course of its formation.[4] If this occurs, microcrystalline hydrolysis product is formed which interferes with the spectrophotometric observations.

Reagent-grade chemicals and double-distilled deionized water were employed throughout the investigation.

Kinetics. The apparatus previously described,[5] in which the photomultiplier signal of a Cary 16 spectrophotometer is digitized and stored in a Hewlett-Packard 2100A computer so as to generate 1000 kinetic points in each run, was used. The points were subjected to weighted, nonlinear least-squares fitting to the first-order kinetic law to produce the observed first-order rate constants. The reactions were carried out in 1-mL cuvettes thermostated by a Lauda circulating constant-temperature bath. Absorbance data were collected at 380 nm. In most cases, runs with protiated and deuterated substrates were conducted in alternation, using the same stock reaction solutions.

References and Notes

(1) This research was supported by the National Institutes of Health through Grants CA 10748, MH 18038 (Yale: J.O.K. and J.K.C.), and GM 20199 (Kansas: I.M. and R.L.S.).
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α-Deuterium and Carbon-13 Isotope Effects for a Simple, Intermolecular Sulfur-to-Oxygen Methyl-Transfer Reaction. Transition-State Structures and Isotope Effects in Transmethylation and Transalkylation[1]

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Abstract: The transmethylation reaction of isotopically labeled *S*-methyldibenzothiophenium ($^{12}CH_3$-$SC_{12}H_8^+$, $^{13}CH_3$-$SC_{12}H_8^+$, and $^{12}CD_3$-$SC_{12}H_8^+$) tetrafluoroborates with methoxide ion in methanol at 25 °C shows $k_{3H}/k_{3D} = 0.97 \pm 0.02$ and $k_{12}/k_{13} = 1.08 \pm 0.02$. The large carbon isotope effect is similar to that for enzymic transmethylation and is consistent with a central, roughly planar methyl group in the transition state. The α-D effect is compared with others for enzymic and nonenzymic transmethylation and transalkylation reactions by estimating the transition-state fractionation factor ϕ_T relative to ethane, using the calculated factors of Hartshorn and Shiner. For 22 transmethylation reactions, ϕ_T is closely described in terms of reactant (ϕ_R) and product (ϕ_P) factors by $\phi_T = 0.99(\phi_R\phi_P)^{0.70}$. Transmethylation transition states appear structurally implastic with a roughly constant, probably high valency to methyl. Transalkylation transition states appear to be looser, relative to reactants and products, than transmethylation transition states and also far more structurally plastic. The enzymic transition state has an unusually large fractionation factor, consistent with transition-state compression as a mechanism of enzymic catalysis.

In the accompanying papers, we have reported the α-deuterium (α-D) isotope effects in transmethylation from the sulfonium methyl donor *S*-adenosylmethionine to the oxygen of the catechol acceptor 3,4-dihydroxyacetophenone, catalyzed by the rat-liver enzyme catechol *O*-methyltransferase[2] (COMT), and in sulfur-to-oxygen transalkylation in the intramolecular model reaction[3] devised by Coward, Lok, and Takagi.[4] These studies were intended to illuminate the origins of the catalytic power of COMT and similar transmethylases by producing information about the structure of the transmethylation transition state in both enzymic and nonenzymic reactions. Together with other information, these structural data could suggest how the enzyme liberates the free energy released upon its combination with the transmethylation transition state and thus how it catalyzes the reaction. The enzymic α-D isotope effect ($k_H/k_D = 0.83 \pm 0.05$) was the most inverse (largest in the direction $k_D > k_H$) of all the effects determined, indicating that the methyl hydrogens experience a greater increase in force constant upon formation of the enzymic transition state than in the model reactions. This is

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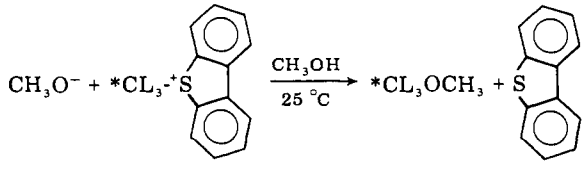
Table I.[a] Observed First-Order Rate Constants for the Reaction of 4.0–4.7 × 10^{-5} M *S*-*CL_3-Dibenzothiophenium Tetrafluoroborate with Sodium Methoxide in Methanol at 25.00 ± 0.04 °C

10^5[$NaOCH_3$], M	10^5k_0, s^{-1}		
	*CL_3 = $^{12}CH_3$	*CL_3 = $^{12}CD_3$	*CL_3 = $^{13}CH_3$
137_0	725, 733, 742, 730, 732	739, 721, 740, 758, 732	
132_4	746, 758, 770, 793, 762, 730		683, 651, 717, 691, 687, 692
232_3	1326, 1343, 1325, 1305, 1352, 1338	1319, 1345, 1323, 1385, 1335, 1348	
247_4	1436, 1471, 1449, 1449, 1448, 1441		1314, 1347, 1325, 1356, 1366, 1358
352_3	2138, 2164, 2152, 2152, 2177, 2175	2078, 2123, 2071, 2109, 2109, 2181	
356_5	2196, 2190, 2172, 2155, 2106, 2210		2046, 2047, 2040, 2021, 2063, 1990
474_9	3075, 3001, 3138, 3119, 3101, 2986	3030, 3048, 3207, 3138, 3187, 2956	
499_8	3140, 3192, 3113, 3370, 3200, 3248, 3171		2923, 2932, 2954, 2898, 3042, 2996, 3131, 3050, 3036
604_6	4028, 3992, 4098, 4206, 3952, 3930	4086, 4140, 4028, 4114, 4280, 3979	
614_8	4113, 4051, 4070, 4170, 4280, 4179, 4053		3702, 3848, 3849, 3916, 3182, 3818

[a] Total salt concentration maintained constant at 0.1000 M by addition of lithium perchlorate.

consistent with the hypothesis of an unusually tight[5] S_N2 transition state for the enzymic reaction (i.e., an unusually short nucleophile-to-leaving group distance) and the derivation of at least part of the enzyme catalytic power from the compression of the transition state (pictorially speaking, giving the methyl group a shorter distance to move and thus a lower barrier to cross in transmethylation).

