Table I. α-Deuteriocarboxylic Acids Prepared by Exchange

| Run | Acid | Structure | Atom % D[a] | Yield, %[b] |
|---|---|---|---|---|
| 1 | Acetic | $CD_3CO_2K$ | 99.6 | 76[c] |
| 2 | Propionic | $CH_3CD_2CO_2H$ | 99.5 | 44 |
| 3 | *n*-Butyric | $CH_3CH_2CD_2CO_2H$ | 99.5 | 30 |
| 4 | Isobutyric | $(CH_3)_2CDCO_2H$ | 99.5 | 34 |
| 5 | Cyclopropanecarboxylic | $(CH_2)_2CDCO_2H$ | <10 | 25 |
| 6 | Cyclobutanecarboxylic | $(CH_2)_3CDCO_2H$ | 97 | 40 |
| 7 | Cyclopentanecarboxylic | $(CH_2)_4CDCO_2H$ | >94 | 40 |
| 8 | Cyclohexanecarboxylic | $(CH_2)_5CDCO_2H$ | 97.7 | 38 |
| 9 | Hydrocinnamic | $C_6H_5CH_2CD_2CO_2H$ | 98.5 | 54 |
| 10 | Phenoxyacetic | $C_6H_5OCD_2CO_2H$ | 99.5 | 67 |
| 11 | 5-Phenoxypentanoic | $C_6H_5O(CH_2)_3CD_2CO_2H$ | 98.9 | 91 |
| 12 | Succinic | $(CD_2CO_2H)_2$ | 99.5 | 81 |
| 13 | Glutaric | $CH_2(CD_2CO_2H)_2$ | 99.5 | 32 |
| 14 | Adipic | $(CH_2CD_2CO_2H)_2$ | 99.5 | 82 |
| 15 | Pimelic | $CH_2(CH_2CD_2CO_2H)_2$ | 99.5 | 78 |
| 16 | Suberic | $(CH_2CH_2CD_2CO_2H)_2$ | 99 | 64 |
| 17 | Phenylacetic | $C_6H_5CD_2CO_2H$ | 99.5 | 66 |
| 18 | 3,4-Dimethoxyphenylacetic | $3,4\text{-}(CH_3O)_2C_6H_3CD_2CO_2H$ | 99 | 55 |
| 19 | α-Naphthylacetic | $\alpha\text{-}C_8H_7CD_2CO_2H$ | 99 | 68 |
| 20 | Diphenylacetic | $(C_6H_5)_2CDCO_2H$ | 99.6 | 60 |
| 21 | Tiglic | *cis*-$CD_3CH{=}C(CH_3)CO_2H$ | 99.5 | 33 |
| 22 | Angelic | *trans*-$CD_3CH{=}C(CH_3)CO_2H$ | 99.5 | 30[d] |
| 23 | Senecioic | $(CD_3)_2C{=}CDCO_2H$ | 99.2 | 25 |
| 24 | *o*-Toluic | $o\text{-}CD_3C_6H_4CO_2H$ | 96.1 | 39 |
| 25 | *p*-Toluic | $p\text{-}CD_3C_6H_4CO_2H$ | 98.2 | 42 |
| 26 | *m*-Toluic | $m\text{-}CD_3C_6H_4CO_2H$ | 94 | 40 |
| 27 | *p*-Tolylacetic | $p\text{-}CD_3C_6H_4CD_2CO_2H$ | $CD_2$ 99<br>$CD_3$ 93 | 24 |

[a] Atom per cent D in the indicated position. [b] Yield of recovered, purified acid. [c] Recovered only as the salt. [d] Prepared from tiglic-$d^3$ acid as by R. E. Buckles and G. V. Mock, *J. Org. Chem.*, **15**, 680 (1950).

21 and 23). It was also found that *o*- and *p*-toluic acids (runs 24 and 25) exchanged the methyl protons, although a temperature of 180° was required for equilibrium to be reached within 48 hr. *m*-Toluic acid (run 26), rather surprisingly, was found to exchange at a rate which was only some three–five times slower than that of the *ortho* and *para* compounds. *p*-Tolylacetic acid (run 27) was then found to exchange the methyl as well as the methylene protons, but toluene did not exchange under the same conditions. It thus appears that the carboxylate group in the toluic acids promotes exchange as much by permitting a homogeneous solution as by direct activation.

