dioassay due to contamination by the product.

In the case of MeMgI + 5 mol % $FeCl_3$, two products, 1,2-adduct and benzopinacol, were formed. Since benzopinacol was liable to decompose under the practical GLC conditions (column temperature >150 °C) used in this experiment,[32] the amount of pinacol was determined by HPLC (reverse phase C18, MeOH-H_2O) by calibrating its sensitivity with an internal standard. The amounts of benzophenone and the 1,2-adduct were measured by GLC (PEG 20M, 0.5 m) with the column temperature of 145 °C. The material balance of the reaction was excellent. In the case of the reaction of the radioactive material, the molar fraction of pinacol was calculated from those of the unreacted ketone and the 1,2-adduct which could accurately be determined by GLC. To determine the KIEs, unreacted benzophenone and the two products were isolated by TLC and purified by recrystallizations, and their radioactivities were measured. The KIEs for the two reaction channels were calculated by using Tong-Yankwich type equations for competitive reaction schemes (see the supplementary material).

For the *t*-BuMgCl reaction, the typical workup procedure could not be used since the 1,6-adduct present in the reaction mixtue decomposed competitively to *tert*-butylbenzophenone and benzophenone during the workup procedure.[4] The GLC analysis (PEG 20M, 0.5 m, 145 °C) of the reaction mixture after the workup gave recovered benzophenone, 1,2-adduct, and *tert*-butylbenzophenone as major components (pinacol did not decompose but could not be detected under the GLC conditions due to a long retention time), but the ratio of benzophenone to *tert*-butylbenzophenone was variable from run to run. In order to determine the KIE, the unreacted benzophenone must be isolated without contamination due to the reversal from the 1,6-adduct. This was realized by adding 2 equiv of MeLi (Merck) into the reaction mixture prior to the usual workup. The unreacted benzophenone was isolated as 1,1-diphenylethanol. The addition reaction of MeLi to benzophenone is known to give the 1,2-adduct exclusively without a carbonyl-^{14}C KIE.[6a] The absence of the reversal from the 1,6-adduct during the procedure was confirmed by carrying out the Grignard reaction of benzophenone with excess *t*-BuMgCl followed by the addition of MeLi; this control experiment gave no 1,1-diphenylethanol. The KIE for the *t*-BuMgCl reaction was calculated from the variation in radioactivity of 1,1-diphenylethanol with the fraction of reaction.

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Supplementary Material Available: Relative reactivities of benzophenones with various Grignard reagents, radioactivity data, and Tong-Yankwich type equations for competitive reaction schemes (8 pages). Ordering information is given on any current masthead page.

Investigation of the Relationship between Rates of Base-Catalyzed Hydrogen Exchange and Anesthetic Potency for Some Halohydrocarbons

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Abstract: Rates of detritiation of the inhalation anesthetics halothane ($CF_3CHClBr$), methoxyflurane ($CH_3OCF_2CHCl_2$), and enflurane (CHF_2OCF_2CHFCl) were determined in dilute aqueous sodium hydroxide solutions; rates for halothane were also measured in six amine buffer solutions. The latter give a Brønsted relation with unit slope, $\beta = 0.92 \pm 0.11$, suggesting that halothane is showing normal acid behavior. The hydrogen bond donating ability of these anesthetics, taken to be proportional to pK_a's estimated from these rate data, does not correlate with their anesthetic potency, and it is therefore suggested that hydrogen bond *accepting* ability is also important in governing anesthetic potency.

Anesthetics are believed to operate by disrupting molecular associations that give nerve cell membranes the structure they need to transmit nerve impulses. Both polar and nonpolar interactions appear to be involved, and prominent among the former are hydrogen-bonding forces. This is apparent from correlations of the potency of anesthetics[1] and especially from an extensive series of spectroscopic investigations[2] which have been supplemented by theoretical calculations.[3] These spectroscopic studies have shown that anesthetics disrupt hydrogen bonds in model systems and that the extent of disruption correlates well with the potency of the anesthetic.[4]

It is thought that anesthetics exert their hydrogen bond disruptive action by forming hydrogen bonds themselves with cell membrane constituents, in competition with the intramembrane hydrogen bonds that give membranes their requisite structure. Some of the most effective anesthetics in general use today, such as halothane (**1**), methoxyflurane (**2**), and enflurane (**3**) have both

$CF_3CHClBr$ (**1**) $CH_3OCF_2CHCl_2$ (**2**) CHF_2OCF_2CHFCl (**3**)

hydrogen bond donor sites (C-H bonds) and hydrogen bond acceptor sites (oxygen and halogen atoms), and this competitive

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hydrogen bond formation could occur at either, or both, locations. In order to probe this matter, we have evaluated the hydrogen bond donating ability of these three anesthetics and have compared that with their anesthetic potency.

