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Initial-state and Transition-state Isotope Effects of Methyl Halides in Light and Heavy Water[1-3]

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Solubilities of four methyl halides at 29.4° and 40.3° are nearly the same in H_2O as in D_2O. Evidently these solutes fit into holes in the water, without either freeing or restricting the motion of surrounding water molecules. Since initial-state isotope effects are so small, calculated transition-state isotope effects for hydrolysis are nearly equal to the observed kinetic isotope effects. Methyl chloride is more ionized than methyl bromide at the transition state in solvolysis in water at 40–70°.

Initial-state isotope effects from relative solubilities of simple solutes in light and heavy water give information on the structure of water solutions. Furthermore, they are essential for interpreting kinetic isotope effects of these solutes, since transition-state isotope effects can be calculated only if initial-state isotope effects are known. Results obtained with four methyl halides at 29.4, 40.3 and 49.6° are presented and discussed in this paper.

Methyl iodide is the most soluble of the methyl halides in water at 29.4°; methyl fluoride is the least soluble. All are more concentrated in aqueous solution than in the gas phase in equilibrium at 20–30°[4]. Table I presents thermodynamic quantities for

$$CH_3X(g) \rightleftharpoons CH_3X(\text{solution}) \qquad (1)$$

at 29.4° in both H_2O and D_2O, where the standard states are perfect gas at 1 atm. and hypothetical perfect 1 M solution in H_2O or D_2O. Initial-state isotope effects (K_{H_2O}/K_{D_2O}) at 29.4° are 0.98-(CH_3F), 1.04 (CH_3Cl), 1.07(CH_3Br), 1.10 (CH_3I); at 40.3°, 0.95, 1.03, 1.065, 1.08; at 49.6°, 1.025 (CH_3Cl), 1.075 (CH_3Br). The solubilities are thus almost the same in light and heavy water.

TABLE I

THERMODYNAMIC QUANTITIES FOR REACTION 1

System	$\Delta F^0_{29.43°}$, cal. mole^{-1}	$\Delta H^0_{29.4-40.3°}$, cal. mole^{-1}	$\Delta S^0_{29.43°}$, cal. mole-$^{-1}$ deg.$^{-1}$
CH_3F–H_2O	1763.5 ± 5.7	−4143 ± 116	−19.52 ± 0.40
CH_3F–D_2O	1753.8 ± 5.4	−3654 ± 126	−17.87 ± .43
CH_3Cl–H_2O	1423.2 ± 2.4	−5212 ± 51	−21.93 ± .18
CH_3Cl–D_2O	1445.0 ± 7.4	−5072 ± 163	−21.54 ± .56
CH_3Br–H_2O	1192.1 ± 6.8	−5175 ± 161	−21.04 ± .55
CH_3Br–D_2O	1231.7 ± 5.4	−5099 ± 126	−20.92 ± .43
CH_3I–H_2O	1119.4 ± 2.8	−5916 ± 80	−23.25 ± .27
CH_3I–D_2O	1178.6 ± 6.2	−5547 ± 179	−22.22 ± .61

The greater concentration in aqueous solution than the gas phase would be an unexpected result if these solute molecules had to "make their own holes." Evidently they utilize pre-existing holes, neither seriously disrupting hydrogen bonds when they dissolve (which would give a higher solubility in light water) nor giving surrounding water molecules a much more rigid or ice-like structure (which would give a higher solubility in heavy water).[5] Such holes, surrounded by 20, 24 or 28 water molecules having the same bond angles, distances and hydrogen bonding as in pure ice, were previously found in the crystalline gas hydrates of the rare gases, methane and the four methyl halides.[4,6] Pauling discusses the structure of pure liquid water in terms of holes filled with water molecules instead of solute molecules.[6]

This conclusion that the adjacent liquid water molecules have a structure similar to pure liquid water at the same temperature (and not like ice) is contrary to the current view[7] that the considerably greater loss in entropy when non-electrolytes dissolve in water compared to alcohols or non-polar solvents is due to ice-like patches surrounding the solute in which the motions and exchanges of water molecules are restricted ("fluttering cluster" hypothesis). Although the smaller rare gases may yet prove to be considerably more soluble in D_2O on this account, a better explanation for the methyl halides seems to be restriction of the motions of the solute in all holes, but much more disruption of the structure of organic solvents than of water when a non-electrolyte dissolves because organic solvents cannot form such perfect holes, their wall molecules are much freer than in the pure solvent, and tend to wander into the holes created by the solute. Thus the structure of organic solvents is broken down whereas that of water is relatively unaffected.

