

Selective Monomethyl Esterification of Dicarboxylic Acids by use of Monocarboxylate Chemisorption on Alumina

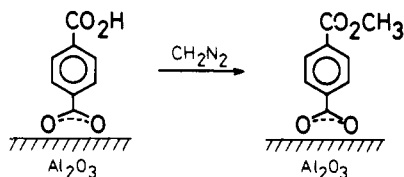
Haruo Ogawa,[†] Teiji Chihara,[‡] and Kazuo Taya*[†]

Contribution from the Department of Chemistry, Tokyo Gakugei University, Koganei-shi, Tokyo 184, Japan, and The Institute of Physical and Chemical Research, Wako-shi, Saitama 351-01, Japan. Received August 1, 1984

Abstract: The application of alumina as a solid support affords a new procedure for selective reactions. Although it is difficult to obtain monoesters in the esterification of dicarboxylic acids by conventional methods, dicarboxylic acids adsorbed on alumina selectively form the monoesters. Terephthalic acid (1), isophthalic acid, *cis*- and *trans*-1,4-cyclohexanedicarboxylic acids, and aliphatic dicarboxylic acids {HO₂C(CH₂)_nCO₂H; *n* = 3-8 and 10} give the corresponding monomethyl esters quantitatively with diazomethane. On the basis of these results, we suggest that dicarboxylic acids are adsorbed on alumina through one of their carboxyl groups, and the carboxyl group not adsorbed on the alumina is esterified selectively. Selective monomethyl esterification of phthalic acid is not successful on alumina, probably as a consequence of the close proximity of the two carboxyl groups and the forced orientation of the second group when one is adsorbed. Dimethyl sulfate and 1-methyl-3-*p*-tolyltriazene were also effective for the selective monomethyl esterification of dicarboxylic acid 1 by this procedure. Even in the absence of an activating reagent such as potassium carbonate, the corresponding monomethyl ester of 1 is obtained selectively with dimethyl sulfate. In addition, by using this procedure, dicarboxylic acid 1 is selectively reduced to 4-carboxybenzyl alcohol with diborane.

Selective reactions have been carried out with alumina, silica gel, and silica-alumina as the solid supports for either the reagent or substrate. Usually the reagents were supported^{1,2} with fewer examples of substrate support. These latter cases consist of the following: (i) substrates which are not dissolved in the reaction solvent but can be brought into the reaction system by adsorption on solid support (examples are the selective reduction of dicarbonyl compounds protected with sodium hydrogen sulfite³ or Girard's reagent⁴); (ii) substrates which are adsorbed on solid supports for regioselective reaction such as ozonation of aliphatic esters adsorbed on silica gel to afford keto esters,⁵ chlorination of octanoic acid on alumina to afford 8-chlorooctanoic acid preferentially,⁶ and photochemical cycloaddition of alkenes to a steroidal enone on silica gel to afford products which become evidence for a hindered direction of approach of alkenes to the adsorbed steroid;⁷ and (iii) substrates such as phenols⁸ and alcohols⁹ which when adsorbed on silica gel or alumina are acetylated by ketene in good yields in the absence of sulfuric acid or *p*-toluenesulfonic acid. This paper presents another new field and procedure for the use of inorganic solid supports in organic reactions.

Infrared spectroscopy¹⁰⁻¹² and inelastic electron-tunneling spectroscopy¹³ show that carboxylic acids are chemisorbed on alumina as monocarboxylate anions and that these anions have symmetric bidentate structures with equivalent oxygen atoms.



The rest of the molecule is held in a position remote from the alumina surface. This gives rise to different reactivities for the two carboxyl groups attached to remote parts of the molecule. By using this phenomena, we have reported briefly that terephthalic acid (1) adsorbed on alumina was selectively esterified to monomethyl terephthalate (2) with diazomethane.¹⁴ This paper presents details of this reaction and applications of this adsorption-reaction procedure to other dicarboxylic acids.