Our method is based upon the fact that hydrogen bond donating ability within a given class of substances is directly proportional to acid strength.[5] We have estimated the acid strengths of the anesthetics **1–3** by measuring rates of their base-catalyzed hydrogen exchange using tritium as a tracer. In order to facilitate translation of the rate constants so obtained into determinations of acid strength, we have also constructed a Brønsted relation for **1**.

Experimental Section

Materials. The anesthetics used were high-purity clinical grades obtained from Fairfield Chemical Co. (halothane), Pitman-Moore (methoxyflurane), and Ohio Medical Canada (enflurane). Buffer bases and other reagents were the best available commercial grades and were used as received. Solutions were prepared with deionized water purified further by distillation.

Tritiated substrates were prepared by allowing a solution consisting of 1.0 mL of the anesthetic, 0.50 g of NaOH, 0.040 mL of tritiated water (5 Ci/mL), and 2.0 mL of dioxane to stand at room temperature for 1 (methoxyflurane) or 2 (halothane, enflurane) days. At the end of this time the solution was poured into 50 mL of 2 M aqueous HCl, the resulting mixture was extracted with ether, the ether extracts were dried with $MgSO_4$, and the ether was then removed by low-temperature rotary evaporation. The molar activities of the resulting products showed that under these conditions exchange was ca. 75% complete in the case of halothane but only 1–2% complete for methoxyflurane and enflurane. Extents of exchange were purposely limited in the latter two cases in order to ensure that only the more acidic of the two different C–H bonds in each of these substrates was labeled.

Kinetics. Rates of detritiation were measured in wholly aqueous sodium hydroxide or amine buffer solutions. The method already described,[6] which uses data collected over 3–4 exchange half-lives, was employed for the most part. This technique, however, proved to be impractical for the very slow reactions of halothane in cyanoethylamine buffers, and an initial rate method was used instead. The new technique involved radioactive assay of the aqueous portion of the reaction mixture rather than the anesthetic substrate; since the radioactivity of this aqueous phase increased from zero (background) to some finite value, linear plots of (counts per minute) CPM vs time with well-defined slopes could be obtained despite the fact that reactions were followed to no more than 1% completion. Quenched aliquots of the reaction mixture were extracted with dichloromethane three times to ensure complete removal of radioactive anesthetic from the aqueous phase. Slopes of plots of CPM vs time were calculated by linear least squares, and first-order rate constants were obtained by dividing these slopes by "infinite-time" values of CPM determined by measuring the radioactivity of unextracted aliquots of the reaction mixture. This method of obtaining infinite-time CPMs requires the counting efficiency of tritiated water to be the same as that of tritiated anesthetic; that this was so is shown by the fact that the hydroxide ion catalytic coefficient for halothane obtained by this zero-order method, $k_{HO^-} = 0.28\ M^{-1}\ s^{-1}$, is consistent with $k_{HO^-} = 0.31\ M^{-1}\ s^{-1}$ determined by the conventional first-order technique, which does not require this assumption.

Results

Halothane (**1**) has only one kind of C–H bond, and hydrogen exchange can therefore occur at only one position in this molecule. Each of the other two substrates investigated here, on the other hand, has two different kinds of C–H bond. Nevertheless, rates of detritiation for each of these two substrates were accurately first order, and exchange at only one position was therefore being monitored in each case. This shows that our attempt to confine isotopic labeling to only one position by limiting the extent of tritium incorporation in the labeling procedure was successful.

Since the tritium labels were introduced by base-catalyzed hydrogen exchange, the positions tritiated by this limited labeling procedure must have been the more acidic C–H bonds. In the case of methoxyflurane (**2**) this is the C–H bond of the $CHCl_2$ group, for this bond is activated by two chlorines and a CF_2 group whereas the C–H bonds of the methoxyl group have the acidifying effect of only one oxygen. The two different sites in enflurane (**3**) can be expected to have much more similar acidities, but deuteration studies have shown that exchange occurs more rapidly at the CHFCl group than at CHF_2;[7] this is consistent with the known greater carbon acid strengthening effect of chlorine over fluorine.[8]

Hydrogen exchange of halocarbons is sometimes accompanied by α-elimination.[8] In the case of the present substrates, this would lead to the formation of chloride ion, but silver nitrate tests showed that no chloride ion was produced during the course of the exchange reactions studied here. Complicating β-elimination can be ruled out as well, for base-catalyzed deuterium exchange in enflurane gives good yields of deuterated product,[7] and any elimination that might take place must therefore occur much more slowly than exchange; this is consistent with the known poor leaving group abilities of the methoxide and fluoride ions,[9] which would be expelled in such β-elimination reactions.