From a preparative point of view, the scope of these exchanges allows the preparation of a number of labeled organic compounds—alcohols, amines, halides, etc.—which are easily obtained from carboxylic acids by standard reactions. Although we have worked only with deuterium, the same procedure should also allow the preparation of the corresponding tritiated compounds.

Bottini and Davidson[6] considered that the exchange of their unsaturated cyclopropylcarboxylates proceeded through a dianion intermediate. Although this is a very reasonable mechanism, two others merit consideration. One involves an intramolecular removal of an α proton by the carboxylate anion which then reacts with the solvent. The other possibility involves the attack of base on the small amount of free carboxylic acid present from hydrolysis of the salt.[11] Work is being carried out[10] to try to distinguish among these different possibilities.

**Acknowledgments.** We thank Mr. S. C. Ho of our analytical laboratories and Professor J.-C. Richer of the University of Montreal for the nmr analyses and valuable discussions. This work has been generously supported by an Industrial Research Grant from the National Research Council of Canada.

(11) As pointed out by a referee, the data in ref 6 show that these alternative mechanisms are not important in the exchange of the methylenecyclopropanecarboxylic acid salts, and by a reasonable extrapolation may not be operating in the exchanges described in the present work.

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## Reaction of Carbon Monoxide at Atmospheric Pressure with Trialkylboranes in the Presence of Lithium Trimethoxyaluminohydride. A Convenient Procedure for the Conversion of Olefins into Aldehydes *via* Hydroboration

*Sir:*

We have previously reported that the carbonylation of organoboranes[1] produced *via* hydroboration[2] pro-

(1) M. E. D. Hillman, *J. Am. Chem. Soc.*, **84**, 4715 (1962); **85**, 892, 1636 (1963).
(2) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

**Table I.** Conversion of Olefins into Aldehydes *via* Carbonylation-Oxidation of Organoboranes

| Olefin | $R_3B$, mmoles | $LiAlH(OCH_3)_3$, mmoles | CO, mmoles | $T_{50}$, min | $T_{100}$, min | Yield,[a] % |
|---|---|---|---|---|---|---|
| 1-Hexene | 50 | 55 | 50 | 5 | 30 | 98[b] |
| 2-Butene | 50 | 55 | 49 | 10 | 60 | 94 |
| Isobutene | 50 | 55 | 49 | 35 | [c] | 91 |
| Cyclohexene | 50 | 55 | 50 | 5 | 25 | 93 |
| Norbornene | 52 | 60 | 48 | 15 | 55 | 87 |

[a] The yields were determined by reducing the THF solutions of the aldehydes and determining the yield of alcohols against authentic samples. [b] The product contains 3% of an isomeric material, presumably 2-methylhexanol, arising from the 6% secondary alkyl groups present in the hydroboration product. This indicates that the primary alkyl groups react preferentially. [c] The reaction was allowed to proceed to completion automatically overnight.

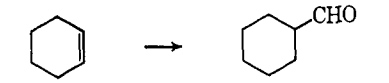
vides convenient synthetic routes to tertiary alcohols,[3a] secondary alcohols,[3b] aliphatic[3b,c] and cyclic ketones[3d] including those with functional groups,[3e,f] methylol derivatives,[3g] and polycyclic compounds.[3h] We now wish to report that the rate of reaction of carbon monoxide with organoboranes at atmospheric pressure is greatly enhanced by lithium trimethoxyaluminohydride,[4] generally proceeding at a rapid rate at either 0 or 25°. Oxidation of the reaction product with hydrogen peroxide in a $NaH_2PO_4$–$Na_2HPO_4$ buffer, to minimize hydrolysis of the intermediate to the methylol derivative, produces the aldehyde in yields of 87 to 98%.

Typical examples are indicated in eq 1–5.

