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Enthalpy of Reaction of Grignard Reagents with Brønsted Acids

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Enthalpies of formation of the magnesium salts BMgBr of 20 Brønsted acids HB have been determined from the enthalpy of reaction of HB with pentylmagnesium bromide in ether. The enthalpy of metallation of hydrocarbons with a Grignard reagent has been shown to vary linearly with the pK_a value of the carbon acid. Metallation of especially oxygen and nitrogen acidic substances has a more negative enthalpy of reaction than found for a carbon acid of the same pK_a. The reason is assumed to be back donation of the lone pairs of the hetero atoms to empty orbitals at magnesium and an attempt is made to quantify the effect.

The acidity of very weak Brønsted acids has been estimated by various methods.[1] Equilibrium methods and acidity function procedures have been useful in determining pK_a values for hydrocarbons forming resonance-stabilized anions; acidities thus determined have been linked to the acidity of alcohols, carboxylic acids, *etc.*, in aqueous solution. For unactivated alkanes the "kinetic acidity" has been studied by measuring the rate of hydrogen isotope exchange in a suitable system and using Brønsted linear free energy plots. pK_a-Values ranging from 18–41 have been determined for hydrocarbons forming charge delocalized anions and values around 50 estimated for unactivated hydrocarbons.

An alternative to the kinetic procedures has been an enthalpic approach utilizing the apparent linear correlation between the enthalpy of protonation of the anion and the pK_a-value. Thus, Arnett *et al.*[2] used the DMSO anion deprotonation of Brønsted acids and established a linear correlation between ΔH_r and pK_a for carbon acids up to pK_a=33, including many types of acids with lower pK_a, even hydrogen chloride and hydrogen iodide. An apparent linear correlation was found also for the enthalpy of protonation[3] of Grignard reagents in ether with HBr and pK_a of the corresponding hydrocarbons:

$$\mathrm{RMgBr+HBr \rightarrow RH+MgBr_2} \qquad (1)$$

The method was especially useful for unactivated hydrocarbons of extremely low acidity. Knowing the enthalpy of formation for the Grignard reagents the enthalpy of reaction could be determined for the metallation of the various hydrocarbons by a reference Grignard reagent, *in casu* pentylmagnesium bromide:

$$\mathrm{C_5H_{11}MgBr+R{-}H \rightarrow C_5H_{12}+R{-}MgBr} \qquad (2)$$

The enthalpy of reaction for this hypothetical reaction is likewise linearly correlated to the pK_a-value of RH.

It was found of interest to extend the thermochemical measurements of the metallation with Grignard reagents from carbon acids to Brønsted acids in general, including oxygen, nitrogen, halogen and sulfur acidic compounds; the general reaction being (solutions in ether):

$$\mathrm{C_5H_{11}MgBr + B{-}H \rightarrow}$$
$$\mathrm{C_5H_{12} + B{-}MgBr} \qquad (3)$$

Determination of the enthalpies of formation for the magnesium salts of alcohols, thiols, amines, *etc.* was thought to be a useful contribution to the little-developed thermochemistry of Grignard reactions, and the relation between $\Delta H_r(2)$ and pK_a was interesting in the light of the results obtained with carbon acids.

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Table 1. Enthalpy of metallation of Brønsted acids HB with pentylmagnesium bromide in diethyl ether. pK_a values taken from Ref. 1 (values in parentheses are estimated). Enthalpies of formation of B-MgBr given for ~0.1 M salt in 0.5 M ethereal pentylmagnesium bromide.

