f_{-1} for 80E was not varied as a parameter but arbitrarily set at values of 0.1, 1.00, and 10, respectively, to determine how variations in the return factors would affect the fit. It is obvious that the results cannot be adequately accounted for by the present mechanism with a return factor for 80E as low as 0.1. Results obtained using a return factor of 0.001 fit much less well and are not given in Table II. Basically, the variations in overall rate due to the incursion of a primary isotope effect on elimination cannot be accounted for if return of the ion pair is not allowed. On the other hand, the calculations with fixed return factors in 80E of 1, 10, and 100 (not shown in Table II) give almost as good a response as the results of column 2 where the return factor in 80E of 2.22 is selected to give the best fit. It would appear that a return factor for 80E of between 1 and 10 is best, but larger values probably cannot be ruled out. In comparing columns 1, 2, 3, 4, 6, and 7, one can see that the variations in the single step isotope effects, the *anti*/*syn* elimination ratios, and even the reaction fractions are not large; we judge that this is indicative of the accuracy with which these parameters are determined. Although they generally seem to be small, the values for F_{16e} are probably not determined very well because, except for solvent 70T, only fairly small proportions (f_2) of the solvolyses go to product through the solvent-separated ion pairs.

Table III compares the *observed* reaction results with those *calculated* using the Table II, column 1 parameters. The results using the parameters from columns 2, 3, 4, 6, and 7 are generally similar. None of the calculated results differ from the observed ones by as much as 0.04, only two differ by as much as 0.03, while eleven differ by as much as 0.02. Four of these eleven values with the worst fit are isotope effects for the cis or the trans deuterated reactant; as we indicate above, these appear to be in error because of our assumption in calculation 1 that the single-step isotope effects for the cis and trans deuterated reactants are identical; the fit is significantly better in calculation 3 where this restriction is relaxed. In view of this and in view of the fact that the effects for the ethanol solvents were observed at 40 °C, those for the TFE solvents at 30 °C, and those for the HFIP solvent at 25 °C, the overall fit seems remarkably good.

The fact that a satisfactory quantitative fit has been achieved indicates that within the limits of experimental error the assumptions made in reducing the number of different parameters were justified. Thus, it appears that the mechanism provides an adequate quantitative accounting of all of our results for cyclopentyl brosylate. In addition, it provides a framework for the correlation of new results for other solvents and other compounds.

From Table II, column 2, we see that the α-*d* effect on ionization (k_1) is 1.132, very similar to the value of 1.15–1.16 which we have observed for pinacolyl *p*-bromobenzenesulfonate in a variety of solvents and have previously associated with rate-determining formation of the tight ion pair.[3a,b,10] The two figures are even more comparable if one remembers that the cyclopentyl results refer to reactions at slightly higher

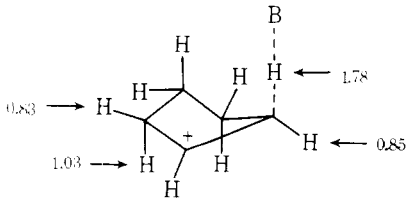
Table III. Reaction Results[a]