The carbon-13 isotope effect was also studied with COMT[2] and was found to be large (1.09 ± 0.05), consistent with the hypothesis of a centrally located, essentially planar methyl group in the tight enzymic transition state. To determine whether the location of the carbon ("symmetry" of the transition state) and the tight-loose character in S_N2 sulfur-to-oxygen transmethylation transition states are sensitive to environmental influences of the sort that may prevail in the COMT active site,[6] we have constructed a model system suitable for both α-D and carbon-13 isotope-effect measurements (eq 1). The observation of Yamataka and Ando[7] that



(1)

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carbon-14 isotope effects for benzylation of *N,N*-dimethyltoluidine by para-substituted arylsulfonates of benzyl alcohol in acetone at 35 °C pass through a clear maximum (1.140 for *p*-CH_3O, 1.160 for no substituent, 1.110 for *m*-NO_2) encourages the use of the carbon isotope-effect probe for this purpose.

The detailed relationship of isotope effects to transition-state structure in these reactions can be expected to emerge from model calculations of the Wolfsberg–Stern type.[8-10] At present, we want in a simpler way to set the results we have into the general context of transmethylation and transalkylation reactions. Here we follow Seltzer and Zavitsas,[11] who showed that α-D effects in S_N2 reactions are related to the properties of both entering and leaving groups. Today it is possible because of the careful isotope fractionation-factor calculations of Hartshorn and Shiner[12] to estimate the transition-state contribution to α-D effects and to examine *its* relationship, rather than that of the overall isotope effect, to reactant and product properties.

In this paper we report the determination of α-D and carbon-13 isotope effects for the process of eq 1 by a direct, noncompetitive technique, and the semiquantitative relationship of these and other S_N2 α-D effects to transition-state properties.

Results

The reaction of eq 1 (with **1** as the tetrafluoroborate salt) was shown to occur as written (in preference to other processes seen under more stringent conditions with related compounds[13]) by isolation and identification of the product dibenzothiophene in high yield. The rates of reaction of the natural isotopic form of **1** (*CL_3 = $^{12}CH_3$) and its two isotopic modifications (*CL_3 = $^{12}CD_3$ and *CL_3 = $^{13}CH_3$) were measured by following the ultraviolet absorbance change at 322 nm. A Cary 118 spectrophotometer, interfaced by a microcomputer system to a teletype paper-tape writer,[14] measured the absorbance each second and prepared a paper tape over 6 half-lives of each kinetic run. The data were fitted to the first-order kinetic law by a weighted, nonlinear least-squares program on the Hewlett-Packard 2100A computer to generate the first-order rate constants of Table I. The first-order rate constants were fitted to eq 2 by the linear least-squares method to generate the second-order rate constants of Table II. The small but real, nonzero, negative intercepts indicate a zero rate constant for an apparent finite sodium methoxide concentration. A possible explanation is a roughly constant erroneous overestimation of this concentration because of oxidation of methanol to formic acid and introduction of atmospheric carbon dioxide in the course of the experiments. The other major source of error in the experiments is inadequate control of temperature, leading to scatter in the observed rate constants.

$$k_0 = k_2[NaOCH_3] + \text{intercept} \quad (2)$$

The second-order rate constants of Table II can be used to generate the following kinetic isotope effects at 25 °C for the

reaction of eq 1:

$$k_{3H}/k_{3D} = 0.974 \pm 0.016$$

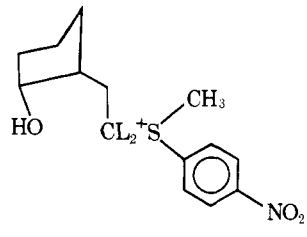
$$k_{12}/k_{13} = 1.083 \pm 0.015$$

Discussion

Carbon Isotope Effect. The carbon isotope effect for the S_N2 reaction of eq 1 is expected[9,15] to be maximal when the C-O and C-S bond orders of the transition state are about equal, and to decrease toward unity if the C-S bond is stronger and toward the equilibrium isotope effect,[2] $k_{12}/k_{13} \simeq 0.98$, if the C-O bond is stronger. A simple zero-point energy estimate of the expected maximum if only a reactant C-S stretching vibration of 700 cm^{-1} is involved produces a value of about 1.05. A number of reported experimental effects exceed this (Willi[16] lists several pertinent values from 1.04 to 1.08), so that the origin of these effects obviously includes more than a simple stretching vibration. However, an effect of 1.08 is at the high end of the spectrum of reported observations and is probably near the effective maximum. This is also the indication of preliminary model vibrational analysis calculations for sulfur-to-oxygen transmethylation. It seems likely, therefore, that the transition state for eq 1 has a "symmetrical" structure, with the methyl roughly planar and the C-O and C-S bond orders of similar magnitude.

The carbon isotope effect observed here (1.08 ± 0.02) and that seen in COMT action[2] (1.09 ± 0.05) are equal within their experimental errors. It can be provisionally concluded (subject to the results of more precise experimental studies and the more complete theoretical investigation now in progress) that the enzymic and nonenzymic transition states have a similar disposition of the methyl group (roughly planar and central).

α-D Isotope Effect. Preliminary Considerations. The α-D effect of 0.97 ± 0.02, being slightly inverse, is indicative of a small increase in the force constants restraining the methyl hydrogens when the transition state for eq 1 is formed from the reactants. The α-D effect for COMT action[2] is considerably more inverse (0.83 ± 0.05) and suggests a greater restriction or compression at the methyl center in the enzymic than in the nonenzymic transition state. The COMT effect is also more inverse (0.94 per deuterium) than any of three α-D effects[3] for ring closure of compound **2** (L = H, D), a reaction which serves



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as a model for COMT action (these effects are 1.08 per deuterium for water-catalyzed ring closure, 1.05 per deuterium for carbonate ion general-base catalysis, and 1.00 per deuterium for hydroxide ion specific catalysis). All of these observations are therefore consistent with the view that the enzymic transition state is unusually tight, having an unusually short nucleophile-to-leaving group distance and thus a high degree of compression and restriction at the transferring methyl group. If this is so, the enzyme may effect catalysis, wholly or in part, through transition-state compression. We want to examine this concept in more detail by attempting to place the α-D effects for the enzymic reaction and for the models we have studied properly within the context of a range of observations on nonenzymic transmethylations and transalkylations.

To develop such a comparison, we have to take account of the factors upon which the α-D effect may depend. The major contribution is likely to be changes in hydrogen bending force constant related to changes in the distance to entering and leaving groups and to the sizes and polarizabilities of these groups.[9,11,17-19] In the case of groups which lose or gain charge during the reaction (such as in the sulfonium compounds of interest here), an electrostatic contribution to the change in force constant may be present.[20-23] Beyond these effects, changes in steric interaction (such as could arise from active-site constituents in the enzymic reaction) might give rise to an isotope effect contribution.[24]

Table II. Second-Order Rate Constants for Reaction of Isotopic Modifications of **1** with Sodium Methoxide in Methanol at 25.00 ± 0.04 °C (Total Salt Concentration Maintained at 0.1000 M with Lithium Perchlorate)

*CL_3 in **1**	10^4k_2,[a] M^{-1} s^{-1}	10^4 (intercept),[b] s^{-1}
$^{12}CH_3$	7052 ± 58	−27 ± 2
$^{12}CD_3$	7239 ± 102	−33 ± 4
$^{13}CH_3$	6512 ± 70	−24 ± 3

[a] Slope of a linear least-squares correlation of k_0 from Table I vs. $[NaOCH_3]$. [b] Intercept of the linear least-squares correlation.