Table I. Selective Formation of Monomethyl Terephthalate (2) on Various Adsorbents

adsorbent	concn of 1 in DMF, % ^a	amt of adsorbed 1 ^b	selectivity for 2, % ^c	amt of DAM ^d added ^e
Al ₂ O ₃	0.100	10.0	99.0	121
	0.300	29.8	98.3	19.3
	1.00	77.6	97.6	8.43
	3.00	91.2	87.8	5.31
SiO ₂	1.00	0.995	98.9	357
SiO ₂ -Al ₂ O ₃ ^f	1.00	24.1	96.6	29.3
SiO ₂ -Al ₂ O ₃ ^g	1.00	51.1	97.0	6.10

^a Solution: adsorbent = 10:1 (w/w). ^b Milligrams of 1 adsorbed per gram of adsorbent. ^c The maximum value of [(2)/{(1) + (2) + (3)}] × 100. ^d Diazomethane. ^e Moles of DAM which give the maximum selectivity per mole of 1 adsorbed. ^f 13.8% Al₂O₃. ^g 28.6% Al₂O₃.

Results and Discussion

Selective Monomethyl Esterification of Terephthalic Acid (1). On the introduction of diazomethane to the cyclohexane suspension

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[†] Tokyo Gakugei University.

[‡] The Institute of Physical and Chemical Research.

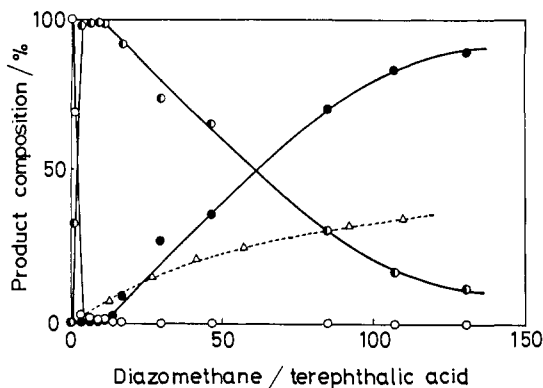


Figure 1. Reaction profile for the heterogeneous esterification of terephthalic acid (1) adsorbed on alumina: (O) 1; (●) 2; (●) 3. The adsorbed sample, which was prepared from a 1% DMF solution, is suspended in cyclohexane. The dotted line shows the formation of methyl benzoate (Δ) from adsorbed benzoic acid (4). The amount of 4 adsorbed on the alumina was the same as that of 1.

of acid 1 adsorbed on alumina, 1 is quantitatively converted into the corresponding monomethyl ester 2. A typical reaction profile is represented in Figure 1. Dimethyl terephthalate (3) is produced only by consecutive addition of a large excess of diazomethane after quantitative formation of 2. The reactivity for the conversion of 1 to its monomethyl ester 2 is 30 times larger than the reactivity of 2 to the dimethyl ester 3. Consequently, 2 is obtained quantitatively by the controlled addition of diazomethane.

The solubilities of the substrate and the products are quite small in cyclohexane. No more than 0.15% of the reactants is dissolved at the top of the curve for 2 in Figure 1, and the extent of the reaction occurring in the suspending agent appears to be negligible.

In a conventional homogeneous reaction, the acid 1 is esterified by introduction of diazomethane into a solution of 1. The mono- and diesters are formed in overlapping consecutive reactions with the monoester 2 reaching a maximum mole fraction when the ratio of diazomethane to the acid 1 is about 1.5. The reactivity of a carboxyl group in free monoester 2 is about equal to that of free acid 1.¹⁵ The selective reaction shown in Figure 1 is consequently attributable not to a difference in the intrinsic reactivity of the carboxyl groups in the free acid and monoester but to the difference of reactivity between free and adsorbed carboxyl groups.