	solvent							
	70E	80E	90E	96E	100E	70T	97T	90H
$k_H/k_{\alpha\text{-d}}$								
obsd	1.180	1.150	1.140	1.150	1.150	1.222	1.222	1.230
calcd	1.178	1.163	1.153	1.147	1.145	1.208	1.208	1.232
R	0.002	−0.013	−0.013	0.003	0.005	0.014	0.014	−0.002
$k_H/k_{c\text{-d}}$								
obsd	1.140	1.130	1.130	1.130	1.100	1.216	1.285	1.353
calcd	1.161	1.148	1.134	1.125	1.121	1.223	1.272	1.330
R	−0.021	−0.018	−0.004	−0.005	−0.021	−0.007	0.013	0.023
$k_H/k_{t\text{-d}}$								
obsd	1.170	1.180	1.150	1.160	1.140	1.205	1.201	1.222
calcd	1.168	1.156	1.139	1.127	1.123	1.206	1.183	1.200
R	0.002	0.024	0.011	0.033	0.017	−0.001	0.017	0.022
$k_H/k_{\beta\text{-d}_4}$								
obsd	1.840	1.770	1.670	1.620	1.580	2.220	2.470	2.864
calcd	1.845	1.774	1.675	1.610	1.587	2.220	2.475	2.864
R	−0.005	−0.004	−0.005	0.010	−0.007	0.000	−0.005	0.000
1-d[c]								
obsd		0.334	0.334		0.334		0.160	0.131
calcd	0.328	0.337	0.337	0.336	0.335	0.239	0.151	0.120
R		−0.003	−0.003		−0.001		0.009	0.011
3-d[c]								
obsd		0.554	0.554		0.554		0.621	0.619
calcd	0.527	0.541	0.541	0.539	0.538	0.524	0.611	0.613
R		0.013	0.013		0.016		0.010	0.006
1-d[t]								
obsd		0.269	0.269		0.269		0.442	0.478
calcd	0.261	0.263	0.263	0.263	0.263	0.465	0.433	0.455
R		0.006	0.006		0.006		0.009	0.023
3-d[t]								
obsd		0.582	0.582		0.582		0.513	0.469
calcd	0.569	0.573	0.573	0.573	0.573	0.286	0.502	0.490
R		0.009	0.009		0.009		0.011	−0.021
F_e^H								
obsd	0.219	0.267	0.233	0.170	0.118	0.418	0.764	0.800
calcd	0.221	0.274	0.229	0.178	0.130	0.406	0.760	0.812
R	−0.002	−0.007	0.004	−0.008	−0.012	0.012	0.000	0.012
F_e^{-c}								
obsd	0.210	0.249	0.196	0.169	0.129	0.417	0.772	
calcd	0.210	0.258	0.215	0.167	0.121	0.391	0.753	0.809
R	0.000	−0.009	−0.019	0.002	0.008	0.026	0.019	
F_e^c								
obsd	0.212	0.249	0.221	0.165	0.117	0.358	0.738	
calcd	0.203	0.249	0.208	0.161	0.117	0.373	0.731	0.789
R	0.009	0.000	0.013	0.004	0.000	−0.015	0.007	
F_e^t								
obsd	0.191	0.238	0.198	0.141	0.118	0.351	0.721	
calcd	0.198	0.244	0.203	0.157	0.114	0.379	0.752	0.809
R	−0.007	−0.006	−0.004	−0.016	0.004	−0.028	−0.031	
$F_e^{d_4}$								
obsd	0.138	0.188	0.132	0.100	0.078	0.278	0.626	
calcd	0.127	0.153	0.125	0.095	0.067	0.259	0.627	0.728
R	0.011	0.035	0.007	0.005	0.011	0.019	−0.001	

[a] Values from calculation 1, Table II. See Table I for notations. The fractions of substitution F_s are $(1 - F_e)$ in each case. The fractions of nondeuterated cyclopentene in the total cyclopentene yields are [1 − (1-d) − (3-d)] in each case. Blanks indicate where experimental values were not observed. The label yields were determined on a combined olefin sample from the reactions in 80E, 90E, and 100E, and the same observed values are used for all three solvents.

temperatures. Similarly, the calculated β-*d* effect on k_1 (r_1^c, 1.112) is very similar to the value predicted (1.117) from the correlation of Sunko, Szele, and Hehre.[11] It should be emphasized that these cyclopentyl values are determined by an *unbiased* minimization procedure to give the best fit of the mechanism to the reaction results and are determined independently of the values for the other compounds with which we compare them. Furthermore, the value of r_1^c/r_{-1}^c, 1.132/0.898 or 1.26, is the value which should apply if the second step (k_2) is completely rate determining. We have previously suggested that the slightly lower value of 1.22–1.23 observed for the solvolysis of 2-adamantyl-2-*d* tosylate represents a typical α-*d* rate effect for a sulfonate ester solvolysis having k_2 as rate determining; it is possible that the value for the adamantyl derivative is a bit low because return may not completely dominate further reaction and k_2 may not be completely rate determining.[3c] The isotope effects in the elimination step are also of considerable interest. The primary effect, 1.78, is low, in the range generally observed in carbonium ion eliminations,[12] and suggests an early, carbonium ion like transition state. The secondary effects, however, contain a significant surprise which, we believe, informs us about the *conformation* of the cyclopentane ring during the process of proton elimination from the carbonium ion. First, the deu-