The small differences in solubility in light and heavy water that are observed and the somewhat less negative entropy of solution for methyl fluoride suggest that methyl fluoride fits easily into its cavity, whereas the other methyl halides stretch their cavities and break up the water structure very slightly. The volume of the solute makes a negative contribution to the entropy.[8] However, $\Delta\Delta F°$ even for methyl iodide is so small (59 cal. mole^{-1}) that it could be accounted for by an average shift in librational frequency from 667 to 663 cm.$^{-1}$ for 28 surrounding water molecules.

Table II gives initial-state, kinetic and transition-state isotope effects for hydrolysis of methyl chlo-

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(1) Supported in part by the Atomic Energy Commission under Contract no. AT(30-1)-905 and by a National Institutes of Health. predoctoral fellowship to E. R. T.

(2) Previous papers by C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **83**, 3884, 3890 (1961); **84**, 817 (1962).

(3) *Cf.* E. R. Thornton, Ph.D. Thesis in Organic Chemistry, M.I.T., September, 1959, for complete data (pp. 55–58) and plots of the data (pp. 20–27).

(4) D. N. Glew and E. A. Moelwyn-Hughes, *Disc. Faraday Soc.*, **15**, 150 (1953).

(5) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960); C. G. Swain, R. F. W. Bader and E. R. Thornton, *ibid.*, 200 (1960).

(6) W. F. Claussen, *J. Chem. Phys.*, **19**, 1425 (1951); N. v. Stackelberg and H. R. Müller, *Z. Elektrochem.*, **58**, 25 (1954); J. C. Platteeuw and J. H. van der Waals, *Mol. Phys.*, **1**, 91 (1958); L. Pauling, "The Nature of the Chemical Bond," ed. 3, Cornell Univ. Press., Ithaca, N. Y., 1960, pp. 472–473.

(7) H. S. Frank and Wen-Yang Wen, *Disc. Faraday Soc.*, **24**, 133 (1957).

(8) R. E. Powell and W. M. Latimer, *J. Chem. Phys.*, **19**, 1139 (1951); D. N. Glew, *Disc. Faraday Soc.*, **15**, 260 (1953); D. D. Eley, *ibid.*, **15**, 263 (1953).

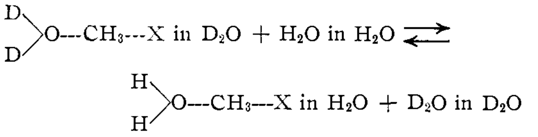
TABLE II

TRASITION-STATE ISOTOPE EFFECTS

Compound	Isotope effects at 40° Init. state	Kinetic[a]	Transit. state	Isotope effects at 70° Init. state[a]	Kinetic	Transit. state
CH_3Cl	1.03	1.36	1.40	1.02–3	1.322[b]	1.35–1.36
CH_3Br	1.065	1.28	1.36	1.06–65	1.245[c]	1.32–1.33
CH_3I	1.08	1.33	1.44	1.02–8	1.285[b]	1.31–1.39

[a] Estimated from a linear extrapolation of a plot of k_{H_2O}/k_{D_2O} *vs.* $1/T$. [b] R. N. Griffin, Ph. D. Thesis in Organic Chemistry, M.I.T., October, 1957, p. 30. For further data and discussion, *cf.* also A. Maclachlan, Ph. D. Thesis in Organic Chemistry, M.I.T., August, 1957, pp. 32–37. [c] P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **34**, 1714 (1956). The kinetic work of these authors is superb.

ride, bromide and iodide in H_2O and D_2O. Since the kinetic isotope effects were determined only down to 70°, it is necessary to extrapolate them to 40°, or to extrapolate the initial state effects to 70°. Both are done in Table II. The transition state isotope effect is the equilibrium constant of the reaction