Brønsted acid HB	pK_a(HB)	$\Delta H_r(1)$ kcal mol^{-1}	Number of experiments	ΔH_f°[B–MgBr]soln in RMgBr/ether kcal mol^{-1}
HBr	−9	−59.8±0.5	(4)	−133.6
HCl	−7	−58.1±0.8	(3)	−145.7
CF_3COOH	−0.5	−65.4	(1)	−242.0
C_2H_5COOH	5	−60.0±0.5	(3)	−237.6
$C_{11}H_{23}COOH$	5	−58.1	(1)	−182.7
C_6F_5OH	5.5	−55.9[b]	(1)	
C_6H_5SH	8	−42.6	(1)	−71.4
C_6H_5OH	10	−48.4±1.0	(3)	−143.6
$CH_2(CN)_2$	11	−48.6	(1)	−59.7
$C_{12}H_{25}SH$	12	−43.8	(1)	
CF_3CH_2OH	12.5	−47.7	(1)	
CH_3OH	16	−52.5[b]	(1)	−165.2
C_2H_5OH	18	−47.7±1.0	(3)	−169.8
$(CH_3)_2CHOH$	18	−46.2	(1)	−177.9
$(CH_3)_3COH$	19	−42.5	(1)	−185.1
$C_{11}H_{23}CONHCH_3$	(25)	−44.5[b]	(1)	
$(C_6H_5)_2NH$	23	−28.4	(1)	−53.0
$C_6H_5NH_2$	28	−36.6±1.0	(2)	−84.8
CH_3NH_2	(41)	−31.2±0.6	(3)	−97.8
Cyclo-$C_6H_{11}NH_2$	41.6	−31.8	(1)	
$C_6H_5CH_3$	41.2	−7.9±1.0	(3)	−60.3
cyclo-$C_6H_{11}NHCH_3$	(43)	−29.3	(1)	
$(CH_2)_5NH$	(45)	−27.9	(1)	−104.7
$(C_2H_5)_2NH$	(46)	−26.6	(1)	−107.1
Cyclopentadiene	16	−35.5[a]	(1)	
$C_6H_5{\equiv}H$	23	−30.1[a]	(1)	−16.6
C_6H_6	43	−6.3±0.5	(4)	−49.8
Cyclopropane	46	−1.6	(1)	−50.5
Methane	48	−3.6±1.0	(3)	−79.3
Cyclopentane	51	+0.5±1.0	(3)	−80.5
Cyclohexane	52	+2.2±1.0	(3)	−90.9

[a] Metallation using dialkylmagnesium. [b] Precipitation.

Since the purpose was to include many substances and not necessarily to obtain the utmost accuracy, a simple calorimetric procedure was followed and the best available commercial quality of substrates was used after simple distillation. Though most of the measurements were single determinations, repetition and control experiments revealed an uncertainty of the results of no more than 2–3 %. Deprotonations of carboxylic acids were carried out in a flow reactor and the temperature measured after 0.01 s so that no Grignard addition to the carboxylate could interfere. Deprotonation was instantaneous with alcohols, thiols and carboxylic acids, but with amines and especially secondary amines it was slow and could last several min; for diethyl amine even between 1 and 2 h. The enthalpies of solution of the substrates in diethyl ether were determined when necessary.

The results are given in Table 1 as $\Delta H_r(3)$ and ΔH_f° [BMgBr] and in Fig. 1 as − $\Delta H_r(3)$ *versus* pK_a for the acid HB.[1]

As seen from Fig. 1, the $\Delta H_r(3)$-values for oxygen and nitrogen acids are more negative than those of carbon acids with the same pK_a values. Thus, cyclohexylamine and toluene both have