The situation can be simplified by use of the Hartshorn-Shiner[12] fractionation factors, which (in stable molecules) empirically generate the correct combination of the contributions described above through vibrational analysis based on observed vibration frequencies. In the form to be used in this paper, the fractionation factor for a particular hydrogenic site in a molecular environment S is given by eq 3:

$$\phi_S = \{X_{SD}/X_{SH}\}/\{X_{CH_3CH_2D}/X_{CH_3CH_3}\} \quad (3)$$

It is thus the ratio at equilibrium of SD to SH relative to the corresponding ratio in a standard molecular environment, taken here as the ethane molecule. Since deuterium tends to accumulate in environments with higher force constants (i.e., inverse isotope effects are associated with tighter binding), values of ϕ_S greater than unity signify tighter binding in S than in ethane and values smaller than unity signify looser binding in S than in ethane.

For a methyl-transfer reaction, the observed kinetic isotope effect is related to the reactant-state fractionation factor ϕ_R and the transition-state fractionation factor ϕ_T as in eq 4a.[9,25] If ϕ_R is known, ϕ_T can be calculated from the experimental isotope effect by eq 4b. Here it is assumed that all hydrogens of the methyl group have the same fractionation factor; if this is not true, then ϕ_T calculated from eq 4b will be an average value, and an average value must be used for ϕ_R. For the transfer of a primary alkyl group in which two hydrogens are isotopically substituted, the corresponding relations are those of eq 5. The advantage of this formulation is that it allows a comparison of ϕ_T values for a wide variety of reactions, so that transition-state properties themselves are directly examined. The reactant-state contributions, which may confuse the picture if observed isotope effects are used,[19,26] are removed by the introduction of ϕ_R.

$$k_{3H}/k_{3D} = \phi_R^3/\phi_T^3 \quad (4a)$$

$$\phi_T = \phi_R(k_{3H}/k_{3D})^{1/3} \quad (4b)$$

$$k_{2H}/k_{2D} = \phi_R^2/\phi_T^2 \quad (5a)$$

$$\phi_T = \phi_R/(k_{2H}/k_{2D})^{1/2} \quad (5b)$$

To apply eq 4 and 5 to α-D isotope effects, a value of ϕ_R for α-deuterium substitution in each reactant molecule of interest is needed. We assume that a sufficiently good approximation will be obtained by assuming that only the atom proximal to the carbon bearing the isotopic hydrogen affects its fractionation factor.[9,12] This permits us to use directly the Hartshorn-Shiner[12] factors for methylamine, methylammonium ion, the methyl halides, and ethyl chloride, as shown in Table

Table III. Deuterium Fractionation Factors at 25 °C Relative to Ethane Used in Estimations of Transition-State Contributions to α-Deuterium Secondary Isotope Effects[a]

X	ϕ, fractionation factor for $CH_2(D)X$	$CH_3CH(D)X$
OR	1.064[b]	1.174[f]
NR_2	**1.036**[c]	1.143[f]
NR_3^+	**1.058**[c]	1.167[f]
CN	**1.009**	1.113[f]
Cl	**1.033**	**1.104**
SR	1.005[d]	1.074[g]
SR_2^+	1.026[e,h]	1.097[g,h]
Br	**0.998**	1.067[g]
I	**0.967**	1.034[g]

[a] Boldface values were taken directly from Harıshorn and Shiner,[12] as were other values referred to in footnotes 10 this table. [b] The result of either graphic or algebraic interpolation using ϕ for CH_3F (1.077), CH_3NH_2 (1.036), and CH_3CH_3 (1.000). [c] Calculated for R = H but used here for all R. [d] From interpolation between ϕ for CH_3Cl (1.033) and CH_3SiH_3 (0.914). [e] From applying the amine/ammonium charge correction: $\phi(CH_3NH_3^+)/\phi(CH_3NH_2) = 1.021$ to the value for SR.[27] [f] From multiplying the value at left by ϕ for CH_3CHDCH_3 relative to ethane (1.103) 10 simulate the effect of adding a methyl next to an atom in this period of the periodic table. [g] From multiplying the value at left by 1.104/1.033 = 1.069, assuming the correction for Cl to apply to its own and all periods below it in the periodic table. [h] Other values used:[27] 1.005, 1.053 for $CH_2DSR_2^+$ and 1.074, 1.126 for $CH_3CHDSR_2^+$.

III. Since no values were calculated for methyl oxygen or methyl sulfur compounds, these were obtained by graphic or algebraic interpolation or both using values for methyl fluoride, methylamine, and ethane (in the former case) and values for methyl chloride and methylsilane (in the latter). To obtain a factor for methylsulfonium species, it was initially assumed that the positive-charge correction for methyl sulfur environments is the same as for methylamine/methylammonium. However, because of the importance of the sulfonium fractionation factor for our considerations, two other positive-charge corrections (no effect; effect as observed in experimental ionization of ammonium ions) were also employed.[27] The effect of adding a methyl group, to convert methyl to primary alkyl fractionation factors, was estimated from the ratio of ethane and 2-propane factors for the elements in the same period with carbon and from the ratio of methyl chloride and ethyl chloride factors for other elements.

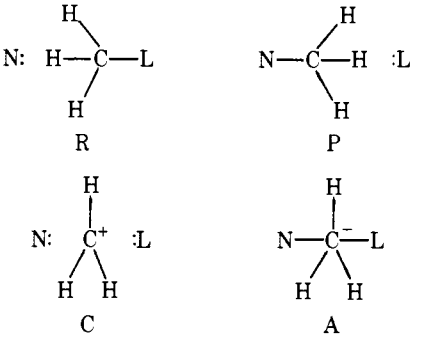
Classification of S_N2 Reactions. With this apparatus, we can proceed to examine the corpus of experimental isotope effects for signs of systematic regularity. Table IV lists 57 examples of transmethylation and primary-transalkylation reactions, their α-D effects, and estimated transition-state fractionation factors. No attempt has been made to consider temperature dependences, ϕ_R for 25 °C being used with the experimental isotope effect at the tabulated temperature in all cases. Sulfonium compound reactions were omitted and will be treated separately. While an exhaustive search was not made, a reasonably broad selection of examples is given and no cases found were excluded except as noted.