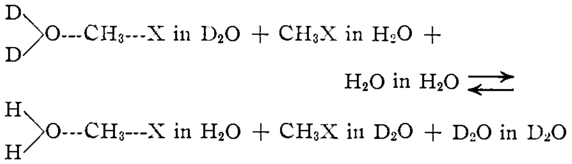


$$\mathrm{D_2{>}O{-}{-}{-}CH_3{-}{-}{-}X\ in\ D_2O + H_2O\ in\ H_2O \rightleftarrows H_2{>}O{-}{-}{-}CH_3{-}{-}{-}X\ in\ H_2O + D_2O\ in\ D_2O} \qquad (1)$$

where the standard states are hypothetical perfect 1 *M* solutions *in the solvents indicated*. It is therefore the product of the initial state isotope effect, *i.e.*, the equilibrium constant for

$$\mathrm{CH_3X\ in\ D_2O \rightleftarrows CH_3X\ in\ H_2O} \qquad (2)$$

and the kinetic isotope effect, *i.e.*, the equilibrium constant for



$$\mathrm{D_2{>}O{-}{-}{-}CH_3{-}{-}{-}X\ in\ D_2O + CH_3X\ in\ H_2O + H_2O\ in\ H_2O \rightleftarrows H_2{>}O{-}{-}{-}CH_3{-}{-}{-}X\ in\ H_2O + CH_3X\ in\ D_2O + D_2O\ in\ D_2O} \qquad (3)$$

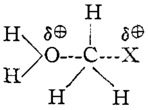
Note that this is a different convention from that used previously,[5] where the standard state for all solutes in both waters was a hypothetical perfect 1 *M* solution in light water (H_2O). It is used here so that the calculated transition state isotope effect will be the equilibrium constant of reaction 1.

This conclusion that these kinetic isotope effects reflect the transition state difference much more than an initial state difference is quite contrary to current views attributing them primarily to differences in the initial state.[9]

It was shown previously[5] that the librational frequency (I) of water is constant between *ca.* 20–70°. This does not imply, as Heppolette and Robertson[9] supposed, that isotope effects should be temperature-independent, since they depend upon $e^{h\nu/2kT}/(1-e^{-h\nu/kT})$. The simple inverse temperature relationship $\log(k_H/k_D)_1/\log(k_H/k_D)_2 = T_2/T_1$ accounts for 75% of the difference between 35 and 80°, their minimum and maximum temperatures. Heat capacities present in the partition function but absent in the simple equation above should account for the rest. A more accurate estimate cannot be made because it would require a knowledge of all the transition state frequencies.

An approximate treatment of solvent isotope effects[10] seems open to some criticism because of their assumptions that the internal frequencies of water molecules solvating ions are changed from those of pure liquid water and that the reduced mass relationship holds for all frequencies of hydrogen and deuterium. The former is unnecessary; the latter is untrue. Although this theory may be regarded as a useful empirical correlation, it appears that the only safe approach is to treat solvent isotope effects by making detailed calculations based on a minimum of approximations. The conclusions of the detailed treatment[5] should be compared with the approximate theory.[10]

Since the transition state isotope effect is smaller for methyl bromide than for methyl chloride in spite of a larger isotope effect for solution of iodide ion (1.95) or bromide ion (1.69) than for chloride ion (1.48),[5] C–X bond breaking at the transition state must be more complete for methyl chloride than for methyl bromide.



This is in accord with a recently proposed rule.[11] It is in disagreement with the order suggested by Heppolette and Robertson and used as evidence that the secondary isotope effect in the transition state is negligible. In fact this, secondary isotope effect could be as large as 2.0,[2] which is not negligible compared to observed kinetic isotope effects of 1.3. The still larger transition state isotope effect for methyl iodide is presumably due not to more bond breaking, but to much more structure breaking by incipient iodide ion in the transition state, since it is believed that iodide is six-coördinated in water, while fluoride, chloride and bromide are only four-coördinated.[5] This extra structure breaking by iodide would explain the abnormal rate effect $k_{Br} > k_I > k_{Cl}$ for methyl, ethyl, isopropyl and *n*-propyl halides, observed only in water.[9,10] Since the rule predicts that the water molecule attacking carbon would be most remote with methyl iodide, the volume of activation might actually be least negative for the iodide. There are no such data on methyl halides, but pressure does speed up methanolysis of ethyl chloride most and ethyl iodide least.[12] Dimethyl sulfate has initial-state, kinetic and transition-state isotope effects of 1.25, 1.13 and 1.41 at 25°.[13] Since structure breaking due to size alone should be at least as large in the transition state as in the initial state, the small effect due to ionic character (1.13) indicates especially incomplete C–X bond breaking here, again

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[9] P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **34**, 1716 (1956); R. E. Robertson and P. M. Laughton, *ibid.*, **35**, 1319 (1957); P. M. Laughton and R. E. Robertson, *ibid.*, **37**, 1491 (1959); R. L. Heppolette and R. E. Robertson, *Proc. Roy. Soc.* (*London*), **A252**, 273 (1959); R. L. Heppolette and R. E. Robertson, *J. Am. Chem. Soc.*, **83**, 1834 (1961).