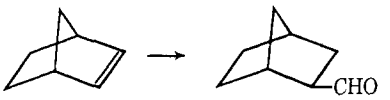
$$CH_3(CH_2)_3CH{=}CH_2 \longrightarrow CH_3(CH_2)_5CHO \quad (1)$$

$$CH_3CH{=}CHCH_3 \longrightarrow CH_3CH_2CH(CH_3)CHO \quad (2)$$

$$(CH_3)_2C{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CHO \quad (3)$$




(4)




(5)

Carbon monoxide does not react with lithium trimethoxyaluminohydride in tetrahydrofuran solution at 25° at any significant rate in the absence of the trialkylborane. In the presence of the organoborane a rapid absorption occurs, 1 mole of carbon monoxide being utilized per mole of organoborane, provided an equimolar quantity of the trimethoxyaluminohydride is present. Thus the reaction exhibits a 1:1:1 stoichiometry between the three reactants (6).

$$R_3B + CO + LiAlH(OCH_3)_3 \longrightarrow [X] \xrightarrow{[O]} 2ROH + RCHO \quad (6)$$

This is in agreement with mechanism 7 (MH = $LiAlH(OCH_3)_3$). However, we have as yet made no attempt to isolate and characterize the intermediate.

The following procedure is representative. The carbonylation apparatus[5] was assembled. In the generator flask was placed 30–50 ml of concentrated sulfuric acid and the flask was maintained at 90°. Anhydrous formic acid, 5 ml, was placed in the buret. The system was flushed with nitrogen, and the organoborane was synthesized in the reaction flask by adding 26.0 ml of a 2.0 *M* solution of borane in tetrahydrofuran (156 mmoles of "hydride") to a solution of 12.6 g of 1-hexene (150 mmoles) and 20 ml of THF. The mixture was stirred for 0.5 hr to ensure completion of hydroboration. Then 55 mmoles of a 2 *M* solution of lithium trimethoxyaluminohydride (prepared by adding 5.27 g, 165 mmoles, of methanol to 27.5 ml of a 2.0 *M* solution of $LiAlH_4$ in THF) was added with the aid of a syringe. With the aid of a syringe 2.0 ml of formic acid was injected into the sulfuric acid in the generator flask to flush the system with carbon monoxide. Carbonylation of the reaction mixture was initiated by starting magnetic stirring of the reaction flask. Absorption of carbon monoxide was rapid, 50% of the calculated quantity being taken up in 5 min, with the absorption being complete in 30 min. The system was then flushed with nitrogen, and 100 ml of a $NaHPO_4$–$Na_2HPO_4$ buffer (the solution was approximately 2.7 *M* in each salt) was added. Oxidation was then achieved by the addition of 18 ml of 30% hydrogen peroxide, with the temperature being maintained at or below 25°. The aqueous phase was then saturated with sodium chloride, the tetrahydrofuran layer was dried over anhydrous magnesium sulfate, and the tetrahydrofuran solution was examined for aldehyde by glpc. Because of the relative instability of aldehydes, we based our quantitative analysis on the methylol derivatives formed after reducing the aldehydes with aqueous sodium borohydride. Authentic samples of the methylol derivatives were available from the earlier study.[3g]

$$R_3B + CO \rightleftharpoons R_3\bar{B}\overset{+}{C}O$$

$$R_3\bar{B}\overset{+}{C}O \rightleftharpoons R_2BCR \quad (O)$$

$$R_2BCR + MH \longrightarrow R_2BCHR \quad (O;\ OM) \quad (7)$$

$$R_2BCHR \xrightarrow{[O]} 2ROH + RCHO \quad (OM)$$

The experimental results are summarized in Table I.