An examination of the data in Table IV suggests that the major features determining ϕ_T are the identities of the entering and leaving groups and whether the transferring group is methyl or primary alkyl; indeed, the classification scheme in the table is based on this observation. In this scheme, a reaction is designated: (i) by M if a transmethylation or by A if a transalkylation; (ii) by two numbers, the first of which gives the principal quantum number of the valence shell of the proximal atom of the nucleophile, the second of which gives the principal quantum number of the valence shell of the proximal atom of the leaving group. Thus, class (M-2,2) contains five examples of oxygen-to-oxygen methyl transfer, class (A-2,3) 14 examples of substituted-benzyl transfer from chlorine to carbon, nitrogen, and oxygen nucleophiles, and so on. This scheme is closely related to the regularity observed by Seltzer and Zavitsas,[11] who found a correlation of α-D effect in S_N2 reactions with the difference in nucleophilicity parameters of entering and leaving groups.

When the reactions are classified according to this scheme, they exhibit regular tendencies in ϕ_T, as can easily be seen in the table. The results for transmethylations (M classes) will be considered first, and then those for primary transalkylations (A classes).

Transmethylations. The values of ϕ_T for transmethylation are well separated by class and show only a narrow range of magnitudes in the two well-populated classes [(M-2,2) with a range of 1.075-1.094 for five examples and (M-2,5) with a range of 0.991-1.013 for ten examples; to be compared with the total range of 0.937-1.094 for 22 transmethylations]. When the nucleophilic and leaving-group atoms are both near the top of the periodic table, with the transferring methyl group held by relatively short bonds to relative "hard" atoms, the ϕ_T is larger than unity (tighter binding than in ethane), an average of 1.083 when both atoms are oxygen [class (M-2,2)]. As either of these atoms lies deeper in the periodic table, forming a longer bond and presenting a more polarizable barrier to motion of the isotopic hydrogen, ϕ_T becomes steadily smaller, reaching 0.944 for iodide-exchange reactions of methyl iodide (looser binding than in ethane).

This simple and logical result suggests a primitive model for semiquantitative description of transmethylation transition states in terms of their isotope effects. We use the idea of Leffler[29] and Ettlinger and Lewis[30] that properties of transition states can be thought of as linear combinations of the properties of other, related species for which the properties may be easier to estimate than for the transition state itself. We consider the four species denoted below as R (the reactant structure), P (the



product structure), C (a cationic structure which would be an intermediate in an ionization mechanism), and A (an "anionic" species in that considerable negative charge is accumulated in the methyl group; this structure is hypothetical and arbitrary but may be envisioned as the tightest possible S_N2 transition state). The free energy of transfer of a deuterium atom from ethane into a methyl hydrogen of a transmethylation transition state, ΔG_T, is assumed to be given by a linear combination of the corresponding free energies of transfer for R, P, C, and A (eq 6, where $\rho + \pi + \gamma + \alpha = 1$):

$$\Delta G_T = \rho\Delta G_R + \pi\Delta G_P + \gamma\Delta G_C + \alpha\Delta G_A \quad (6)$$

This leads to eq 7 in terms of fractionation factors:

$$\phi_T = \phi_R{}^{\rho}\phi_P{}^{\pi}\phi_C{}^{\gamma}\phi_A{}^{\alpha} \quad (7)$$

We now introduce the following particular assumptions: (i) let ϕ_C be independent of entering and leaving group; (ii) let ρ

Table IV. Estimated Transition-State Fractionation Factors (Relative to Ethane) from α-Deuterium Secondary Isotope Effects[a]