terium effect geminal to the eliminating hydrogen, k_5^c, is inverse, 0.85; this is understandable if it is realized that the calculated equilibrium β-d effect for ion-pair formation is 1.112/0.899 or 1.236 and that elimination of the geminal β-proton will necessarily push this hydrogen (or deuterium) into an orientation about 60° or more out of parallel with the vacant p orbital on the α carbon.[11,13] In this orientation nearly all of the isotope effect of the first step would be reversed.[11] If all of the isotope effect were lost, the inverse effect would be 1/1.236 or 0.809. The next thing to be noted is that one of the secondary effects on the opposite β-carbon atom is also inverse while the other is near unity or slightly normal. These values are mutually consistent because if one of these C–H bonds is forced away from parallel with the vacant p orbital, the other would be forced more toward parallel. The most interesting observation is that it is the opposite β hydrogen oriented trans to the eliminating proton which the isotope effect indicates is near parallel, while the cis hydrogen is indicated to be near perpendicular to the p orbital. Thus, the conformation must be a kind of twisted envelope as shown in the following formula with the calculated β-d effects *for the elimination step* indicated:



It is of interest to compare the solvolytic reaction scheme which we favor with the alternative one favored by Bentley and Schleyer.[14] These differing points of view basically continue one of the historic arguments of organic reaction mechanisms, namely, the argument concerning the nature of the mechanism(s) for solvolyses in the "borderline" region between classical S_N1 and classical S_N2 reactions. The two points of view have identified this borderline region as being characterized by either a mixture of mechanisms in varying proportions[15,16] or by a single hybrid mechanism defined by a spectrum of transition states of varying extent of solvent nucleophilic attachment.[17] The current dispute is, of course, on a somewhat more sophisticated level. We have proposed, following Winstein,[16] that there are basically four S_N substitution routes identified as involving nucleophilic attack on the reactant, the tight ion pair, the solvent-separated ion pair, and the free carbonium ion. Within each route, except the first, at least two different steps can be rate determining or partly rate determining. Thus, the potential for mixtures of mechanisms is greatly multiplied over that for the simple S_N1–S_N2 scheme. However, for the classical borderline reactions of simple secondary alkyl sulfonates in the usual aqueous alcohol solvents and in fluorinated alcohol solvents, the actual pathways seem to be largely limited to the following four: (1) S_N2, (2) rate-determining formation of the tight ion pair, (3) rate-determining nucleophilic attack on the reversibly formed tight ion pair, and (4) nucleophilic attack on the solvent-separated ion pair with the *formation* of the solvent-separated ion pair being rate determining. We also accept that for each rate-determining step there may be "reaction coordinate" effects which attend changes in reactivity[18] and which can be correlated by rules such as the ones formulated by Hammond[19] and by Thornton.[20] However, in solvolysis we do not believe that these transition state structural variations suffice generally to explain broad-scale changes in reactivity such as those which attend S_N type solvolyses on changing solvent from ethanol–water to TFE–water or HFIP–water mixtures. Bentley and Schleyer prefer to explain borderline solvolyses of secondary sulfonates in terms of a strongly nucleophilically solvent-assisted process which they designate as S_N2 (intermediate). This proposed mechanism involves the rate-determining formation of a nucleophilically solvated ion-pair intermediate which can be partitioned to various products but which does not undergo significant internal return. This hybrid mechanism postulate suggests that the variations of reaction properties with reactant structure and with solvent occur mainly through a virtually continuous possible range of variation in the extent of nucleophilic solvation of the ion-pair intermediate. They further propose that the α-d kinetic isotope effect varies inversely with the extent of nucleophilic solvation. They propose that nucleophilic solvation is negligible for 2-adamantyl sulfonate solvolyses in all solvents and that the observed α-d isotope effects in the range 1.22–1.24 correspond to rate-determining formation of the nonnucleophilically solvated 2-adamantyl toluenesulfonate ion pair.[14] They further propose that the α-d effects for 2-propyl p-toluenesulfonate vary roughly linearly with the degree of nucleophilic solvation, as measured by $\log k_s/k_c$, from a maximum of 1.22 in trifluoroacetic acid to ~1.06 in ethanol.[14b] They fail to comment on the α-d isotope effects for pinacolyl p-bromobenzenesulfonate, which are 1.15–1.16 in the whole range of solvents of ethanol–water to trifluoroacetic acid.[3a,b,10] Is this reaction assisted by solvent nucleophilicity? If so, why does the effect not vary with solvent? If not, why is the effect not more nearly the same as that for the 2-adamantyl sulfonates? The Bentley–Schleyer analysis indicates that cyclopentyl sulfonate solvolyses vary from nearly no solvent nucleophilic assistance in TFA and HFIP to strong assistance in ethanol (k_s/k_c = 1680). Our results show overall observed α-d isotope effects for this compound of ~1.15 in 80–100E, 1.18 in 70E, and 1.22–1.23 in 70T, 97T, and HFIP. This is not a smooth variation with $\log k_s/k_c$. Further, we do not believe that the Bentley–Schleyer mechanism without return can explain the large, noncumulative β-d effects or the correlation between β-d isotope effects on product yields and on reaction rates, both of which suggest rate-determining elimination.

