CHEMISTRY LETTERS, pp. 525-528, 1993.

Prediction of the Optimum Reaction Time for Carbon-11 Labelling Reactions. The Rate Constants for the Carboxylation of Grignard Reagents

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The rate constants for the carboxylation of a series of aliphatic Grignard reagents were measured as part of the development of a computer assisted automated synthesis apparatus. A good correlation was obtained between the rate constants and Taft's Es values.

One of the most commonly used methods for incorporating CO_2 into organic compounds is carboxylation utilizing the Grignard reaction. By the use of this reaction with $^{11}CO_2$, several ^{11}C-labelled carboxylic acids have been prepared as radiopharmaceuticals for Positron Emission Tomographic (PET) imaging of cardiovascular functions.1) Furthermore, the ^{11}C-labelled carboxylic acids thus obtained are also useful as intermediates for preparing many kinds of radiopharmaceuticals.2) However, difficulties are sometimes encountered in the production of these carboxylic acids in good radiochemical yield because of the shortness of the physical half-life of ^{11}C (only 20 minutes), and the low concentration of $^{11}CO_2$ in the reaction mixture.3) Labelling reactions using carbon-11 differ from ordinary chemical syntheses as they are always accompanied by both competitive and consecutive ones, which thus produce an optimum reaction time for obtaining the maximum radiochemical yield. In accordance with the kinetic equation,4) the optimum reaction time is greatly dependent upon the rate constant and the concentrations of the labelling reagent and substrate. In order to synthesize a variety of ^{11}C-labelled carboxylic acids consistently, it is necessary to control the labelling by predicting the optimum reaction times from knowledge of the rate constants. Furthermore, establishment of a correlation between the rate constants and structural parameters of the Grignard reactants should be important to estimate the labelling conditions for carboxylation of a variety of compounds, without the time consuming measurement of rates for each.

Although there is much literature5) analyzing the kinetics of the Grignard reaction, most of them use aldehydes and ketones as the substrate of the reaction and kinetic studies of the carboxylation of Grignard reagents have rarely been reported. As part of our study on the development of a fully automated apparatus for preparing a variety of ^{11}C-carboxyl labelled compounds, we measured the rate constants for the carboxylation of a series of aliphatic Grignard reagents and established a correlation between structure and rate constants.6)

Initially, we established a reaction system for measuring the rate constants. THF was chosen as a solvent and was distilled freshly over $LiAlH_4$ for each run. The reaction was carried out by adding a THF solution of CO_2 to a solution of the Grignard reagent7) in THF at 0±1 °C. The initial concentrations of CO_2 were adjusted in the range of 2.2×10^{-3} to 3.6×10^{-3} mol/l8) and twelve times molar excess of Grignard reagent, based on CO_2, was used. The yields of the carboxylic acid were measured by HPLC using a conductivity detector,9) for the carboxylation of methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *s*-butyl magnesium bromides.10) The initial rate constants of each reaction were calculated from the part of reaction that obeyed second-order kinetics. The results are summarized in Table 1. With these results in hand, we could calculate the optimum labelling reaction times for each Grignard reagent at appropriate $^{11}CO_2$ concentrations.4) As shown in Table 1, the optimum reaction times for each Grignard reagent at the CO_2 concentration of 2.0×10^{-4} mol/l, which is the average concentration used for the labelling reactions, were found to be in the range of 170 seconds to 350 seconds.4)

Next, we plotted the relative rates against Taft's Es values11) in order to examine the correlation between rates and the steric parameter. As shown in Fig. 1, a very good correlation was obtained, and the reaction constant was calculated as $\rho^*=0.37$. The regression coefficient of 0.954 indicates that this reaction constant can be used to estimate rate constants for a variety of aliphatic Grignard reagents.

$$\mathbf{RMgBr + CO_2 \longrightarrow RCOOH}$$

Table 1. Rate constants and optimum reaction times for the [^{11}C]carboxylation of typical Grignard reagents

R	Rate constant		Relative rate	ORT a)	RCY a)	Es b)
	k/l·mol^{-1}·s^{-1}	σ c)	log kR/kMe	s	%	
CH_3	9.23	0.46	0.00	170	88.2	0
C_2H_5	7.67	0.55	-0.08	200	86.5	-0.07
n-C_3H_7	6.49	0.85	-0.15	220	84.8	-0.36
n-C_4H_9	6.59	0.75	-0.15	220	85.0	-0.39
i-C_3H_7	6.97	0.68	-0.12	210	85.5	-0.47
i-C_4H_9	4.25	0.85	-0.34	300	79.7	-0.93
s-C_4H_9	3.26	0.51	-0.45	350	75.9	-1.13

a) ORT: predicted optimum reaction time; RCY: predicted radio chemical yield, see Ref. 4. b) Taft's Es value, see Ref. 11. c) σ: Standard deviation.