[10] C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42, 3207, 3214 (1961).

[11] C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962).

[12] S. D. Hamann and D. R. Teplitzky, *Disc. Faraday Soc.*, **22**, 118 (1956).

[13] R. F. W. Bader, Ph.D. Thesis in Organic Chemistry, M.I.T., December, 1957, pp. 198–201, 274–296.

in accord with the rule because this has the best leaving group of all.

The still smaller kinetic isotope effect for hydrolysis of *t*-butyldimethylsulfonium ion (1.05) cannot be interpreted since initial state isotope effects have not yet been measured. Initial state isotope effects at 26° have been reported for nitromethane (1.06), furfural (1.14), ethyl acetate (1.12) and methyl acetate (1.37).[14]

Experimental

All pressures are in mm. of mercury, corrected to 0° for mercury expansion, unless otherwise noted.

Methyl fluoride from reaction of methyl iodide and silver fluoride[15] was washed with concentrated aqueous potassium hydroxide and concentrated sulfuric acid and stored in a stainless-steel cylinder. For runs 10–13, the gas was passed through two more gas-washing bottles, the first containing concentrated aqueous potassium hydroxide, the second containing concentrated sulfuric acid, into an evacuated Pyrex U-tube (U of Fig. 1) cooled with liquid nitrogen (−195.8°), where it condensed. It was then evacuated under a pressure of 5×10^{-4} mm. or less for some time (McLeod gauge) and finally distilled into a storage bulb (P) from its liquid phase until is pressure was nearly one atm. (manometer N). The temperature of the liquid methyl fluoride was less than −78.4° (b.p. at 760 mm.) at all times. The 75% which distilled first was used. When the methyl fluoride in the storage bulb was frozen in liquid nitrogen, the pressure in the bulb was less than 0.1 mm. Each time a sample was taken from the storage bulb for a run, the vapor was condensed with liquid nitrogen, pumped for a few minutes under a pressure of 5×10^{-4} mm. or less, and then allowed to evaporate slowly from its liquid phase into the measurement apparatus. This technique removed any air present in the bulb and provided an additional fractionation of any water and methanol impurities. A mass spectrum (sample collected at T) indicated less than 0.1% methanol and difluoromethane. The methyl fluoride for runs 14–16, 22 and 23 was purified in a slightly different way as a check on possible impurities. It was passed directly from the cylinder into the U-tube cooled with liquid nitrogen, with the U-tube under constant high-vacuum pumping at 5×10^{-4} mm. or less while the methylfluoride was being collected. The methyl fluoride was then allowed to distil from its liquid phase as described above.

Methyl chloride from a Matheson Co. lecture bottle was bubbled through the two gas-washing bottles as described above before being collected in the U-tube cooled with liquid nitrogen. Any vapors present in the washing bottles had been removed by passage of air through them. A mass spectrum indicated that less than 0.1% of other methyl halides contaminated the methyl chloride. The methyl chloride was then distilled from Dry Ice–acetone into liquid nitrogen, to remove methanol and water (runs 2–4, 29 and 30). The vapor pressure measured at Dry Ice temperature was 33.0 mm. in agreement with the recorded value[16] at −78.5°, but the temperature variation caused an uncertainty in the vapor pressure of approximately 0.5 mm. In run 1 the methyl chloride was not bubbled through the gas-washing bottles. In runs 17–19 the procedure was similar to that for runs 2–4, 29 and 30 except that the methyl chloride was distilled from its liquid phase under a maximum pressure of 0.5 atm. instead of from a Dry Ice–acetone-bath. A mass-spectral analysis indicated less than 0.1% methanol and dichloromethane. The samples for measurements were taken by freezing, pumping at a pressure of less than 5×10^{-4} mm., and slowly distilling the methyl chloride from its liquid phase, as with methyl fluoride.

Methyl bromide from a Dow Chemical Co. cylinder was bubbled through the two gas-washing bottles as above, then collected in a U-tube immersed in liquid nitrogen at a pressure of 5×10^{-4} mm. or less. It was distilled from a Dry Ice–acetone-bath into the storage bulb by condensation with liquid nitrogen. The vapor pressure of the methyl bromide used in runs 5–9 in a water–ice-bath was 659.9 mm. compared to values recorded in the literature of 660.0[17] and 662[16] mm. The methyl bromide used in runs 20 and 21 had a vapor pressure of 661.7 mm. at 0°. The methyl bromide used in runs 31 and 32 had a vapor pressure of 661.6 mm. at 0°. Samples of methyl bromide for measurements were taken by the same method as with methyl fluoride, by freezing, pumping at a pressure of 5×10^{-4} mm. or less, and distilling from the liquid.