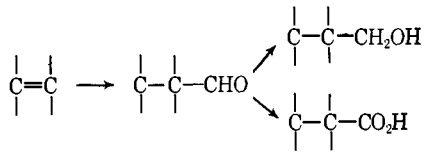
Hydrolysis of the reaction with alkali, without reduction, produces essentially quantitative yields of the corresponding methylol derivatives.[3g]

(3) (a) H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2737 (1967); (b) H. C. Brown and M. W. Rathke, *ibid.*, **89**, 2738 (1967); (c) H. C. Brown and M. W. Rathke, *ibid.*, **89**, 4528 (1967); (d) H. C. Brown and E. Negishi, *ibid.*, **89**, 5477 (1967); (e) H. C. Brown, G. W. Kabalka, and M. W. Rathke, *ibid.*, **89**, 4528 (1967); (f) H. C. Brown and E. Negishi, *ibid.*, **89**, 5258 (1967); (g) H. C. Brown and M. W. Rathke, *ibid.*, **89**, 2740 (1967); (h) H. C. Brown and E. Negishi, *ibid.*, **89**, 5478 (1967).

(4) H. C. Brown and C. J. Shoaf, *ibid.*, **86**, 1079 (1964); H. C. Brown, and P. M. Weissman, *ibid.*, **87**, 5614 (1965).

(5) The apparatus is essentially the hydrogenator described by C. A. Brown and H. C. Brown, *ibid.*, **84**, 2829 (1962). We utilized a commercial model of the hydrogenator available from Delmar Scientific Laboratories, Maywood, Ill. 60154.

A disadvantage of this procedure is that only one of the three alkyl groups of the organoborane is converted into the aldehyde. Fortunately, we have found a means of circumventing this difficulty.[6] However, it is apparent that this reaction is so simple and clean that it promises to provide a major new synthesis of aldehydes, readily converted into the corresponding methylol or carboxylic acid derivatives (8).



(8)

(6) Research in progress with E. Knights.

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## Proton-Transfer Reactions with Copper(II)–Triglycine ($CuH_{-2}L^-$)

*Sir:*

The copper(II)–triglycine complex is known to ionize peptide protons to form $CuH_{-1}L$ (or CuA) and $CuH_{-2}L^-$ (or $CuB^-$) with the loss of one and two protons, respectively ($pK_a$ = 5.4 and 6.6).[1,2] We have measured the kinetics of the proton-transfer reactions between acids and $CuH_{-2}L^-$ using a variety of techniques including temperature-jump relaxation, pH-jump relaxation,[3] and ligand-exchange reactions by stopped flow. The latter reactions using EDTA or CyDTA (cyclohexylenediaminetetraacetate ion) are general acid (HX) catalyzed with eq 1 as the rate-determining step. The subsequent substitution reactions included in eq 2 are rapid by comparison.

$$CuH_{-2}L^- + HX \xrightarrow{k_{HX}} CuH_{-1}L + X^- \quad (1)$$

$$CuH_{-1}L + HEDTA^{3-} + H^+ \xrightarrow{\text{fast}} CuEDTA^{2-} + HL \quad (2)$$

The rate of conversion of $CuH_{-2}L^-$ to $CuEDTA^{2-}$ was followed spectrophotometrically by observing the disappearance of $CuH_{-2}L^-$ at 235 or 555 mμ. We observed that the rate was responsive to diprotonated EDTA rather than to the monoprotonated species, although the latter is a much better nucleophilic agent. Tests with CyDTA, which because of steric hindrance is very poor as a ligand displacing agent, showed similar behavior. The exchange reaction with EDTA also was catalyzed by buffers where the base form has little or no complexing ability (*e.g.*, borate ion and 2,6-lutidine). The reaction rate responded to the concentration and strength of the acid form of the buffer. Finally, the values measured for $k_{HX}$ with HX = $H_3O^+$ were in agreement with our temperature-jump and pH-jump measurements. Hence, the EDTA exchange reaction provides a convenient way to measure proton-transfer rate constants between acids and $CuH_{-2}L^-$.