Effect of Surface Coverage on Selectivity. Table I presents data for the effects on varying the terephthalic acid/alumina ratio. The selectivity for formation of monoester 2 decreases with the increasing amounts of 1 adsorbed. The formation of 2 vs. the amount of diazomethane is plotted in Figure 2. An alumina sample containing 9.1 wt % 1 gives a lower selectivity than those samples containing 7.8 or 3.0 wt % 1. Furthermore, the range of the diazomethane-to-acid ratio which is suitable for obtaining the monoester 2 became narrower with increasing amounts of adsorbed 1. The efficiency with which diazomethane produces 2 is roughly equal among these three samples, though the tendency to produce diester 3 decreases as the 1-to-alumina ratio decreases. These findings indicate that when the surface coverage of the acid 1 on alumina was smaller, 1 interacted more strongly with the alumina surface. Usually the surface of an adsorbent is not uniform, and stronger adsorption sites are preferentially used for adsorption by the substrate. It is known that the differential heat of adsorption decreases when the surface coverage increases and that adsorbed molecules in a region near saturated adsorption have rotational and translational freedom comparable to those in a two-dimensional liquid.¹⁶ The results shown in Figure 2 are consistent with these facts about near saturated adsorption since the reaction profile of the sample of saturated adsorption (9.1 wt % 1 on alumina, in Figure 2) shows an intermediate character

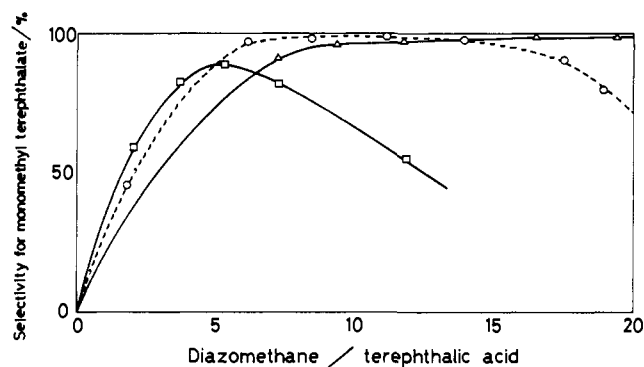


Figure 2. Formation of monomethyl terephthalate (2) from different amounts of terephthalic acid (1) on alumina: (□) 9.1 wt % 1 on alumina; (○) 7.8 wt % 1 on alumina; (Δ) 3.0 wt % 1 on alumina. Cyclohexane was used as a suspending agent.

in between those shown in Figure 1 and the conventional homogeneous esterification.

Application of Silica Gel and Silica-Alumina as Adsorbents. Selective monomethyl esterification of terephthalic acid (1) can be carried out by using silica gel and silica-alumina as adsorbents. The results are summarized in Table I. The amount of 1 adsorbed on the silica gel is about 1.4% of that adsorbed on the alumina. However, the sample of 1 adsorbed on the silica gel gives monoester 2 quantitatively. Selective monomethyl esterification is also successfully accomplished by using silica-alumina (13.8% and 28.6% alumina). It is difficult to obtain reproducible results for the adsorbed state of carboxylic acids on silica gel,¹⁷ probably because of the weak adsorption and consequent measuring difficulty. From the adsorption data about the silica gel and silica-alumina in Table I, the acid 1 may be adsorbed on the aluminum fraction preferentially. The state of adsorbate on the silica-alumina is likely the same as on the alumina. The state of adsorbate on silica gel is not clear.

Effect of Water Addition. Benzoic acid (4) adsorbed on alumina was esterified with diazomethane, and the result is shown in Figure 1. The reactivity of 4 to form the ester is much lower than that of terephthalic acid (1) to form the monoester 2 but similar to that of 2 to form the dimethyl ester 3. It has been reported that 4 is adsorbed on alumina as a symmetric bidentate carboxylate anion.¹³ The proton of the carboxyl group is an essential element for the complete reaction



Consequently, a free carboxyl group in 1 which is not adsorbed on alumina is easily available for esterification; on the other hand, a dissociated carboxyl group, whose proton is lost on adsorption to the alumina, cannot readily react with diazomethane. This is consistent with the results of the experiment described above.