On the other hand, the present analysis quantitatively explains all of the variations in α-d and β-d rate effects and product yields with the assumption that the isotope effects on the single steps of the mechanism are solvent independent; the observed effects change principally because the reaction course is shifted by solvent. The treatment also illustrates how internal return is necessary to explain the primary isotope effects on product ratios as well as rates and quantitatively accounts for the noncumulative nature of the β-d effects. Furthermore, the single-step α-d isotope effects are consistent with those shown in the solvolyses of 2-adamantyl and pinacolyl derivatives.

The hybrid mechanism adopts some of the attributes of the ion-pair mechanism through the postulate that even though covalent nucleophilic attack is strong enough to be significantly accelerating, it may nevertheless be weak enough to give rise to an ion-pair intermediate which can be diverted from completing that initial covalent attack. Moreover, the Bentley–Schleyer analysis, while apparently allowing in principle for ion-pair return, concludes that it has a kinetically insignificant role. If one were to relax that conclusion sufficiently to allow for return factors of as much as ten, a reasonable fit of the isotope effects could probably be achieved. However, one is then left with the conflicting evidence on the nature of the solvation, covalent or electrostatic, of the carbonium ion fragment of the ion-pair intermediate. We have shown that if one allows for a mixed mechanism with return from the intermediate, the isotope effect results do not require any nucleophilic solvation, at least for the present case, for the pinacolyl and adamantyl esters and probably for isopropyl sulfonates which show a significant S_N2 component in etha-

nol–water solvents. On the other hand, the linear free-energy correlations of Bentley and Schleyer suggest that solvent *nucleophilically* accelerates almost all secondary sulfonate solvolyses. We have shown here in detail how we believe the solvent acts nucleophilically to accelerate the cyclopentyl *p*-bromobenzenesulfonate solvolyses simply through attack on the ion-pair intermediate. There remains the problem of whether or not our branched mechanistic scheme will suffice to explain relative reactivity, as well as isotope effects, for the wide range of different reactants considered by Bentley and Schleyer. We expect that it can, but if so the demonstration must await further results. Thus, we do not believe at present that either scheme has been shown to adequately account for *all* of the relevant information. We believe that while we have shown significant shortcomings in the ability of the hybrid mechanism to explain isotope effects, some modification of it might nevertheless suffice. On the other hand, more work is needed to determine if the branched scheme can explain relative reactivities over a wide range of reactants. We hope that work presently underway in our laboratory will contribute to the future resolution of this problem.

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Registry No.—Cyclopentyl *p*-bromobenzenesulfonate, 4596-40-1; cyclopentyl *p*-bromobenzenesulfonate-α-*d*, 50793-72-1; *cis*-cyclopentyl *p*-bromobenzenesulfonate-β-*d*, 51017-66-4; *trans*-cyclopentyl *p*-bromobenzenesulfonate-β-*d*, 50793-73-2; cyclopentyl *p*-bromobenzenesulfonate-β-d_4, 50981-27-6.

Supplementary Material Available: A list of the steady state equations and a description of the simplex method of calculations is supplied (9 pages). Ordering information is given on any current masthead page.

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