

A great advantage of the calorimetric method is the direct determination of ΔH^0 and ΔS^0 (table). For the system examined, the main contribution to complex stability seems to be due to energy changes rather than entropy change.

We are indebted to the *Swiss National Foundation* and to *CIBA-GEIGY Ltd.*, Basel, for financial support.

BIBLIOGRAPHY

- [1] *D. A. Deranleau*, J. Amer. chem. Soc. *91*, 4044, 4050 (1969).
 [2] *R. Schwyzer, Aung Tun-Kyi, M. Caviezel & P. Moser*, Helv. *53*, 15 (1970).
 [3] *W. E. Klopfenstein*, Biochim. biophys. Acta *187*, 272 (1969).
 [4] *M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, E. I. Vinogradova, A. M. Shkrob, G. G. Malenkov, A. V. Evstratov, I. A. Laine, E. I. Melnik & I. D. Ryabova*, J. Membrane Biol. *7*, 402 (1969).
 [5] *M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, A. M. Shkrob, I. I. Mikhaleva, A. V. Evstratov & G. G. Malenkov*, Biochem. biophys. Research Commun. *29*, 834 (1967).
 [6] *Yu. A. Ovchinnikov, V. T. Ivanov, A. V. Evstratov & I. A. Laine*, Proc. 10th European Peptide Sympos., Abano Terme, Sept. 1969, North Holland Publ. Co., Amsterdam.
 [7] *H.-K. Wipf, L. A. R. Pioda, Z. Stefanac & W. Simon*, Helv. *51*, 377 (1968).

149. Catalytic Aminomethylation of Alkenoic Compounds:

I. Reaction of Monoolefins with Secondary Amines, Carbon Monoxide, and Water in the Presence of Rhodium and Iron Catalysts

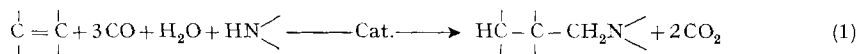
by **Abul F. M. Iqbal**

Monsanto Research S.A., Eggbühlstrasse 36, 8050 Zürich, Switzerland

(5. V. 71)

Summary. Reactions, in the presence of rhodium oxide and/or iron pentacarbonyl, of cyclic or acyclic higher olefins with carbon monoxide, water, and secondary amines to give the corresponding aminomethyl-cycloalkanes or -alkanes (equ. 1) are described. As catalyst rhodium oxide is by far superior to iron carbonyl; however, optimum results are obtained with combinations of the two. The method can be applied to synthesis of long-chain alkylamines, which are valuable as intermediates for synthetic detergents.

Introduction. – Aliphatic amines have found widespread application in industry. The most frequently employed commercial methods of preparation involve reduction of nitriles or carboxamides, or alkylation of ammonia or amines by aldehydes, alcohols, or alkyl halides. The increasing availability of cheap olefinic raw material stimulated our interest in olefins as alkylating agents for amines. This paper deals with the one-step, catalytic, reductive alkylation of secondary amines by mono-olefins, carbon monoxide and water according to equation 1, referred to as ‘amino-methylation’ of olefins.



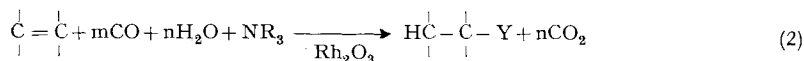
The reaction, discovered by *Reppe* [1], required large quantities of toxic iron carbonyl or its derivatives as catalyst. The value of the process was however limited by the considerable consumption of the catalyst involved (due to loss of carbon

monoxide and subsequent conversion to inactive iron carbonates) [2], slow rate of reaction, and poor yields; moreover, the reaction was found to be restricted to ethylene and propylene. Although higher olefins have also been found to react with other metal carbonyls and hydrogen instead of water [3], such reactions being non-selective afforded only modest yields of amines.

Consequently we focussed our attention on transition metal systems which, in the light of latest advances in this field, appeared to be potentially better catalysts for the aminomethylation of olefins.

Recent investigations [4] have shown that rhodium carbonyls form carbonyl rhodates by reaction with alkalis in the presence of carbon monoxide. These reactions are reminiscent of the analogous formation of carbonyl ferrates [5], postulated as catalysts for the aminomethylation reaction. An investigation of the catalytic behaviour of the rhodate species in this reaction thus seems justified.

As previously established [6], rhodium is highly effective in hydroformylation or hydroxymethylation of higher olefins according to equ. 2. The hydroxymethyl com-



NR_3 = strongly basic tert. amine solvent

Y = $-\text{CHO}$, when $m = 2$ and $n = 1$

= $-\text{CH}_2\text{OH}$, when $m = 3$ and $n = 2$

pound results by the reduction of the aldehyde, first formed. This suggests the possibility of achieving a reductive amination of the intermediary aldehyde by substituting the tertiary base (NR_3) in the above reaction by an excess of secondary amine.