With this in mind, the effects of adding water to the adsorbed sample are very significant. When 4 wt % water is added to an adsorbed sample of acid 1, the maximum selectivity for the formation of 2 decreases to 70% and the reaction profile is intermediate between those shown in Figure 1 and the conventional homogeneous esterification. When 10 wt % water is added, the maximum selectivity falls to 49.2%, which is equal to that of the homogeneous reaction. Since dissolution of the reactants in the suspending mixture is not more than 0.3% in these experiments, the increased reactivity of the adsorbed carboxyl group following the addition of water can be interpreted in terms of the capture of the proton by the adsorbed carboxyl group and hence decreased selectivity for formation of the monoester 2.

Consequently all the results are consistent with a drastic loss of reactivity of diazomethane with the carboxyl group when the

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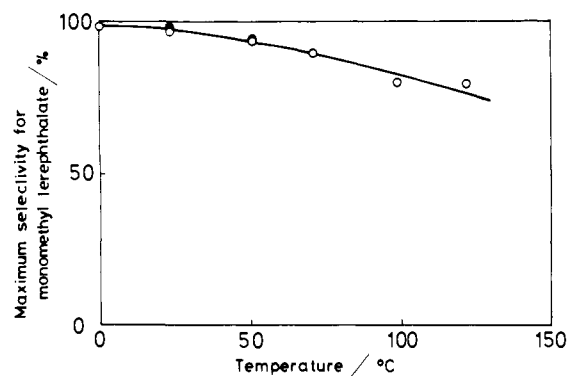


Figure 3. Temperature effect on formation of monomethyl terephthalate (2). Adsorbed sample, which had been prepared from a 1% DMF solution of 1, was used in cyclohexane (●) or *trans*-decalin (○) as a suspending agent.

Table II. Selective Monomethyl Esterification of Cyclic Dicarboxylic Acids

substrate	amt of adsorbed substrate ^a	selectivity for monomethyl ester, % ^b	selectivity for monomethyl ester in homogeneous reaction, % ^{b,c}
isophthalic acid (5)	63.8	98.0	45.4
phthalic acid (6)	72.9	17.0	16.2
<i>cis</i> -1,4-cyclohexane-dicarboxylic acid (7)	56.5	99.8	52.9
<i>trans</i> -1,4-cyclohexane-dicarboxylic acid (8)	53.5	99.9	52.2

^a Milligrams of substrate adsorbed per gram of alumina, prepared from a 1% DMF solution (10 mL) and alumina (1 g). ^b The maximum value of [(monomethyl ester)/(dicarboxylic acid) + (monomethyl ester) + (dimethyl ester)] × 100. ^c In a 1% DMF solution.

carboxyl group is adsorbed to alumina.

Temperature Effect on Selectivity. The maximum selectivity for the formation of monoester 2 is plotted against the reaction temperature in Figure 3. For these reactions, *trans*-decalin is the suspending agent, as it provides a wider temperature range than cyclohexane. As can be seen from this figure, there is no significant suspending agent effect on the selectivity in the experiments at 25 and 50 °C. The maximum selectivity for 2 decreases with increasing temperature. At 122 °C, 2 is obtained in 80% selectivity, while at 0 °C, 2 is obtained quantitatively. In the experiment at 122 °C, desorbed 1 and 2 are not detected in the suspending agent. Accordingly, the reaction is carried out dominantly on the alumina surface, not in the suspending agent.

At higher temperatures, the regeneration of the free carboxyl group from the adsorbed one is accelerated by the capture of the proton on the alumina surface, as in the case of water addition to the alumina. This causes a decrease of selectivity for 2 as shown in Figure 3.