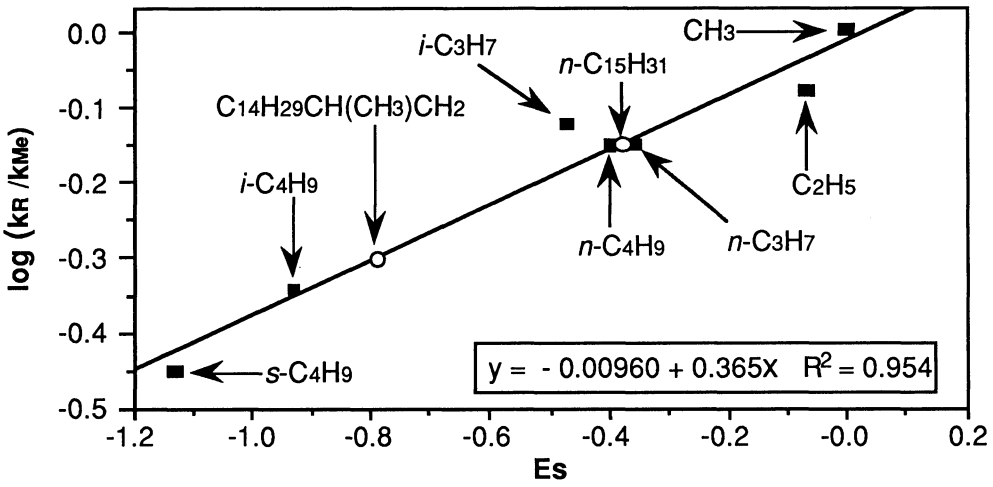

Fig. 1. Linear free energy equation plots of the carboxylation of aliphatic Grignard reagents.

Subsequently, we used this correlation to estimate Es values for several substituents. Since the Es values of pentadecyl and 3-methylhexadecyl substituents are not found in the literature, the rate constants of the carboxylations of these Grignard reagents were measured.[12] As shown in Table 2, Es values of -0.38 and -0.80 were obtained for these substituents, respectively, using the reaction constant and the measured rate constants. These results show that the Es values are similar to those of similar substituents and it is thus feasible to predict rate constants based on Taft's Es values. Furthermore, as reported by Charton,[13] the Taft Es values are a linear function of the van der Waals radii, thus we can also use the van der Waals radii for estimating the rate constants.

Table 2. Estimation of the Es values for the carboxylations of long chained Grignard reagents

R	Rate constant		Relative rate	Estimated Es
	k/l·mol^{-1}·s^{-1}	$\sigma^{a)}$	log kR/kMe	
n-$C_{15}H_{31}$	6.54	0.65	-0.15	-0.38
$C_{14}H_{29}CH(CH_3)CH_2$	4.63	0.82	-0.30	-0.80

a) σ: Standard deviation.

From these results we are now developing an automated apparatus in which the correlation equation has been incorporated into a computer control algorithm to determine labelling conditions for the carboxylation of Grignard reagents.

This work was carried out in collaboration with the National Cardiovascular Center. We wish to thank the President, Dr. Teruo Omae.

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2) B. Långström, G. Antoni, and P. Gullberg, *Appl. Radiat. Isot.*, **37**, 1141 (1986).

3) The concentration of $^{11}CO_2$ in N_2 gas is usually lower than 1 ppm.

4) N. Hayashi and M. Shintani, 3rd International Symposium on the Medical Application of Cyclotrons, Turku, June 1984, Abstr., p. 182. RCY = $e^{-\lambda t} \cdot P_t/A_o$ where A_o = initial concentration of CO_2 [$mol \cdot l^{-1}$], P_t = calculated concentration of product at time t [$mol \cdot l^{-1}$], t = reaction time [s], λ = decay constant [s^{-1}].

5) K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, **108**, 6263 (1986); K. Maruyama, Y. Matano, and T. Katagiri, *J. Phys. Org. Chem.*, **4**, 501 (1991) and the references cited therein; T. Holm, *Acta. Chem., Scand., Ser. B*, **37**, 567 (1983); E. S. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 272 (1974) and references cited therein.

6) Part of this work has already been reported. H. Yamazaki and N. Hayashi, 6th International Symposium on the Medical Application of Cyclotrons, Turku, June 1992, Abstr., p. A 45.

7) The Grignard reagents were freshly prepared and diluted to an appropriate concentration with freshly distilled THF and the reagents were used immediately after dilution. The concentration of the Grignard reagents was determined by titration with iodine in toluene.

8) The concentrations of CO_2 were measured by the use of an HPLC system. S. Ino, H. Yamazaki, and N. Hayashi, 64th National Meeting of the Chemical Society of Japan, Niigata, October 1992, Abstr., No. 3C733.

9) HPLC analysis: Conductivity detector (Shimadzu, Model CDD-6A); packed column [Shim-Pak SCR-102(H) (8 mm I.D. X 300 mm)]; mobile phase (5 mM *p*-toluenesulfonic acid aqueous solution, 0.8 ml/min flow rate).

10) The kinetic data were obtained by quenching individual reactions at appropriate intervals of time and following the production of the carboxylic acid by HPLC analysis. Typical procedure: To a solution of MeMgBr (257.4 μmol) in THF (0.92 ml) was added a THF (0.05 ml) solution of CO_2 (21.5 μmol) at 0±1 °C. The reaction was quenched by the addition of aqueous HCl (6 M, 0.1 ml).

11) R. W. Taft Jr, *J. Am. Chem. Soc.*, **74**, 3120 (1952); Although a better correlation (R^2=0.995) was obtained for substituents containing no branch at the 1-position using Hansch's Es values (Es^e), we used Taft's Es values so that we could include *i*-Pr and *s*-Bu substituents. For Es^e, see S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, **12**, 91 (1976).

12) Palmitic acid and 3-methylheptadecanoic acid thus obtained are useful tracers for monitoring myocardial metabolic functions. See, Ref. 1.

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(Received December 11, 1992)