Prompted by the above considerations and by the fact that rhodium systems are better catalysts than those of iron in most olefin and carbon monoxide condensation reactions, a comparative study of the effect of rhodium and iron derivatives on the aminomethylation of olefins was undertaken.

Results and Discussion. – The aminomethylation of olefins by action of iron pentacarbonyl, rhodium oxide, or combinations of the two, was studied using certain acyclic and cyclic olefins. Reaction conditions and results are compiled in tabs. 1 and 2.

The products formed were identified, where possible, by gas chromatographic and spectroscopic comparison with authentic samples; identifications were confirmed by elemental micro analysis. Exploratory experiments were carried out with cyclohexene, since it precluded the formation of isomeric condensation products; the knowledge there acquired of was utilized for exploring the reaction of dodecenes and of tetradecenes with dimethylamine. Irrespective of the location of the double bond, mixtures of isomeric aminomethylalkanes resulted.

Depending upon the catalyst, varying amounts of the corresponding carboxamides and hydroxymethyl derivatives were formed besides the aminomethylated olefin. Furthermore, the secondary amine is partially formylated; data pertaining to this last reaction are not included in the tables.

Fe(CO)₅ as catalyst (see tab. 1). Iron pentacarbonyl afforded, from both cyclic and acyclic olefins, 1–6% (calculation based on olefin) of the desired tertiary amines. The

Table 1. *Catalytic Aminomethylation of Olefins*

Olefin	Sec. Amine	Aminomethylation Product	Yield [% calcd. on olefin] of aminomethylation products in the presence of		
			Fe(CO) ₅	Rh ₂ O ₃	Fe(CO) ₅ + Rh ₂ O ₃
Cyclohexene	Pyrrolidine		6.0 ^{a)}	80.0 ^{b)}	93.5 ^{a)}
Cyclohexene	Dimethylamine		Traces ^{a)}	51.0 ^{c)}	91.0 ^{a)}
Dodecenes	Dimethylamine	(Dimethylamino-methyl)-dodecanes	1.8 ^{d)}	50.0 ^{e)}	90.0
Tetradecenes	Dimethylamine	(Dimethylamino-methyl)-tetradecanes	1.5 ^{d)}	55.0 ^{e)}	92.0

Reaction conditions: Olefin, 0.25 mole; sec. amine, 0.5 mole; Fe(CO)₅, 0.025 mole; Rh₂O₃, 5 · 10⁻⁴ mole; solvent, 60 ml N-methylpyrrolidine; initial CO pressure, 140 atm; reaction period, 3 h; temperature, 170°; 0.5 l stainless steel rocking autoclave.

a) plus 1-2%

b) plus 6-11%

c) plus 5-9%

d) determined by non-aqueous titration (see experimental).

e) plus 4-8% oxo-compounds (chiefly carboxamides).

only byproduct of the iron catalyzed reaction was the corresponding hydroxymethyl alkane formed in 1-2% yields. In all cases, olefin conversion corresponded to that of iron pentacarbonyl, thus indicating the essentially non-catalytic nature of the latter compared with higher olefins. Regeneration of the spent iron carbonyl did not take place apparently under the conditions used.

Rh₂O₃ as catalyst (see tab.1). With rhodium(III)-oxide, tertiary amines were obtained in yields ranging from 50 to 80% based on olefin; the olefin conversion was usually between 60 and 90%. The reaction, as exemplified by the experiments with cyclohexene, seemed to be influenced by the type of secondary amine used, and no pronounced selectivity with respect to olefinic structure could be observed. Thus, whereas dimethylamine and various olefins gave only 50-55% yields of the amino-methylated products, an 80% yield was obtained with pyrrolidine.

In contrast to iron carbonyl, rhodium oxide led to the formation of considerable amounts of byproducts; with cyclohexene as much as 11% of the carboxamide (based on fed cyclohexene) was formed. Carboxamide formation was dependent on the reaction conditions, and increased considerably at higher temperatures in the presence of strong heterocyclic bases.

Table 2. *Aminomethylation of Tetradecenes in the presence of Rhodium Oxide and varying quantities of Fe(CO)₅*

Catalyst concn. (mole %, calculated on olefin)		Yield (% calculated on olefin) of (dimethylamino-methyl)-tetradecanes
Rh ₂ O ₃	Fe(CO) ₅	92.0
0.2	10	92.0
0.2	5	90.8
0.2	2	89.0
0.2	1	88.0
0.2	0.5	71.5
0.2	0	55.0

Reaction conditions: Olefin, 0.25 mole; dimethylamine, 0.5 mole; water, 0.5 mole; solvent, 60 ml N-methylpyrrolidine; initial CO pressure, 140 atm; temperature, 170°; reaction period, 3 h; 0.51 stainless steel rocking autoclave.