class designations & ident no.'s	reaction	solvent	temp, °C	$(k_H/k_D)^b$	estimated $\phi_T^{c,aa}$
part I. transmethylations					
class (M-2,2)[d]					
1	$H_2O + CD_3ONO_2$	H_2O	100	0.92[e]	1.094
2	$H_2O + CD_3OSO_2CH_3$	H_2O	60	0.96[e]	1.079
3	$H_2O + CD_3OSO_2C_6H_4CH_3(p)$	H_2O	70	0.96[e]	1.079
4	$CH_3OH + CD_3OSO_2C_6H_4Br(p)$	CH_3OH	70	0.94[f]	1.086
5	$H_2O + CD_3OSO_2OCD_3$	H_2O	25	0.97[e]	1.075
class (M-2,3)					
6	$H_2O + CD_3Cl$	H_2O	90	0.92[e]	1.062
class (M-2,4)					
7	$H_2O + CD_3Br$	H_2O	80	0.90[e]	1.034
class (M-2,5)					
8	$CN^- + CD_3I$	H_2O	40	0.93[g]	0.991
9	$N_3^- + CD_3I$	H_2O	40	0.91[h]	0.998
10	$(CH_3)_3N + CD_3I$	C_6H_6	50	0.88[i]	1.009
11	$(n\text{-}C_3H_7)_3N + CD_3I$	C_6H_6	50	0.89[i]	1.005
12	$(n\text{-}C_4H_9)_3N + CD_3I$	C_6H_6	50	0.90[i]	1.002
13	$C_5H_5N + CD_3I$	C_6H_6	50	0.92[i]	0.994
14	$2\text{-}CH_3\text{-}C_5H_4N + CD_3I$	C_6H_6	50	0.88[i]	1.009
15	$2,6\text{-}(CH_3)_2C_5H_3N + CD_3I$	C_6H_6	50	0.88[i]	1.009
16	$CH_3CO_2^- + CD_3I$	H_2O	40	0.88[h]	1.009
17	$H_2O + CD_3I$	H_2O	70	0.87[e]	1.013
class (M-3,4)					
18	$^-O_3S\text{-}S^- + CD_3Br$	50% v/v ethanol/H_2O	25	1.03[j]	0.988
class (M-3,5)					
19	$^-O_3\text{-}S^- + CD_3I$	H_2O	20	0.97[k]	0.977
class (M-5,3)					
20	$I^- + CD_3Cl$	DMF	25	1.131[l]	0.991
class (M-5,5)					
21	$I^- + CD_3I$	H_2O	20	1.10[m]	0.937
22	$I^- + CD_3I$	CH_3OH	20	1.05[m]	0.951
part II. transalkylations at primary carbon					
class (A-2,2)					
23	$H_2O + CH_3CD_2OSO_2C_6H_4CH_3(p)$	H_2O	60	1.04[n]	1.151
24	$CH_3CO_2H + CH_3CD_2OSO_2C_6H_4Br(p)$	CH_3CO_2H	100	1.09[f]	1.124
25	$CH_3OH + CH_3CD_2OSO_2C_6H_4Br(p)$	CH_3OH	56	1.04[f]	1.151
26	$H_2O + CH_3CH_2CD_2OSO_2C_6H_5$	H_2O	54	1.03[n]	1.157
27	$H_2O + m\text{-}CF_3C_6H_4CD_2ONO_2$	H_2O	70-91	0.976[o]	1.188
28	$H_2O + p\text{-}ClC_6H_4CD_2ONO_2$	H_2O	65	1.252[o]	1.049
29	$H_2O + m\text{-}CH_3OC_6H_4CD_2ONO_2$	H_2O	46	1.239[o]	1.055
30	$H_2O + C_6H_5CD_2ONO_2$	H_2O	50-64	1.241[o]	1.054
31	$H_2O + p\text{-}CH_3C_6H_4CD_2ONO_2$	H_2O	30	1.386[o]	0.998
class (A-2,3)					
32	$CN^- + m\text{-}ClC_6H_4CD_2Cl$	*p*	50	1.001[q]	1.103
33	$CN^- + C_6H_5CD_2Cl$	*p*	50	1.024[l]	1.091
34	$CN^- + p\text{-}CH_3C_6H_4CD_2Cl$	*p*	50	1.25[q]	0.987
35	$N_3^- + C_6H_5CD_2Cl$	*r*	60	1.067[s]	1.069
36	$N_3^- + p\text{-}CH_3C_6H_4CD_2Cl$	*r*	60	1.008[s]	1.100
37	$H_2O + m\text{-}ClC_6H_4CD_2Cl$	*p*	50	1.007[q]	1.100
38	$H_2O + p\text{-}ClC_6H_4CD_2Cl$	H_2O	69-80	1.061[o]	1.072
39	$H_2O + m\text{-}CH_3OC_6H_4CD_2Cl$	H_2O	56	1.076[o]	1.065
40	$H_2O + C_6H_5CD_2Cl$	H_2O	64	1.093	1.056
41	$H_2O + C_6H_5CD_2Cl$	*p*	50	1.025[q]	1.090
42	$H_2O + C_6H_5CD_2Cl$	*r*	60	1.006[s]	1.101
43	$H_2O + p\text{-}CH_3C_6H_4CD_2Cl$	H_2O	41	1.278[o]	0.976
44	$H_2O + p\text{-}CH_3C_6H_4CD_2Cl$	*p*	50	1.068[q]	1.068
45	$H_2O + p\text{-}CH_3C_6H_4CD_2Cl$	*r*	60	0.996[s]	1.106
class (A-3,2)					
46	$C_6H_5S^- + C_6H_5CD_2N(CH_3)_2C_6H_5^+$	DMF	0	1.42[t]	0.979
class (A-2,4)					
47	$H_2O + CH_3CD_2Br$	H_2O	80	1.08[n]	1.027
48	$H_2O + CH_3CH_2CD_2Br$	H_2O	80	0.98[n]	1.078
class (A-4,2)					
49	$Br^- + C_6H_5CD_2N(CH_3)_2C_6H_5^+$	$CHCl_3$	30-60	1.250[u,v]	1.043
		acetone	30-55	1.199[u,v]	1.066
class (A-3,3)					
50	$Cl^- + C_6D_5CD_2Cl$	DMF	35	1.084[w]	1.060[x]
51	$Cl^- + C_6H_4CD_2Cl$	DMF	40	1.06[z]	1.072
52	$Cl^- + 2\text{-}C_4H_3SCD_2Cl$[y]	DMF	40	1.08[z]	1.062
53	$Cl^- + 3\text{-}C_4H_3SCD_2Cl$[y]	DMF	40	1.10[z]	1.051
class (A-2,5)					
54	$H_2O + CH_3CD_2I$	H_2O	80	0.97[n]	1.050
55	$H_2O + CH_3CH_2CD_2I$	H_2O	90	1.01[n]	1.029
class (A-3,4)					
56	$^-O_3SS^- + CH_3CD_2Br$	50% v/v	25	1.068[j]	1.032
57	$^-O_3SS^- + CH_3CH_2CD_2Br$	ethanol/H_2O	25	1.075[j]	1.029

[a] For transmethylation & primary transalkylation reactions. Fractionation factors used in the calculations are listed in Table III. [b] Observed isotope effect for the number of deuteriums indicated in the molecular formula at left. [c] Expressed as a deuterium fractionation factor (one site) relative to ethane. [d] In the class designations, M means transmethylation and A transalkylation; the first number is the principal quantum number of the valence shell for the nucleophilic atom and the second number is the principal quantum number of the valence shell for the proximal atom of the leaving group. [e] J. A. Llewellyn, R. E. Robertson and J. M. W. Scott, *Can. J. Chem.*, **38**, 222 (1960). [f] E. S. Lewis, J. C. Brown, and W. C. Herndon, *ibid.*, **39**, 954 (1961). [g] A. V. Willi and C. M. Won, *J. Am. Chem. Soc.*, **90**, 5999 (1968). [h] C. M. Won and A. V. Willi, *J. Phys. Chem.*, **76**, 427 (1972). [i] K. T. Leffek and J. W. McLean, *Can. J. Chem.*, **43**, 40 (1965). [j] K. T. Leffek, *ibid.*, **42**, 851 (1964). [k] A. V. Willi and C. M. Won, *ibid.*, **48**, 1452 (1970). [l] W. E. Buddenbaum and V. J. Shiner, Jr., in *Isot. Eff. Enzyme-Catalyzed React., Proc. Annu. Harry Steenbock Symp., 6th, 1976* (1977). [m] S. Seltzer and A. A. Zavitsas, *Can. J. Chem.*, **45**, 2023 (1967). [n] K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *ibid.*, **38**, 1505 (1960). [o] K. M. Koshy and R. E. Robertson, *J. Am. Chem. Soc.*, **96**, 914 (1974). [p] Fifty-five percent by volume methyl Cellosolve. [q] A. V. Willi, C.-K. Ho, and A. Ghanbarpour, *J. Org. Chem.*, **37**, 1185 (1972). [r] Bicarbonate-buffered aqueous acetone. [s] V. F. Raaen, T. Juhlke, F. J. Brown, and C. J. Collins, *J. Am. Chem. Soc.*, **96**, 5928 (1974). [t] K. C. Westaway, *Tetrahedron Lett.*, 4229 (1975). [u] Temperature dependence ± 0.005. [v] E. C. F. Ko and K. T. Leffek, *Can. J. Chem.*, **49**, 129 (1971). [w] H. Strecker and H. Elias, *Radiochim. Acta*, **7**, 22 (1967). [x] No account was taken of the ring deuterium. [y] C_4H_3S refers to thienyl. [z] B. Östman, *J. Am. Chem. Soc.*, **87**, 3163 (1965). [aa] The isotope effects are commonly reliable to 2% or better, suggesting that the fractionation factors (ignoring errors in the computed standard fractionation factors) should be significant to about ±0.007.