Selective Monomethyl Esterification of Phthalic Acids and 1,4-Cyclohexanedicarboxylic Acids. Isophthalic acid (5), phthalic acid (6), and *cis*- and *trans*-1,4-cyclohexanedicarboxylic acids (7 and 8, respectively) can be reacted with diazomethane in the same way as terephthalic acid (1). The results are summarized in Table II. This table shows that 5, 7, and 8 are monomethyl-esterified in the same highly selective manner as in the case of terephthalic acid and consistent with their adsorption on the alumina through only one carboxyl group. On the other hand, 6 gives monomethyl phthalate only at a maximum 17% mole fraction, which is equivalent to the amount obtained in a homogeneous reaction in a DMF solution. These results suggest that the two carboxyl groups of 6 interact strongly with each other and that they do not react independently on the alumina surface and/or in solution.

Table II also shows that *cis*-dicarboxylic acid 7 is quantitatively converted into the monomethyl ester. This indicates that the cyclohexane ring of 7 assumes the chair form and its two carboxyl groups are apart from each other and extended in different di-

Table III. Selective Monomethyl Esterification of Aliphatic Dicarboxylic Acids

substrate HO ₂ C(CH ₂) _n CO ₂ H <i>n</i>	amt of adsorbed substrate ^a	selectivity for monomethyl ester, % ^b	selectivity for monomethyl ester in homogeneous reaction, % ^{b,c}
3	56.8	99.9	62.6
4	47.8	99.5	54.8
5	57.1	99.5	54.3
6	56.3	98.4	54.7
7	58.8	99.0	60.2
8	65.4	99.9	61.3
10	50.5	99.9	53.4

^a Milligrams of substrate adsorbed per gram of alumina, prepared from a 1% DMF solution (10 mL) and alumina (1 g). ^b The maximum value of [(monomethyl ester)/(dicarboxylic acid) + (monomethyl ester) + (dimethyl ester)] × 100. ^c In a 1% DMF solution.

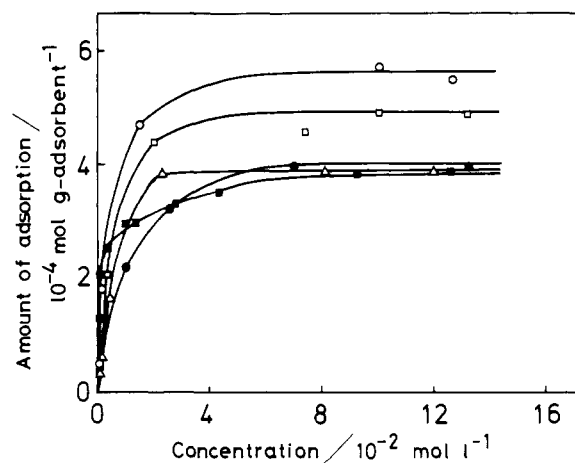


Figure 4. Adsorption isotherm of dicarboxylic acids on alumina at 30 °C: (○) 1; (Δ) 5; (□) 6; (●) 9; (■) 10.

rections. If the cyclohexane ring of 7 assumes the boat form, its carboxyl groups are brought closer together, and hence selective monomethyl esterification using alumina would be unsuccessful because of either the interaction between the two carboxyl groups as in the case of 6 or the adsorption by both carboxyl groups at the same time.

Reaction of Aliphatic Dicarboxylic Acids with Straight Chains. The results for the selective monomethyl esterification of aliphatic dicarboxylic acids with straight chains are summarized in Table III. The table shows that all the carboxylic acids tested are quantitatively converted to the corresponding monomethyl esters by use of alumina; whereas, in solutions they are converted to the monomethyl esters with only a 50–60% selectivity. On the alumina the reaction profiles of these acids are in accord with that of the acid 1 (Figure 1), and the ranges of diazomethane yielding the monomethyl esters are wider than that yielding the monoester 2. For example, the range for the amounts of diazomethane yielding the monomethyl substrate is 5.6 times as wide as that for 2. On the other hand, the reaction profiles in solution are in accord with that of 1.