Methyl iodide from a fresh 100-g. Eastman Kodak Co. bottle was poured into a flask, attached to the U-tube, and frozen in liquid nitrogen. The air was pumped off until a pressure of less than 5×10^{-4} mm. was obtained in the vacuum line. The liquid nitrogen trap was removed from the flask and placed around the U-tube. As the methyl iodide thawed, it distilled into the U-tube. During the distillation the U-tube was pumped at a pressure of less than 5×10^{-4} mm. The U-tube was then immersed in a Dry Ice–acetone-bath and the methyl iodide was distilled into the storage bulb by condensation with liquid nitrogen. In both distillations, the 75% of the methyl iodide which distilled first was used. The methyl iodide was surrounded by an ice-water-bath. The methyl iodide vapor in equilibrium with the liquid was pumped away several times until the vapor pressure at 0° corresponded closely with the value of 139 mm.[16] recorded in the literature. This material was used without additional purification for the measurements. The pumping to produce the proper vapor pressure was repeated immediately before each run.

Water.—Protium oxide was laboratory distilled water which was again distilled from potassium permanganate in an aged Pyrex still. Deuterium oxide (> 99.5%) was obtained in 100-g. ampuls from Liquid Carbonic Co. For each sample of protium or deuterium oxide, the water was connected to a vacuum line so that it could be degassed by pumping thoroughly several times over a period of days. Initially, each sample was heated to roughly 70–100° and the vapor above it pumped off while it was hot. Then the vapor was pumped off several times when it had reached room temperature. Each pumping of the vapor was for 5–10 min. It is probable that the degassing was sufficient since different samples, treated in slightly different ways, gave no noticeable change in the results. For example, a sample of protium oxide pumped many times over a period of about two weeks with magnetic stirring gave the same results as a sample which had been pumped over a period of only two days without magnetic stirring. Samples of 10–20 ml. of water were used, and the pressures were usually 150–200 mm., although a few runs were done at pressures of about 100 mm. Since Glew and Moelwyn-Hughes[4] have shown the equilibrium constants to be independent of pressure in the case of protium oxide, it was not necessary to vary the pressure systematically in this study.

Apparatus.—Temperatures were controlled to better than 0.01° in all but a few cases. The bath was stirred with a 1550 r.p.m. motor having a propeller on its shaft. The circulation of air bubbles could be observed, and incicated that circulation to all parts of the bath was excellent. The bath thermometer was standardized at the temperatures used by comparison with a totally immersed thermometer with corrections by the National Bureau of Standards. The bath thermometer was kept immersed to its 10° mark. The bath was rectangular, 30 cm. long, 30 cm. wide and 60 cm. high, with glass walls, one wall with plate glass for accuracy in reading an immersed manometer. With a Gaertner M908 cathetometer, the manometer was readable to 0.05 mm., corresponding to an error in volume of about 0.03%.

The measuring system,[18] methyl halide storage system and water storage system are shown in Fig. 1. The vacuum line was evacuated by a Welch DuoSeal two-stage vacuum pump and a Pyrex mercury diffusion pump. Apiezon N stopcock grease was used for all joints and stopcocks except those in the methyl halide storage system, where Dow Corning high-vacuum silicone grease was used.

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[14] I. B. Rabinovich, V. D. Fedorov, N. P. Pashkin, M. A. Avdesnyak and N. Y. Pimenov, *Doklady Akad. Nauk S.S.S.R.*, **105**, 108 (1955); *C. A.*, **50**, 9845 (1956).

[15] E. Moles and T. Batuecas, *J. chim. phys.*, **17**, 537 (1919).

[16] R. T. Sanderson, "Vacuum Manipulation of Volatile Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 129.

[17] C. J. Egan and J. D. Kemp, *J. Am. Chem. Soc.*, **60**, 2097 (1938).

[18] H. C. Brown, M. D. Taylor and M. Gerstein, *ibid.*, **66**, 431 (1944).