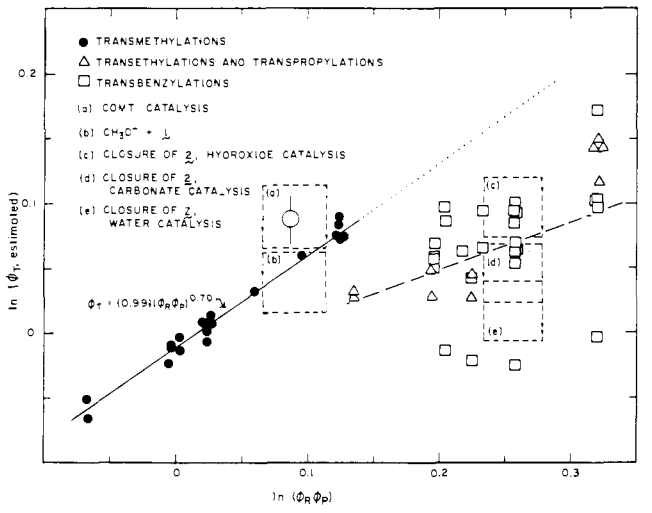


Figure 1. Plot of eq 9b for transmethylations and transalkylations. The solid line for transmethylation reactions and its dotted extension are for the function of eq 10. The dashed line for transalkylations is for the function of eq 11. The dashed boxes are for sulfur-to-oxygen transmethylations [(a) and (b)] and ring closures [(c), (d), (e)]. The circle in (a) and attached bars show the value of ln ϕ_T for the enzymic reaction, and its experimental error, calculated from $\phi_R = 1.026$.

$\sim \pi$, which signifies a roughly central transition state with respect to reactant-product character; this gives rise to a simple algebraic form but is unlikely to be really true in general; (iii) let $\phi_A = q(\phi_R\phi_P)^m$, so that both reactant and product features are equally represented in A and intensified as described by m and q. The choice of m and q really specifies what structure one *chooses* to employ for A in the description of the transition state. These assumptions convert eq 7 to eq 8:

$$\phi_T = \phi_C^{\gamma}(\phi_R\phi_P)^{\rho+m\alpha}q^{\alpha} \quad (8)$$

ϕ_T for various transmethylation reactions should be described by a function like that of eq 9a and, as eq 9b shows, ln ϕ_T (with ϕ_T calculated from the isotope effect by eq 4b) should then be a linear function of ln $(\phi_R\phi_P)$ (with ϕ_R and ϕ_P from Table III):

$$\phi_T = a(\phi_R\phi_P)^b \quad (9a)$$

$$\ln \phi_T = \ln a + b \ln (\phi_R\phi_P) \quad (9b)$$

Such a relationship indeed holds, as Figure 1 demonstrates;[31] the equation of the solid line is:

$$\phi_T = (0.99)(\phi_R\phi_P)^{0.70} \quad (10)$$

What can be properly concluded from this finding is that:

(1) Transmethylation transition states are very well described (at least as probed by α-D isotope effects) in terms of restrictions to methyl hydrogen motions (tightness) introduced by entering and leaving groups, as calibrated by the effects of these groups in reactant and product molecules, with elements early in the periodic table (which are unpolarizable—"hard"—and form short bonds) giving tight transition states, and elements late in the periodic table ("soft", with long bonds) giving loose transition states.

(2) The tightness of the transition state, when referred to the stiffness of hydrogen motions in reactant and product molecules as a calibration for bond length, size, and polarizability, is roughly constant, so that eq 10 describes any transmethylation transition state well.

(3) This constancy of structure, or lack of plasticity, holds over quite wide ranges of conditions, so that each of the classes of Table IV shows only a narrow range of ϕ_T. This is so even when, as in class (M-2,5), both neutral and anionic nucleophiles are included, water and benzene are used as solvents, and a temperature range from 40 to 70 °C is employed. This is consistent with the view that the transferring methyl group adopts a roughly constant, probably rather high total valency in the transition state and that alterations from this value are energetically costly.

Transalkylations. Also shown in Figure 1 are points for alkyl-transfer reactions involving ethyl, propyl, and benzyl groups (from the second part of Table IV). The following points are notable:

(1) If the dependency of eq 10 is applied to these reactions (dotted extension of the solid line), all the observed fractionation factors are smaller than predicted, usually much smaller. This shows that transalkylation transition states tend to be looser, when scaled against their reactant and product structures, than do transmethylation transition states.

(2) The points for the transalkylation reactions are far too scattered to describe a line like the solid line for transmethylation, indicating a much greater plasticity of structure for transalkylation transition states. However, the least-squares fit to eq 9b for the 35 examples, shown as the dashed line in Figure 1, passes roughly through the centers of gravity for the individual reaction classes, suggesting that the average structures for a reaction class can be described by a function of this type. The equation of the dashed line is:

$$\phi_T = (0.98)(\phi_R\phi_P)^{0.37} \quad (11)$$

(3) As just noted, the scatter of the transalkylation points arises from a much greater range of ϕ_T within each reaction class, although the average ϕ_Ts for the reaction classes are approximately described by eq 11. This suggests that (a) transalkylation transition states are, on the average, looser, relative to reactants and products, than are transmethylation transition states;[32] (b) transalkylation transition states are more plastic than transmethylation states, giving rise to much greater variation in ϕ_T within each reaction class. The greater looseness[32] of the transalkylation transition states probably arises from two factors: (i) steric repulsions between the group attached to the transferring carbon and both the entering and leaving groups, leading to longer transition-state bonds to both of the latter; (ii) greater capacity of the primary alkyl center (compared to the methyl center) for bearing positive charge, which can be stabilized by polarization and delocalization of electrons in the group attached to the transferring carbon. The greater plasticity of the transalkylation transition states would also arise logically from this same capacity of the alkyl group to accommodate varying amounts of positive charge, allowing for expansion and contraction of the bonds to entering and leaving groups. Part of the price paid for the greater looseness and plasticity is in energy, since transalkylations at ethyl and propyl centers are commonly 30- to 60-fold slower than the corresponding transmethylations.[33]

Sulfur-to-Oxygen Transmethylation and Transalkylation. It is now possible to place the α-D effects for the enzymic and model reactions[2,3] for sulfur-to-oxygen nucleophilic displacements among those for other reactions. As explained above, there is uncertainty in the magnitude of the positive-charge correction to fractionation factors for hydrogen next to sulfonium centers. Therefore, we have employed three values[27] of ϕ_R, assuming (1) no effect of charge (1.005 for methyl, 1.074 for alkyl); (2) the effect of positive charge calculated by Hartshorn and Shiner[12] for methylamine/methylammonium ion (1.026 for methyl, 1.097 for alkyl); (3) the effect experimentally observed for ionization of trimethylammonium ion (1.053 for methyl, 1.126 for alkyl). These generate the range of ϕ_T values given in Table V. Also shown there are expected values calculated from eq 10 and 11. The resulting ranges of ϕ_T are shown as the dashed boxes in Figure 1.