Rates of detritiation of halothane (**1**) and methoxyflurane (**2**) were measured in dilute sodium hydroxide solution over the concentration range [NaOH] = 0.0025–0.025 M and, of enflurane, over the range [NaOH] = 0.0050–0.025 M; the data are summarized in Table S1.[10] For all three substrates, observed first-order rate constants were accurately proportional to hydroxide ion concentration; least-squares analysis gave the catalytic coefficients listed in Table I and produced zero-concentration intercepts that were less than the experimental uncertainty.

Rates of detritiation of halothane were also measured in buffer solutions of six primary amines and their ammonium ions. Series of buffer solutions of constant buffer ratio and constant ionic strength (0.10 M) but varying buffer concentration were used; buffer concentrations were varied by factors ranging from 2.5 to 10, and in each case four to six different concentrations were used.

Table I. Comparison of Acidity and Anesthetic Potency of Some Halocarbon Substrates

substrate	k_{HO^-}[a]/10^{-3} M^{-1} s^{-1}	pK_a	MAC[b]/vol %[b]
$CF_3CHClBr$ (**1**)	310	23.8	0.75
$CHCl_3$	163[c]	24.1	0.77
$CH_3OCF_2CHCl_2$ (**2**)	1.75	26.1	0.16
CHF_2OCF_2CHFCl (**3**)	0.447	26.7	1.68

[a] Aqueous solution, 25 °C, ionic strength = 0.10 M. [b] Gray, T. C.; Nunn, J. F.; Utting, J. E. *General Anaesthesia*; Butterworths: London, 1985; p 47. [c] Reference 6.

Table II. General-Base Catalytic Coefficients for the Detritiation of Halothane ($CF_3CHClBr$) in Aqueous Solution at 25 °C, Ionic Strength = 0.10 M

base	$pK_a(BH^+)$	$k_B/10^{-5}$ M^{-1} s^{-1}
CH_3NH_2	10.62[a]	53.5 ± 4.9
$HOCH_2CH_2NH_2$	9.50[b]	11.2 ± 1.0
$CH_3OCH_2CH_2NH_2$	9.40[c]	3.10 ± 0.54
$PhCH_2NH_2$	9.35[d]	8.54 ± 0.95
$(CH_3O)_2CHCH_2NH_2$	8.54[e]	0.547 ± 0.048
$CNCH_2CH_2NH_2$	7.80[f]	0.192 ± 0.014

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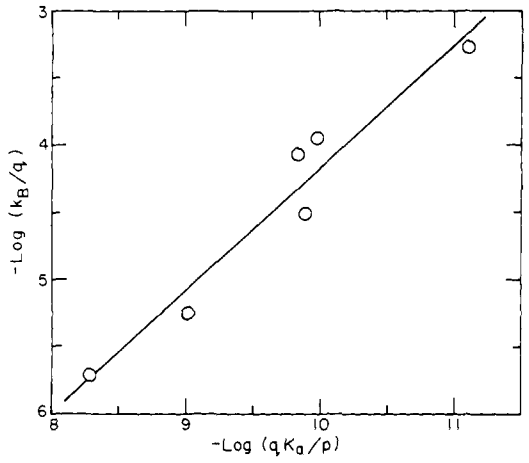

Figure 1. Brønsted relation for the detritiation of halothane catalyzed by primary amines in aqueous solution at 25 °C.

These data are summarized in Table S2.[10]

For each buffer system, observed first-order rate constants decreased with buffer concentration, consistent with the general-base catalysis expected for this reaction. Least-squares analysis of the relationship between observed rate constants and buffer base concentration gave the general-base catalytic coefficients listed in Table II. Hydroxide ion catalytic coefficients were also calculated from the zero-concentration intercepts of these buffer-dilution relationships and the known hydroxide ion concentrations of the buffers; the average of the results for all six buffers is $k_{HO^-} = 0.343 \pm 0.048\ M^{-1}\ s^{-1}$, which is consistent with the value measured directly in sodium hydroxide solutions, $k_{HO^-} = 0.310 \pm 0.007\ M^{-1}\ s^{-1}$. The hydroxide ion concentrations required for this purpose were obtained by calculation from the known basicity constants of the buffer bases and the activity coefficient $f = 0.76$ for the hydroxide ion[11] and $f = 0.795$ for the ammonium ions;[12] activity coefficients of the amines were taken to be unity.