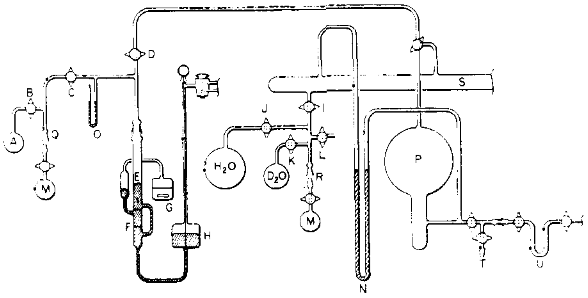

Fig. 1.—The measuring apparatus.

Procedure.—In Fig. 1, S is the vacuum manifold. The detachable water weighing bulb M was evacuated, weighed after removal of grease from the ground-glass joint with toluene, and then attached by a ground-glass joint at R. After evacuation, stopcock J or K was opened and the vapor above the deuterium or protium oxide pumped away. Stopcock I was then closed and the water distilled into bulb M by cooling M in an ice–water-bath and heating the water reservoir with either a heating mantle or hot water in a Dewar flask. When a sufficient amount of water had condensed in M, stopcock J or K was closed and stopcock I opened so that the vapor above the liquid water in M was pumped away. Then the stopcock on bulb M was closed and bulb M was removed by closing stopcock I and admitting air through stopcock L. Bulb M was weighed and the amount of water determined by difference. The tares of bulb M showed deviations of less than 0.01 g. between different runs. Bulb M was then attached at Q by a ground-glass joint, and pumped for at least 30 min. to remove air from the grease in the joint.

The volume of bulb G plus the remainder of the system down to the etched line at F was determined beforehand by measuring the pressure of a known amount of carbon dioxide. A glass bulb with a stopcock on it, with a known volume determined by weighing it empty and full of water, was attached by a ground-glass joint at Q. A measured pressure of carbon dioxide was trapped in the bulb and its stopcock was closed. The measuring apparatus was evacuated. Stopcock D was closed and the stopcock on the bulb opened. The carbon dioxide was condensed quantitatively in bulb G with liquid nitrogen. The mercury reservoir H had a glass rod with rubber tubing seal above and ground into a glass valve below and a stopcock for connecting to vacuum or admitting air. The mercury was raised to isolate bulb G from the rest of the system and stopcock D opened to the vacuum line. The mercury was adjusted so that the lower level was at the line at F, and the pressure was read. The volume V_2 of the measurement apparatus down to the etched line could be calculated from $p_1 V_1 = p_2 V_2$ since both the bulb of known volume and bulb G were at room temperature during the entire operation. The volume was 139.5 ± 0.2 ml. The volumes of the stirring bars used were determined separately by volume of water displaced, before they were put into bulb G. They had volumes of about 0.5 ml.

The desired pressure of methyl halide was admitted to the measurement apparatus shown in Fig. 1 from the storage bulb P by distillation from its liquid phase as described above. After raising the level of mercury by letting air into the mercury reservoir H, so that a sample of methyl halide was trapped in bulb G, the remainder of the apparatus was evacuated. The pressure was then measured by recording the differences in the mercury levels, which were at the places indicated by E and F. The etched line at F allowed the volume of the cell to be adjusted to the same value each time a reading was made, by adjusting the lower mercury level to the line. During the pressure measurement the constant-temperature bath was raised around the measurement apparatus.

After the initial pressure of methyl halide had been determined as described above, the bath was lowered. The methyl halide in bulb G was condensed with liquid nitrogen, stopcock D closed and the mercury lowered so that the methyl halide could be distilled from bulb G into bulb A by condensation with liquid nitrogen. Stopcock B was closed, while the methyl halide remained condensed in bulb A. The stopcock on bulb M was opened, and bulb M was surrounded by warm water while bulb G was surrounded by ice-water. The water in bulb M distilled into bulb G. It might seem easier merely to condense the methyl halide with liquid nitrogen, leaving it in bulb G all the time, and then distil the water from bulb M into bulb G cooled with liquid nitrogen. The procedure was abandoned because it condensed large amounts of mercury in bulb G. A small amount of mercury collected even in the above procedure, but the final volume of the mercury allowed to accumulate over the several runs was only about 0.05 ml. Finally the water in bulb G was frozen in liquid nitrogen, stopcock B was opened, and bulb A was allowed to warm up. After all of the water and methyl halide was in bulb G, and manometer O indicated no vapor pressure, stopcock D was opened for a few seconds to remove any traces of air. The vapor pressures of water and methyl halides are so low at liquid nitrogen temperature that none was lost. This is demonstrated by the consistent results obtained in various runs in which the time of this pumping was varied from 0 to approximately 10 seconds. The mercury level was again raised so as to cut off the contents of bulb G from the vacuum line. The water–methyl halide system was thawed. It was found expedient to heat the mixture to a temperature above the proposed temperature of equilibration to eliminate supersaturation effects. This was found not to be necessary with methyl bromide and iodide.