The ring-closure reactions produce values of ϕ_T that are in exact accord with expectation for their reaction class [class (A-2,3)]. The considerable plasticity of the ring-closure

Table V. Estimated Transition-State α-D Fractionation Factors for Enzymic and Model-Reaction Methyl and Alkyl Transfers from Sulfur to Oxygen

reaction	isotope effect	estimated[a] ϕ_T	expected[b] ϕ_T
COMT-catalyzed methylation of 3,4-dihydroxyacetophenone by *S*-adenosylmethionine, 37 °C (ref 2).	k_{3H}/k_{3D} = 0.83 ± 0.05	1.069, 1.092, 1.120	1.038, 1.053, 1.072
methylation of methoxide ion by **1**, methanol, 25 °C (this work)	k_{3H}/k_{3D} = 0.97 ± 0.02	1.015, 1.036, 1.064	1.038, 1.053, 1.072
ring closure of **2**, water catalysis, water, 40 °C (ref 3)	k_{2H}/k_{2D} = 1.17 ± 0.02	0.993, 1.014, 1.041	1.068, 1.076, 1.086[c]
ring closure of **2**, carbonate general catalysis, water, 40 °C (ref 3)	k_{2H}/k_{2D} = 1.104 ± 0.014	1.022, 1.044, 1.072	1.068, 1.076, 1.086[c]
ring closure of **2**, hydroxide specific catalysis, water, 40 °C (ref 3)	k_{2H}/k_{2D} = 0.998 ± 0.001	1.075, 1.098, 1.127	1.068, 1.076, 1.086[c]

[a] From eq 4b for transmethylations and eq 5b for ring closures. The three numbers result from the use of ϕ_R = 1.005, 1.026, and 1.053 for transmethylations and ϕ_R = 1.074, 1.097, and 1.126 for ring closures (see Table III). [b] From eq 10 for transmethylations and eq 11 for ring closures, using the three values of ϕ_R given in the previous note. [c] If eq 10 for transmethylations had been applied, rather than eq 11, then the expected ϕ_T values for ring closure would be 1.164, 1.182, and 1.204, respectively.

transition states is also just what is anticipated for a transalkylation process. It is interesting, and will be remarked below, that increasing reaction rate (from water catalysis through carbonate general catalysis to hydroxide specific catalysis) is associated with increasing tightness of the transition state.

The intermolecular, nonenzymic transmethylation reaction generates a value of ϕ_T also in strong agreement with expectation, as Figure 1 shows. The enzymic transmethylation has a value of ϕ_T substantially in excess of that expected for a reaction in this class [class (M-2,3)]. This indicates an unusually tight transition state for the enzymic reaction and lends quantitative confirmation to the conclusion previously drawn[2,3] that enzymic catalytic power may be associated with transition-state compression.

Some other measurements of α-D effects for displacements on sulfonium centers have been made. Wu and Robertson[34] studied effects on reactions of $(CD_3)_3S^+$ which are thus complicated by possible leaving-group contributions. Their findings [k_{9H}/k_{9D} = 1.21 (phenoxide as nucleophile in water at 76 °C), 1.07 (ethoxide as nucleophile in water at 76 °C), 0.91 (thiophenoxide as nucleophile in water at 59 °C)] are generally in agreement with a view that faster reactions have tighter transition states in this series, thiophenoxide being 100-fold and ethoxide 1.6-fold faster than phenoxide. Because of the unknown leaving-group contribution, however, no definitive conclusion is possible. Islam and Leffek[35] found k_{2H}/k_{2D} = 1.08 for bromide attack on $C_6H_5Cl_2S(CH_3)_2^+$ (L = H, D) in an "ion-triplet" reaction in chloroform at 25–50 °C. This yields ϕ_T = 1.033–1.083 (ϕ_Rs as in Table V) compared to an expectation from eq 11 of 1.031–1.049.

Rate and Compression. A possible association of rate with transition-state compression is examined finally in Figure 2. There variations are considered in ln ($\phi_T^{estd}/\phi_T^{theor}$) where $\phi_T^{theor} = (0.99)(\phi_R\phi_P)^{0.70}$. Thus, one is considering deviations from the normal ϕ_T expected for a simple S_N2 transition state of the transmethylation type. As can be seen, this discrepancy is linearly related to the logarithm of the second-order rate constant for the three ring-closure reactions, the reaction of eq 1, and the enzymic transmethylation. Throughout the series, the tighter the transition state becomes relative to the expected transmethylation transition state, the faster is the reaction, an increase of about 20% in the fractionation factor corresponding to a factor of 10^{10} in the rate. While this apparent correlation does not definitely establish any cause-effect relationship between rate and transition-state tightness, it lends further support to the hypothesis of transition-state compression as associated with the catalytic power of methyl transferases.

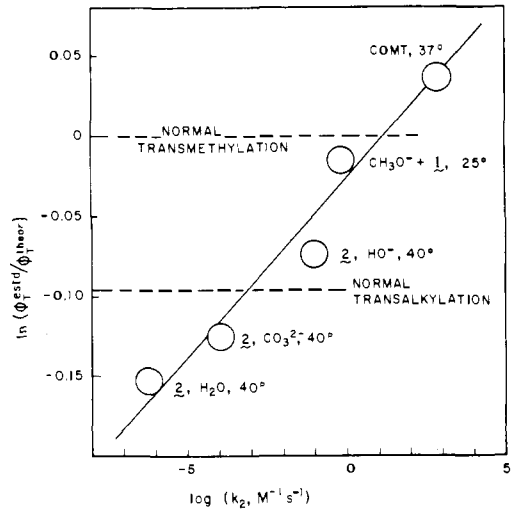


Figure 2. Plot of ln ($\phi_T^{estd}/\phi_T^{theor}$) as a function of the logarithm of the second-order rate constant. Here ϕ_T^{estd} is obtained from the experimental isotope effects (eq 4 and 5) using ϕ_R = 1.026 for transmethylations and 1.097 for ring closures and $\phi_T^{theor} = (0.99)(\phi_R\phi_P)^{0.70}$. The horizontal dashed lines show the expected values for "normal" transmethylation (for which $\phi_T^{estd} = \phi_T^{theor}$) and transalkylation [for which ϕ_T^{estd} is expected, on the average, to be $(0.98)(\phi_R\phi_P)^{0.37}$].