Two models of adsorption can be considered for these acids. One is a molecule bridging the adsorbent surface by adsorption of both carboxyl groups, and the other involves only one carboxyl group from the molecule adsorbed on the alumina. In the latter case, it is possible to produce monomethyl esters selectively by esterification of the free carboxyl group like in the case of terephthalic acid (1). On the basis of molecular models, glutaric acid can be adsorbed with both carboxyl groups at one time. Dicarboxylic acids with longer carbon chains are expected to be adsorbed stably through both carboxyl groups. However, the results in Table III for aliphatic dicarboxylic acids with straight chains are similar to the results for 1 and are consistent with the adsorption of one carboxyl group on the alumina similar to 1.

Table IV. Selective Monomethyl Esterification of Terephthalic Acid (1)^a

reagent	molar ratio ^b	reaction time, min	reaction temp. °C	selectivity for monoester, % ^c	selectivity for monoester in homogeneous reaction, % ^{c,d}
CH ₃ C ₆ H ₄ - <i>p</i> -N=N-NHCH ₃	1.0	120	25	84.1	46.4
(CH ₃ O) ₂ SO ₂	1.5	120	25	72.2	55.4
(CH ₃) ₂ NCH(OCH ₃) ₂	41.3	120	60	72.4	68.1
BF ₃ ·CH ₃ OH	136.6	15	100	49.6	48.3

^a The alumina sample held 77.6 mg of adsorbed **1** per gram of alumina. ^b Moles of reagent per mole of **1** adsorbed. ^c The maximum value of $[2/(1 + 2 + 3)] \times 100$. The compound **3** is the dimethyl ester. ^d In a 1% DMF solution.

Adsorption isotherms for phthalic acids, suberic acid (**9**), and dodecanedioic acid (**10**) have been measured on alumina. These acids attain actual equilibrium after 5 h at 30 °C. As shown in Figure 4, the adsorption of all these acids reaches saturation if the concentration of the solution is higher than 0.04 mol/L. In the case of both **9** and **10**, saturation amounts to 4.0×10^{-4} mol per gram of alumina. The specific surface area of the alumina powder used is 158 m²/g by BET measurement. Thus, one molecule of **9** and/or **10** occupies 0.66 nm² on the alumina surface. Although the critical cross section for aliphatic carboxylic acid determined from their monomolecular layers spread over a flat surface of water is 0.205 nm²,¹⁸ a value 0.66 nm² is determined on an alumina surface with micropore structure. This is fairly good agreement between these two values taking into account the differences in the experimental conditions. The aliphatic dicarboxylic acids are considered to be adsorbed as a monomolecular layer on alumina and to form a stable membranelike structure with the aid of van der Waals interactions among the methylene groups. This explains why a wider range of diazomethane yields only the aliphatic monomethyl esters compared to the range of diazomethane that yields **2**.

Similarly, ozonation of aliphatic acetates and succinates adsorbed on silica gel⁵ and terminal chlorination of octanoic acid on alumina⁶ are also interpreted by this effect.

Methyl Esterification by Other Reagents. Some other methylating reagents also lead to the selective monomethyl esterification of terephthalic acid. The reaction with dimethyl sulfate proceeds without addition of potassium carbonate. As can be seen from Table IV when dimethyl sulfate and 1-methyl-3-*p*-tolyltriazene are used, the selective formation of monoester **2** on alumina is higher than the usual method. Usually several moles of the reagent per mole of carboxyl group are used for the reaction.^{19,20} A little improvement is observed in the selective reaction on the alumina when *N,N*-dimethylformamide dimethyl acetal is used. When the boron trifluoride-methanol complex is used, no improvement is observed in the selectivity. The results of all these experiments show that diazomethane is the best reagent. Not only does it have the highest reactivity among all the reagents tested, but in addition it gives nitrogen as the only byproduct from the reaction.