The bath was raised around the apparatus so that bulb G and the entire length of the mercury column were sub-

TABLE III

SOLUBILITIES

Solvent	Run no.	Temp., °C.	$(p_2/c_2) \times 10^{-4}$, mm. M^{-1}	Temp., °C.	$(p_2/c_2) \times 10^{-4}$, mm. M^{-1}
		Methyl fluoride			
H_2O	10	29.44	1.440	40.34	1.804
H_2O	12	29.42	1.410	...	...
H_2O	14	29.45	1.431	40.35	1.794
H_2O	16	...	...	40.35	1.832
H_2O	22	...	...	40.35	1.829
H_2O	23	29.45	1.431	...	...
D_2O	11	29.42	1.396	40.34	1.743
D_2O	13	29.45	1.401	40.34	1.714
D_2O	15	29.45	1.416	40.35	1.747
		Methyl chloride			
H_2O	1	29.44	0.811	...	...
H_2O	2	29.44	.814	40.34	1.099
H_2O	17	29.44	.805	40.35	1.094
H_2O	19	29.43	.810	40.35	1.095
H_2O	30	29.43	.813	49.59	1.343
D_2O	3	29.43	.850	40.35	1.137
D_2O	4	29.43	.850	40.33	1.129
D_2O	18	29.44	.827	40.35	1.116
D_2O	29	29.41	.834	49.59	1.380
		Methyl bromide			
H_2O	5	29.43	0.547	40.35	0.735
H_2O	7	29.43	.550	40.35	.744
H_2O	20	29.44	.558	40.35	.754
H_2O	31	...	...	49.59	.940
D_2O	6	29.43	0.593	40.39	.785
D_2O	8	29.43	0.585	...	...
D_2O	9	...	...	40.34	0.790
D_2O	21	29.44	0.589	40.35	0.801
D_2O	32	...	...	49.59	1.010
		Methyl iodide			
H_2O	24	29.45	0.490	40.35	0.692
H_2O	26	29.44	.488	...	...
H_2O	28	...	...	40.34	0.685
D_2O	25	29.43	0.545	40.35	.745
D_2O	27	29.45	0.534	40.34	.742

merged. Equilibration was speeded by agitating manually a Pyrex-enclosed magnet in bulb G by means of a horseshoe magnet outside bulb G. The mercury level was kept adjusted at the etched line at F during this equilibration. Two thermoregulators were used so that equilibration of each sample of water and methyl halide could be carried out at two temperatures.

When the pressures had been determined, the total number of moles of methyl halide present and the number of moles present in the vapor above the solution at equilibrium could be calculated. The perfect gas law was used in the calculations. For methyl bromide the correction afforded by the use of the second virial coefficient is about 0.5%. For methyl chloride and fluoride the correction would be even smaller percentage-wise. Since the second virial coefficient of methyl iodide is apparently not available, it is not thought necessary to make this small correction. It could only change the magnitude of the results and not the isotope effect in any case. Therefore, both the pressure of the methyl halide at equilibrium and the concentration of methyl halide in solution could be calculated. The equilibrium constant in mm. M^{-1} is the ratio of these two quantities. The pressure is in mm. at 0°. The densities of light and heavy water were also necessary.[19]

After a run, the water and methyl halide were removed by distillation into a bulb immersed in liquid nitrogen. Since a small amount of mercury had condensed into bulb G in each run, there was a residue of mercury plus (probably) mercury halides in bulb G. However, the consistency of results (*e.g.*, methyl chloride runs 1 and 19 in Table III) suggests that no appreciable error was incurred from this source. Further, the vapor pressure of pure water, measured in the same way as the actual runs were performed except that no methyl halide was introduced, was nearly the same as the results recorded in the literature.

Our results agree quite well with those of Glew and Moelwyn-Hughes.[4] We have noted some inconsistencies in the Glew and Moelwyn-Hughes paper between equilibrium constants calculated from the equation they give and the experimentally observed constants recorded in their tables. These are probably attributable to typographical errors.