Experimental Section

Materials. Methanol (Mallinckrodt reagent grade) was dried with magnesium and distilled, then titrated with sulfuric acid, and redistilled from sufficient benzoic acid to neutralize basic impurities. It was stored in a sealed glass container over 3-Å molecular sieves. Sodium methoxide solutions were prepared by dissolution of clean sodium in methanol under nitrogen. Stock solutions at 0.1 M were standardized with potassium hydrogen phthalate (Fisher reagent grade, dried at 120 °C) and diluted with appropriate amounts of stock solutions of lithium perchlorate (G. Frederic Smith reagent grade, dried under vacuum and stored over phosphorus pentoxide). Solutions were stored in a drybox containing Ascarite.

***S*-Methyldibenzothiophenium tetrafluoroborate** was prepared according to Acheson and Harrison[36] by reaction of silver tetrafluoroborate (Ventron, dried in vacuum) with dibenzothiophene (Eastman) and methyl iodide (Mallinckrodt Analytical Reagent) in 1,2-dichloroethane (dried over calcium hydride and distilled into 4-Å molecular sieves). Crystals melting at 146.5–147.5 °C (lit. 149–151 °C)[20] were obtained in 71% yield. Isotopic modifications were prepared in identical fashion using methyl-d_3 iodide (Stohler, 99.5 atom % D) or methyl-^{13}C iodide (Stohler, 90 atom % ^{13}C).

Stoichiometry. A reaction mixture consisting of 8.75 mL of methanol, 0.04 M in *S*-methyldibenzothiophenium tetrafluoroborate and 0.4 M in sodium methoxide, was maintained at room temperature for 24 h. Then 20 mL of diethyl ether and 15 mL of saturated aqueous sodium chloride were added. After agitation, the ether layer was separated, dried with magnesium sulfate, and removed to yield 56.7

mg (88%) of dibenzothiophene, identified by comparison with an authentic sample.

Kinetics. Stock solutions of substrate were prepared fresh and kept on ice. Sodium methoxide–lithium perchlorate reaction solutions were prepared from stock solutions at the desired concentration, standardized, and stored in 1.000-mL volumes in cuvettes in the thermostated cell compartment of the Cary 118. After insertion of a cuvette in the cell holder and completion of thermal equilibration, 20 μL of substrate stock solution was injected by Gilson Pipetman, the solution was manually mixed, and observations were begun. Isotopic compounds were studied in alternating runs. The digital (BCD) absorbance output of the Cary 118 panel meter was read by a programmed SBC 80/10 microcomputer at intervals of 1 s, as measured by a SC/MP microprocessor programmed to function as a precision timer.[37] After brief storage in the microcomputer memory, each digital point was transmitted to a teletype as a hexadecimal number and was recorded both in typed form and on paper tape. After completion of the experiment, the tape was read into the Hewlett-Packard 2100A computer for data reduction. Details of construction and programming of the microcomputer system are available elsewhere.[14]

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(27) The ratio $\phi(CH_3NH_3^+)/\phi(CH_3NH_2)$ is 1.021, suggesting that the relative acidity of $CD_3NH_3^+$ and $CH_3NH_3^+$ should be 1.064, while van der Linde and Robertson[21] observed $K_{3H}/K_{3D} = 1.12–1.16$ from 5 to 45 °C. This would correspond to a fractionation-factor ratio of 1.042 at 25 °C. The isotope effects for dimethylamine and trimethylamine generate even larger ratios of 1.047 and 1.048. Kaplan and Thornton[22] observed a *kinetic* effect for reaction of methyl tosylate with $(CL_3)_2NC_6H_5$ (L = H, D) at 51 °C in nitrobenzene of $k_D/k_H = 1.021$ per deuterium. Assuming no complications, this effect should be similar to a protonation effect and smaller than the equilibrium value. Thus, the ratio of calculated fractionation factors, while clearly in the correct direction, probably underestimates the positive-charge effect. This is mainly of importance here only insofar as it affects the estimation of $\phi(CH_3SR_2^+)$. It is probable that the effect of positive charge in the sulfur species is smaller than in the nitrogen species because of the longer carbon–sulfur bond length and the greater polarizability of sulfur and because any hyperconjugation[28] of the CH electrons will reduce the electrostatic effect on the force constant. For this reason, the true correction factor for positive charge on sulfur should be less than that for positive charge on nitrogen. In line with this view, Kaplan and Thornton[22] found a kinetic effect for reaction with methyl tosylate of $(CL_3)_2PC_6H_5$ of only 1.008 per deuterium, although this reduction from the amine effect (see above) might have come from a change in transition-state structure rather than from a smaller equilibrium value. In considering the sulfonium compound isotope effects, three values of $\phi(CH_3SR_2^+)$ have therefore been used: 1.026 (calculated methylamine/methylammonium correction) 1.005 (no electrostatic correction), and 1.053 (empirical electrostatic correction from ionization of trimethylammonium ion, equal to 1.048).
(28) This kind of delocalization, while opposite in effect to the electrostatic influence, is unlikely to override it substantially because conjugative stabilization even of fully formed carbanions adjacent to sulfur (neutral of positive) seems minimal in comparison to polarization: S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972); A. Streitwieser, Jr., and S. P. Ewing, *J. Am. Chem. Soc.*, **97**, 190 (1975); A. Streitwieser, Jr., and J. E. Williams, Jr., *ibid.*, **97**, 191 (1975); S. Wolfe, P. Chamberlain, and T. F. Garrard, *Can. J. Chem.*, **54**, 2847 (1976).
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(31) For the 22 transmethylation reactions, the observed rms difference of ϕ_T from unity is 46×10^{-3}. These differences are predicted by eq 10 with an rms residual of 2.8×10^{-3} or 6%.
(32) It is important to keep in mind that the greater looseness of transalkylation than transmethylation transition states is *relative* to expectations from reactant and product fractionation factors. In fact, the ϕ_T values are frequently larger for transalkylation than for transmethylation, but this is because of the extra group attached to the transferring carbon.[8,12] The point is that the ϕ_T for transalkylations *never* approach the expectation from eq 10 (dotted extension of the solid line in Figure 1).
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