Selective Reduction of Terephthalic Acid (1) to 4-Carboxybenzyl Alcohol with Diborane. An attempt to selectively reduce **1** adsorbed on alumina with diborane results in the formation of 97% 4-carboxybenzyl alcohol and 3% intact acid **1**. The reaction profile for homogeneous reduction in a diglyme solution is similar to that for homogeneous esterification of acid **1** with diazomethane, and 4-carboxybenzyl alcohol is obtained with a maximum 50% selectivity. Thus, the present procedure is useful for the selective reduction of **1** to 4-carboxybenzyl alcohol. It is reported that carboxylic acids such as benzoic acid (**4**) and caproic acid are reduced by diborane to benzyl alcohol and 1-hexanol, respectively, but that the carboxylic salts are not reduced under the same conditions.²¹ The situation for a carboxyl group in a salt is similar to that for the carboxyl group adsorbed on alumina. Other

reagents which have different reactivities toward the free carboxyl group and the carboxylate anion are likely to yield selective reaction products following this procedure.

Experimental Section

Materials. Diazomethane was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide²² without ether and was carried in a stream of nitrogen through a drying tube containing potassium hydroxide pellets and then into the reaction vessel. A mixture of *cis*- and *trans*-1,4-cyclohexanedicarboxylic acid (**7** and **8**, respectively) was commercially obtained, and the *cis* and *trans* isomers were separated by fractional crystallization from water (*cis*, mp 169 °C; *trans*, mp 313 °C). Alumina [a gift from the Catalysis Society of Japan (JRC-ALO-5); γ -type, 60–200 mesh, modal pore diameter 55 Å, Na₂O content 0.02%] [it was certified that Merck's neutral and basic aluminum oxide 90 for column chromatography (Art. 1077 and 1076, respectively) were also effective adsorbents for the selective monomethyl esterification of dicarboxylic acid **1** by this procedure] silica gel (Wako Chemicals; 200 mesh, for column chromatographic use, average pore diameter 80 Å), 28.6% alumina SiO₂-Al₂O₃ (JRC-SAH-1; Na₂O content 0.013%), and 13.8% alumina SiO₂-Al₂O₃ (JRC-SAL-2; Na₂O content 0.012%) were dried at 110 °C for a day and stored in a desiccator. Other materials were commercially available and used without further purification.

Preparation of Adsorbed Samples. One gram of alumina powder was added to 10 mL of a 1% solution of terephthalic acid (**1**) in DMF. The mixture was allowed to stand for 8 h at 30 °C with occasional shaking. Then the alumina was filtered off, washed with a small amount of DMF, and dried under reduced pressure for 30 min. This alumina sample contained 77.6 mg of **1** and about 20 mg of DMF per gram of alumina.

Reaction Procedure. About 6.4 mL (5 g) of cyclohexane and 500 mg of the alumina sample were placed in a reaction vessel. A calculated amount of diazomethane was introduced into the reaction vessel with vigorous stirring. After all the diazomethane had been consumed or passed through the reaction vessel, the alumina was transferred to a glass column and eluted with DMF. After the eluate was concentrated, the product was analyzed. No reaction other than esterification was observed.

Another simple procedure was also used without cyclohexane. About 300 mg of the alumina sample was packed into a glass column (4-mm i.d.), and diazomethane was introduced to the column in a stream of nitrogen. Formation of monomethyl terephthalate (**2**) was not detected by this reaction method, and dimethyl terephthalate (**3**) was produced at the entrance end of the column, where diazomethane might be present in high concentrations. Consequently, this method was not suitable for the selective reaction.