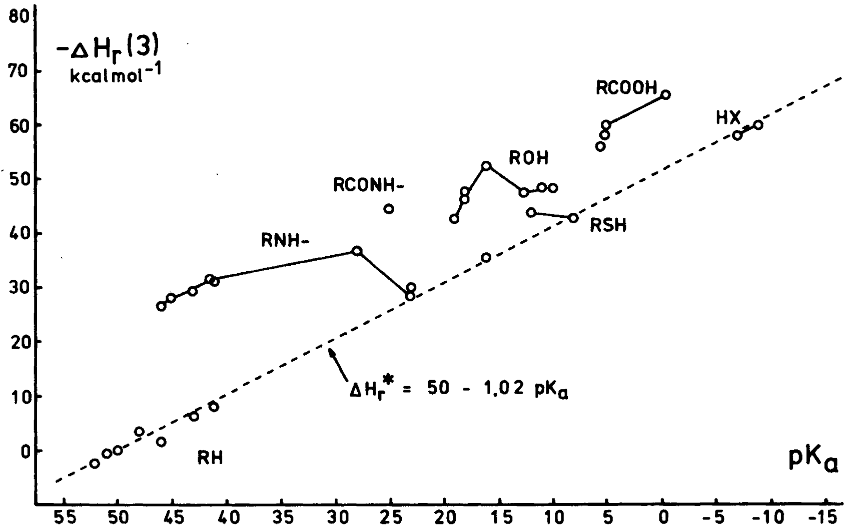


Fig. 1. Plot of $-\Delta H_r(3)$ *versus* pK_a. For explanation of the regression line, see text.

$pK_a=41$, but the reaction:

$C_6H_5CH_2MgBr+C_6H_{11}NH_2\rightarrow C_6H_5CH_3+C_6H_{11}NHMgBr$

is exothermic by 23.9 kcal mol^{-1}. Likewise cyclopentadiene and methanol both have $pK_a=16$, but the exchange reaction is exothermic by 17 kcal mol^{-1}. In analogy it is known from the literature[7] that diphenylmethyl lithium will easily metallate ammonia, while diphenylmethyl potassium will not.

In an attempt to explain these phenomena the author has chosen to abstain from an analysis of possible solvent and entropy effects and ascribe the results solely to enthalpy factors. It seems obvious that nitrogen and oxygen, in comparison with carbon, form relatively strong bonds to magnesium and lithium. The reason for this must be the Lewis acidity of *e.g.* the magnesium ion, which enables it to share the lone pairs on the hetero atoms by back donation:

$$R-\ddot{O}-MgBr\rightarrow R-\overset{+}{O}=\overset{-}{Mg}Br$$

Hydrogen and magnesium form covalent σ bonds to carbon. A more electronegative carbon atom forms a somewhat stronger bond to hydrogen, but a much stronger bond to the more electropositive magnesium. In reaction (1) which concerns carbon acids, the reaction enthalpy varies mainly with the difference $D(R-H)-D(R-MgBr)$, and this term, which concerns σ bonds is linearly correlated to pK_a (RH). When back donation occurs, the σ bond is enforced by a donor–acceptor bond, which we may call a π-bond contribution so that:

$$D(B-MgBr)=D_\sigma(B-MgBr)+D_\pi(B-MgBr)$$

It seems to be a useful abstraction, however, to postulate that for a given pK_a of HB there will be approximately the same difference $D_\sigma-(B-H)-D_\sigma(B-MgBr)$ regardless of the nature of B. The same linear relation between pK_a and $\Delta H_r(2)$ then is obtained for all Brønsted acids, when only the σ-bonding is considered. In Fig. 1 the correlation line has been drawn through points belonging to Brønsted acids for which the magnesium salts are not expected to be stabilized by back donation. These include the carbon acids, but also the halogen acids and sulfur acids like thiols, since the lone pairs on halogen and sulfur are not easily shared with magnesium. The best linear fit to these points is:

$$\Delta H_r^*=50-1.02\ pK_a$$

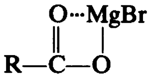
in which ΔH_r^* is the hypothetical fraction of $\Delta H_r(3)$ which pertains only to the σ bonding in the salt B−MgBr.