A sample calculation for run 28, methyl iodide–H_2O follows.[3] Methyl iodide initial pressure was 151.15 mm., or 150.11 mm. after a −1.04 mm. correction for expansion of mercury from 40.34 to 0°. Since the total volume of the cell in absence of water was 138.9 ml., this was 10.6655×10^{-4} mole. The volume of the cell corrected for 15.0230 g. water was 123.8 since the density of water at 40.34° is 0.99211 g. ml.$^{-1}$. The total pressure at equilibrium was 182.05 mm. After corrections of −1.25 mm. for expansion of mercury from 40.34 to 0° and −55.94 for the vapor pressure of water at 40.34°, the methyl iodide in the gas phase is 124.86 mm. (p_2) or 7.9070×10^{-4} mole. Therefore the concentration in solution (c_2) is 1.8217×10^{-2} M and the equilibrium constant is p_2/c_2 or 6854 mm. M^{-1}.

Table III gives equilibrium constants from all the runs. Table I gives thermodynamic quantities (for a standard state of 1 atm.) derived from the data in Table III. The value of $\Delta H°$ was computed by multiplication of the least squares straight-line slope of log (p_2/c_2) *vs.* $(1/T)$ by $2.303R$. The least-squares slope was calculated from the formula for a in the equation $y = ax + b$

$$a = (n\Sigma xy - \Sigma x\Sigma y)/(n\Sigma x^2 - (\Sigma x)^2)$$

where $x = 1/T$ and $y = \log(p_2/c_2)$. The squares of the deviations in y were thus minimized. This $\Delta H°$ is therefore only an approximation, since it is known from the work of Glew and Moelwyn-Hughes[4] that the plot is not linear. However, the results at three temperatures for methyl chloride in light and heavy water were plotted[3] as log(p_2/c_2) *vs.* $1/T$ and it was found that when the three points for H_2O were fitted with a flexible curve, this same curve almost exactly fitted the points for D_2O when merely shifted along the $1/T$ axis. This is an interesting observation since it has been found that H_2O at one temperature has a viscosity like D_2O at a temperature 8.5° higher.[20] The curves for methyl chloride in H_2O and D_2O are also superimposable by a shift in the vertical direction. Therefore, it is probable that the two curves for each methyl halide have the same shape, and that the differences in thermodynamic quantities for reaction 1 are comparable between light and heavy water even though it has been assumed in the calculations that $\Delta H°$ is independent of temperature. The results for both methyl chloride and bromide at 50° were approximately corrected for hydrolysis, but hydrolysis contributed so much to the result for methyl bromide that the figures at 50° are very crude.

The standard deviations are given after the computed thermodynamic quantities in Table I. They were computed from the standard deviations σ_y and σ_a for the least-squares plot where

$$\sigma_y^2 = \Sigma(y_{\text{obs}} - y_{\text{calc}})^2/(n - 2) \text{ and } \sigma_a^2 = n\sigma_y^2/(n\Sigma x^2 - (\Sigma x)^2)$$

$\Delta F°$ was computed from the formula $\Delta F° = -RT \ln K$ where K is p_2/c_2, p_2 is the pressure in atm., R is 1.987 cal. mole^{-1} deg.$^{-1}$, and 0°C. is 273.15°K. $\Delta S°$ was then computed from $\Delta F° = \Delta H° - T\Delta S°$.

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Nucleophilic Catalysis of Semicarbazone Formation by Anilines[1]

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The following lines of evidence demonstrate that catalysis of semicarbazone formation by aniline and several of its ring-substituted derivatives proceeds *via* the rate-determining formation of a Schiff base between substrate and catalyst, followed by a rapid attack of semicarbazide on the Schiff base to yield the semicarbazone. (1) Catalysis by anilinium ions is very much more efficient than catalysis by other acids of comparable acid strength. (2) The rate of Schiff base formation accounts quantitatively for the rate of aniline-catalyzed semicarbazone formation. (3) Schiff bases react rapidly and quantitatively with dilute aqueous solutions of semicarbazide to yield the semicarbazone. (4) Except in very dilute solutions, the rate of aniline-catalyzed semicarbazone formation is independent of semicarbazide concentration. (5) The rate of aniline-catalyzed semicarbazone formation is the same as the rate of aniline-catalyzed oxime formation.

In a study of general acid catalysis of semicarbazone formation by a number of acids of varying structure and acid strength,[2] aniline and several of its ring-substituted derivatives were found to be 10–1000 times more effective catalysts than predicted from their pK_a values. Such abnormal catalytic ability suggested that anilines may function *via* a mechanism other than classical general acid catalysis. Evidence presented in

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[1] Presented at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1960 (Abs. 46P).

[2] E. H. Cordes and W. P. Jencks, unpublished experiments.