Rh₂O₃/Fe(CO)₅ as catalyst. Although iron pentacarbonyl itself is a poor catalyst for aminomethylation of olefins, small amounts as co-catalyst strongly promoted the rhodium catalysed reaction by suppressing side reactions and by raising the yield of the aminomethylated products to over 90% (see tab.1). Iron pentacarbonyl concentrations as low as 1-2 mole% (based on olefin) could be employed with success as co-catalyst in the aminomethylation reaction (see tab.2). To a great extent this reduces the hazards involved in handling large quantities of toxic iron carbonyl.

The rhodium catalysed aminomethylation thus possesses the following advantages over the conventional *Reppé* synthesis with iron pentacarbonyl: (a) Very small amounts of the noble metal (0.1 mole% based on olefin) suffice. (b) The catalyst is not decomposed during the reaction. (c) The noble metal carbonyl need not be employed as such, but may be formed *in situ* from easily available metal derivatives, e.g., Rh₂O₃. (d) Low and high molecular cyclic or acyclic olefins can be employed. (e) Shorter

reaction periods lead to higher yields. (f) Combinations of the noble metal derivative with very small quantities of iron pentacarbonyl, as compared to those employed in the *Reppé* synthesis, promote the process enormously.

The author wishes to thank Professor *H. H. Zeiss* for his keen interest and support.

Experimental – B.p.'s and m.p.'s are not corrected. Gas chromatograms were run on an *F and M Scientific* 700 instrument fitted with TC detector (V-filament). Column: 6 m $\frac{1}{4}$ " steel with Carbowax 20 M 20% on Chromosorb W (NAW) 60–80 mesh; He flow rate: 75 ml/min; column temp.: 170°. For IR. spectra a *Grubb-Parsons* Spectromaster instrument was used.

For the non-aqueous titration of tertiary organic amines, an aliquot (0.1–1 g) of the fraction considered was dissolved in 30 ml glacial acetic acid (*Fluka, puriss.*) and 5 ml acetic anhydride (*Fluka, puriss.*) and titrated with 0.1N perchloric acid in glacial acetic acid (*Merck*), using methyl violet as indicator. The first complete disappearance of a violet tinge was taken as the end point; a sample was titrated potentiometrically (*Metrohm AG*, Herisau, Potentiograph E 436 D, Glass/Calomel electrodes), in order to select the correct colour for end point. Hydroxymethyl alkanes, such as those formed in the experiments, did not interfere with the titration. The method was particularly suitable for determination of small quantities of amines admixed with olefins and hydroxymethyl alkanes.

1. *Aminomethylation of cyclohexene by pyrrolidine*. A stainless steel rocking autoclave was filled with the required amounts of cyclohexene (*Fluka, purum*), pyrrolidine (*Fluka, puriss.*), N-methylpyrrolidine (*Fluka, pract.*) and water and carbon monoxide introduced to give a pressure of 140 atm. It was then heated to 170°C within ca. 45 minutes and rocked at this temperature for two hours. The vessel was cooled, the gases vented, and the reaction mixture washed 2–3 times with water in order to remove residual secondary amines, their N-formyl derivatives (formed in a side reaction), and the N-methylpyrrolidine solvent. A pentane extract of the aqueous phase was then combined with the organic phase, the whole dried over sodium sulfate and fractionally distilled.

With rhodium oxide catalyst, two fractions (b.p. 86–90°/11 Torr and 140–145°/10 Torr, respectively) were obtained, whereas iron carbonyl or iron carbonyl/rhodium oxide combinations yielded only the lower boiling fraction (b.p. 86–90°/11 Torr). The latter was shown, by gas chromatographic and IR. spectroscopic comparisons with authentic samples, to contain hydroxymethylcyclohexane and N-hexahydrobenzyl-pyrrolidine. The amine yields were determined by titration with perchloric acid (see above) as well as by separating the tertiary amines as hydrochlorides followed by reconversion to the bases by use of sodium hydroxide.

N-Hexahydrobenzyl-pyrrolidine, b.p. 89–90°/11 Torr

$C_{11}H_{21}N$ Calc. C 78.97 H 12.65 N 8.37% Found C 78.09 N 12.65 N 8.50%

The higher boiling fraction, which solidified in the cooler, was identified as *N-hexahydrobenzyl-pyrrolidine* by mixed m.p. and spectroscopic comparison with an authentic sample, confirmed by micro analysis: b.p. 140–145°/10 Torr; m.p. 71° (from hexane).