The extent to which a given value of $-\Delta H_r(3)$ exceeds $-\Delta H_r^*$ is ascribed to π-bonding caused by back donation within the magnesium salt:

$$D_\pi(\mathrm{B{-}MgB}) = \Delta H_r^* - \Delta H_r(3) \tag{4}$$

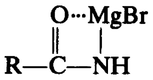
From Fig. 1 it is seen that D_π(B–Mg) as defined in eqn. (4) varies not only with the heteroatom, but also with the substitution on the heteroatom. $\Delta H_r(3)$ is almost the same for ethanol, trifluoroethanol and phenol, with pK_a values of 19, 12.5 and 10, respectively. This means that with more electronegative substitution the increase in O-Mg σ-bond strength is offset by a decrease in the strength of the coordinative bond. In the series RNH_2, $PhNH_2$, Ph_2NH having pK_a=41, 28 and 23, respectively, the values for $\Delta H_r(2)$ are −31.8, −36.6, and −28.8 kcal mol^{-1}, indicating that the increase in σ-bond strength is more than offset by the decrease in π-bonding in the magnesium salt of diphenyl amine.

For carboxylic acids and amides the π-bonding is much greater than for amines or alcohols of the same acidity. This indicates that magnesium is coordinated to both the σ-ligand and to the carbonyl oxygen:



$$\begin{array}{lll} & O\cdots & MgBr \\ & \| & | \\ R— & C— & O \end{array}$$

and



$$\begin{array}{lll} & O\cdots & MgBr \\ & \| & | \\ R— & C— & NH \end{array}$$

The π-contribution to the bonding in the magnesium enolate of malononitrile is low, but significant and may indicate that the $N^+{=}Mg^-$ bond is weaker for sp^2 hybridized nitrogen than for amine nitrogen.

Besides the electronic factors steric interactions also play a role for the intensity of the π-bonding. The rather considerable increase in π(O–Mg) observed on going from *tert*-butyl alcohol to ethanol and methanol seems to indicate a steric hindrance for bonding in alcohols having a bulky alkyl group.

A complication which has not yet been discussed is the possibility of a change in the amount of solvent coordination during reaction (3). This problem has not been studied in detail. The reactions of phenol and of benzenethiol with pentylmagnesium bromide were carried out in THF as well as in ether and were found to be 5 kcal mol^{-1} and 0 kcal mol^{-1}, respectively, more exothermic in THF. This indicates that either in THF or in ether the solvation of reactants and products differ. Since the enthalpies of coordination of C_2H_5MgBr and $MgBr_2$ are −16 and −26 kcal mol^{-1}, respectively, in THF, but 7.4 and 7.4 kcal mol^{-1} in ether,[4] there is some indication that differences in solvation between reactants and products are not very great in diethyl ether solution. The possibility exists, however, to investigate the problem since it is possible to study the coordination equilibrium between magnesium compounds and diethyl ether by infrared spectroscopy.[5]

EXPERIMENTAL

Materials. Pentylmagnesium bromide was prepared in the usual way from sublimed magnesium and ether distilled from lithium aluminium hydride. Substrates were distilled to obtain a center cut.

Calorimetric procedure. The calorimeter was a 60 ml spherical Dewar flask with an 8 mm Ø opening fitted to a 200 mm inlet tube, through which was passed (1) the leads for a manganin heating coil, (2) the leads for a copper/constantan thermocouple, and (3) an 0.8 mm Teflon capillary for the addition of substrate. The calorimeter was sealed with a rubber stopper. The reference junction of the thermocouple was placed in water of 20.0 °C. The calorimeter was flushed with nitrogen and 50 ml of 0.5 M ethereal pentylmagnesium bromide was added. The temperature of the closed calorimeter was adjusted to 20.0 °C, and the substrate adjusted to 20.0 °C was added in a known amount, usually as a solution in dry ether from a 5 ml Metrohm piston burette through the Teflon capillary. The calorimeter was shaken by hand and the temperature was read after thermal equilibrium was obtained, usually after 30 s. For calibration was used a current calibrator, Fluke Model 382 A and the thermocouple was read by means of a Keithley Model 177 microvoltmeter. The enthalpies of solution of the reactants were determined similarly and corrections were introduced when reactions were run on undiluted substrates.

Flow stream measurements were performed as described.[6] The specific heat of the reaction mixture was determined in the calorimeter.

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