The Brønsted plot constructed with these amine catalytic coefficients is shown in Figure 1. Least-squares analysis gave the relationship $\log (k_B/q) = -(13.34 \pm 0.11) - (0.92 \pm 0.11) \log (qK_a/p)$. Statistical factors $p = 3$ and $q = 1$ were used in establishing this relationship.

Discussion

The exponent of the Brønsted relation constructed here for the detritiation of halothane is essentially unity: $\beta = 0.92 \pm 0.11$. This is similar to the near-unity exponent, $\beta = 1.12 \pm 0.05$, found for the detritiation of chloroform,[6] and it suggests that halothane, like chloroform, is displaying normal,[13] or near-normal, acid behavior. Most carbon acids behave as pseudo, rather than normal, acids and give Brønsted relations with exponents decidedly less than unity; however, terminal acetylenes,[6,14] hydrogen cyanide,[15] and thiazolium ions[16] appear to be exceptions.

We did not construct Brønsted relations for methoxyflurane and enflurane because their very slow rates of reaction made determination of the necessary rate constants impractical. It seems likely, however, on the basis of their structural similarity to halothane, plus the fact that chloroform, the only other saturated halocarbon investigated in this way, also gives a unit Brønsted exponent, that the Brønsted exponents for detritiation of methoxyflurane and enflurane would be unity as well. If this is so and all four of these halocarbons are showing normal acid behavior, then the proton-transfer step of their base-catalyzed hydrogen-exchange reactions will be rapid and reversible and separation of the proton-transfer products will be rate-determining (eq 1).

$$RT + B \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} R^-{\cdot}TB^+ \xrightarrow[\text{r.d.}]{k} R^- + TB^+ \qquad (1)$$

The observed rate constants in such a situation are equal to equilibrium constants for the first step, K, times the rate constants for the second, $k{:}k_{obs} = Kk$. For a series of structurally similar carbon acids, RT, reacting with a common base, B, the rate constant k is likely to remain constant or nearly so; the equilibrium constant K, however, will vary in direct proportion to the acidity constants, K_a, of the carbon acids, and changes in k_{obs} will therefore reflect changes in K_a. On the basis of this assumption we have used the hydroxide ion catalytic coefficients shown in Table I to calculate acidity constants for the present substrates relative to $pK_a = 24.1$ estimated before[6] for chloroform. The results are listed in Table I, These pK_a's are necessarily approximate, but because they cover a sufficiently broad range, their accuracy is good enough to allow a conclusion to be reached regarding the relationship between acid strength and anesthetic potency.

A number of different methods of measuring anesthetic potency have been used in the past, but a leading authority[17] states that the best criterion available today is MAC. MAC is an acronym that stands for the minimum alveolar concentration of anesthetic vapor mixed with ordinary air, expressed in volume percent at a total pressure of 1 atm, that is required to produce immobility in 50% of the subjects exposed to a noxious stimulus. MAC values for the anesthetics examined here plus chloroform are listed in Table I, It may be seen that the two most acidic substances, halothane and chloroform, have similar values of MAC, consistent with their similar pK_a's. Methoxyflurane, however, is 5 times more potent despite the fact that it is a weaker acid by 2 pK units. Enflurane, on the other hand, is similar to methoxyflurane in acid strength, but it is a factor of 10 less potent.

This lack of correlation between anesthetic potency and acidity, and therefore between potency and hydrogen bond donor ability, suggests that more than one factor is important in determining anesthetic efficiency. A possible additional influence, in view of the dependence of potency upon overall hydrogen-bonding ability,[1-3] is hydrogen bond acceptor ability. This hypothesis is supported by the superior potency of methoxyflurane, for this substance, in addition to having a moderately acidic C–H bond, has a good hydrogen bond accepting site in its methoxyl oxygen. A similar site exists in enflurane, but the basicity of the site in that molecule, and therefore its hydrogen bond accepting ability, is lowered by fluorine substitution, and the anesthetic potency consequently drops.

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Registry No. 1, 151-67-7; **2**, 76-38-0; **3**, 13838-16-9; hydrogen, 1333-74-0.

Supplementary Material Available: Tables S1 and S2 listing rate data (3 pages). Ordering information is given on any current masthead page.

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