$C_{11}H_{19}NO$ Calc. C 72.88 H 10.56 N 7.73 Found C 73.48 H 10.62 N 7.54

2. *Aminomethylation of cyclohexene by dimethylamine*. The reaction of cyclohexene with dimethylamine in the presence of carbon monoxide and water and the subsequent processing of the resulting products were carried out as in 1. Depending on the nature of the catalyst employed, either one or two product fractions were obtained on distillation, as in 1.

The lower boiling fraction consisted of (dimethylamino-methyl)-cyclohexane, identified by gas chromatographic and spectroscopic comparison with an authentic sample, confirmed by micro analysis. B.p. 55–56°/11 Torr.

$C_9H_{19}N$ Calc. C 76.53 H 13.56 N 9.92 Found C 76.65 H 13.49 N 10.09

The higher boiling fraction (88–118°/11 Torr) obtained, particularly when working with rhodium oxide, was found, by gas chromatography, to be formyl-, together with hydroxymethyl- and dimethylcarbamoyl-cyclohexane.

3. *Aminomethylation of dodecenes and tetradecenes by dimethylamine and carbon monoxide in aqueous media* was effected as for cyclohexene above. The resulting mixtures were distilled and the fractions boiling between 90–140°/10 Torr and 90–140°/4 Torr respectively, were collected. The

aminomethylated products were assayed either directly *via* the intermediate hydrochlorides, or by titration with perchloric acid.

Dimethylaminomethyl-dodecanes, b.p. 120–140°/10 Torr.

C₁₅H₃₃N Calc. C 79.21 H 14.62 N 6.16% Found C 79.83 H 14.81 N 5.48%

Dimethylaminomethyl-tetradecanes, b.p. 120–140°/4 Torr.

C₁₇H₃₇N Calc. C 79.92 H 14.59 N 5.48% Found C 80.48 H 14.59 N 5.22%

BIBLIOGRAPHY

- [1] *W. Reppe*, *Experientia* 5, 93 (1949); Ger. Patents 839800 (1952); 909937 (1954); 931948 (1955); Brit. Pat. 803778 (1958).
- [2] *W. Reppe & H. Kindler*, *Liebigs Ann. Chem.* 582, 148 (1953).
- [3] U.S. Patents 2422631 (1947); 2497310 (1950); 3234283 (1966); 3513200 (1970).
- [4] *P. Chini & S. Martinengo*, *Chem. Commun.* 1969, 1092.
- [5] *I. Wender & P. Pino*, 'Organic Syntheses *via* Metal carbonyls' p. 100, Interscience Publishers, New York 1968; *Houben-Weyl*, 'Methoden der organischen Chemie', Vol. IV/2, p. 392, Georg Thieme Verlag, Stuttgart 1957.
- [6] *A. F. M. Iqbal*: Dissertation, Technische Hochschule Aachen 1969; *F. Asinger, B. Fell & A. F. M. Iqbal*, *Forschungsber. des Landes Nordrhein-Westfalen* Nr. 2128, Westdeutscher Verlag, Köln und Opladen 1970.

150. Determination of ΔH^0 , ΔG^0 , and ΔS^0 of the Interaction of Ions with Carrier Antibiotics by Computerized Microcalorimetry

by **P. U. Früh**, **J. T. Clerc**, and **W. Simon**

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule Zürich

(12. VI. 71)

Summary. ΔH^0 , ΔG^0 , and ΔS^0 – and thereby the equilibrium constant of the interaction of carrier antibiotics with ions – are determined using a microcalorimeter on-line with a dedicated computer. Thermodynamic data of the interaction of monensin, macrotetrolides and valinomycin with sodium and potassium ions in methanol at 25°C are given.

1. Introduction. – In 1966 [1] we have shown that the ion selectivity of certain electrically neutral antibiotics in biological systems [2] is largely due to selective complex formation between the antibiotics and alkali metal cations. Considerable effort has been made to understand the carrier-mediated alkali cation transport across cellular membranes on the basis of the characteristics of such antibiotics [3] [4] and model compounds [5–8]. For a detailed study [7] the free energy (ΔG^0), enthalpy (ΔH^0), and entropy (ΔS^0) of complex formation with cations had to be measured. Because of sample limitations we have replaced the precision thermometric titration calorimeter [5] by a microcalorimetry system [9] with an on-line computer as suggested earlier [10].

2. Instrumentation. – The signal of the thermopile of a batch microcalorimeter¹⁾ is boosted by a DC amplifier²⁾ and simultaneously fed into a recorder/integrator³⁾ as

¹⁾ Model 10700-2, *LKB-Produktier AB*, Bromma, Sweden.

²⁾ Microvolt Ammeter, 150 B, *Keithley Instruments, Inc.*, Cleveland, Ohio, USA.

³⁾ Recorder model SRG (*E. H. Sargent & Co.*, Chicago, Ill., USA) equipped with an integrator (DISC model 204-DM, *Disc Instruments, Inc.*, Santa Ana, Calif. USA).