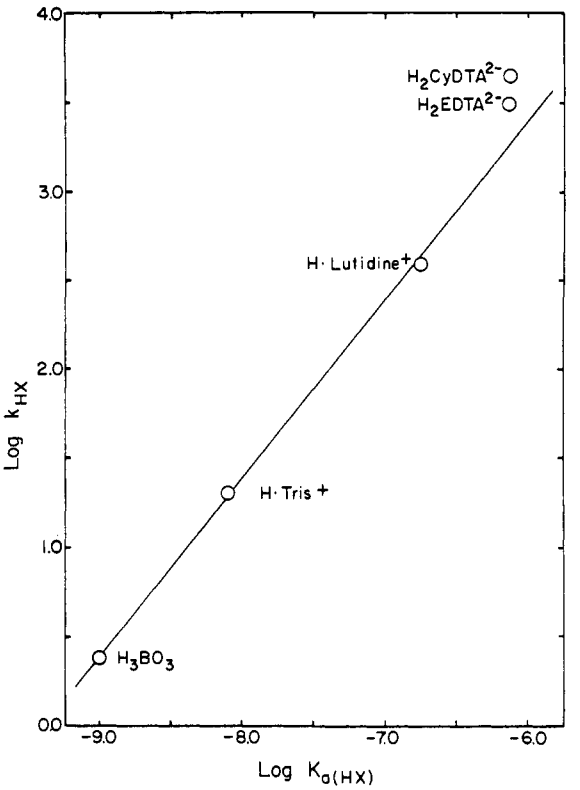


Figure 1. Brønsted plot for the reaction of acids with $CuH_{-2}L^-$. The slope, $\alpha$, is equal to unity which fits proton-transfer reactions far removed from the diffusion-controlled limit. The $\Delta pK$ is zero at $\log K_{a(HX)} = -6.6$. The $k_{HX}$ values are determined from the EDTA exchange reactions, at 25.0°, $\mu$ = 0.10 ($NaClO_4$), [$CuH_{-2}L^-$] = (2.5–20) × $10^{-4}$ *M*, [HX] and [EDTA] = (5–20) × $10^{-3}$ *M*. Tris is tris(hydroxymethyl)aminomethane, lutidine is 2,6-dimethylpyridine, and $CyDTA^{4-}$ and $EDTA^{4-}$ are *trans*-cyclohexylenediaminetetraacetate ion and ethylenediaminetetraacetate ion.

The experimentally observed first-order rate constant, $k_0$, is the sum of the contributions of all acid species to reaction 1.

$$k_0 = \sum_{HX} k_{HX}[HX]$$

The $k_0$ values were resolved by varying the pH (6.1–8.6) and the concentrations of each acid. The rate constant for $H_3O^+$ and $CuH_{-2}L^-$ is only 6.6 × $10^6$ $M^{-1}$ $sec^{-1}$, which is much smaller than typical diffusion-controlled rate constants. However, it is similar to the value of 1.2 × $10^7$ $M^{-1}$ $sec^{-1}$ for the $H_3O^+$ reaction with the acetylacetonate anion to give the keto product.[4]

The rate constants for the other acids tested are shown in Figure 1 to follow a Brønsted general acid catalysis, and log $k_{HX}$ against log $K_{a(HX)}$ gives a linear relationship with a slope ($\alpha$) of unity. The decrease of $k_{HX}$ with decrease in the acidity of HX is to be expected when the $\Delta pK$ ($pK_{acceptor} - pK_{donor}$) is near or less than zero.[4] However, the fact that $\alpha$ = 1 when $\Delta pK$ = 0 and that the $H_3O^+$ reaction is four orders of magnitude less than the limiting diffusion-controlled reaction indicates that the proton addition to $CuH_{-2}L^-$ is associated with a charge displacement and structural modification of the complex.[4] The addition of the proton to the

(1) H. Dobbie and W. D. Kermack, *Biochem. J.*, **59**, 257 (1955).
(2) M. K. Kim and A. E. Martell, *J. Am. Chem. Soc.*, **88**, 914 (1966).
(3) In this technique stopped-flow mixing permits a small change in pH to be imposed on the equilibrium between $CuH_{-2}L^-$ and $CuH_{-1}L$. The relaxation of the system to the new equilibrium position is followed with low concentrations of indicators.
(4) M. Eigen, *Angew. Chem.*, **75**, 489 (1963).