Methyl esterification of terephthalic acid adsorbed on alumina with dimethyl sulfate was carried out according to the usual method¹⁹ by use of cyclohexane as a suspending agent at room temperature. However, potassium carbonate to activate the carboxyl groups was not necessary in this procedure. Methyl esterification with 1-methyl-3-*p*-tolyltriazene was carried out in cyclohexane as a suspending agent at room temperature. Other details are described in the literature.²⁰ Methyl esterification with *N,N*-dimethylformamide dimethyl acetal was carried out according to the literature²³ in cyclohexane at 60 °C. Methyl esterification with a boron trifluoride-methanol complex was carried out according to the literature without a suspending agent at 100 °C.²⁴

Analysis. All the reaction products were identified as being identical with authentic samples, commercial products, or synthetic products. The reaction samples were analyzed by GLC with a poly(ethylene glycol) 20 000 column, GSC with a Chromosorb 101 column, or HPLC with a

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C18 or C8 column. The adsorption amounts of benzoic acid (4), phthalic acid (6), isophthalic acid (5), and terephthalic acid (1) on alumina were determined by measurement of the UV absorption of the supernatant solution at 270.4 nm (ϵ 899.6), 276.4 (1292), 288.2 (846.3), and 283 (1840), respectively. For the other dicarboxylic acids, the adsorption amounts adsorbed were determined by acid-base titration of the supernatant solution.

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Registry No. 1, 100-21-0; 2, 1679-64-7; 3, 120-61-6; 4, 65-85-0; 5,

121-91-5; 5 (monomethyl ester), 1877-71-0; 6, 88-99-3; 7, 619-81-8; 7 (monomethyl ester), 1011-85-4; 8, 619-82-9; 8 (monomethyl ester), 15177-67-0; 6 (monomethyl ester), 4376-18-5; $\text{HO}_2\text{C}(\text{CH}_2)_6\text{CO}_2\text{H}$, 505-48-6; $\text{HO}_2\text{C}(\text{CH}_2)_{10}\text{CO}_2\text{H}$, 693-23-2; $\text{HO}_2\text{C}(\text{CH}_2)_3\text{CO}_2\text{H}$, 110-94-1; $\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$, 124-04-9; $\text{HO}_2\text{C}(\text{CH}_2)_5\text{CO}_2\text{H}$, 111-16-0; $\text{HO}_2\text{C}(\text{C}-\text{H}_2)_7\text{CO}_2\text{H}$, 123-99-9; $\text{HO}_2\text{C}(\text{CH}_2)_8\text{CO}_2\text{H}$, 111-20-6; $\text{HO}_2\text{C}(\text{CH}_2)_3\text{CO}-\text{OCH}_3$, 1070-62-8; $(\text{CH}_3\text{O})_2\text{SO}_2$, 77-78-1; $\text{HO}_3\text{C}(\text{CH}_2)_4\text{COOCH}_3$, 627-91-8; $\text{HO}_2\text{C}(\text{CH}_2)_5\text{COOCH}_3$, 20291-40-1; $\text{HO}_2\text{C}(\text{CH}_2)_6\text{COOCH}_3$, 3946-32-5; $\text{HO}_2\text{C}(\text{CH}_2)_7\text{COOCH}_3$, 2104-19-0; $\text{HO}_2\text{C}(\text{CH}_2)_8\text{COOCH}_3$, 818-88-2; $\text{HO}_2\text{C}(\text{CH}_2)_{10}\text{COOCH}_3$, 3903-40-0; *p*- $\text{CH}_3\text{C}_6\text{H}_4\text{N}=\text{NNHCH}_3$, 21124-13-0; $(\text{CH}_3)_2\text{NCH}(\text{OCH}_3)_2$, 4637-24-5; $\text{BF}_3\text{CH}_3\text{OH}$, 373-57-9; diazomethane, 334-88-3; alumina, 1344-28-1.

α - and β -Carboxylic Groups as Primary Ligating Groups in Promoting Amide Deprotonation. Solid-State Behavior of *N*-Tosylalaninate-Copper(II) Complexes: Crystal and Molecular Structures of Bis(*N*-tosyl- β -alaninato)bis(imidazole)copper(II), Polymeric (*N*-Tosyl- α -alaninato)diaquacopper(II) Monohydrate, and Dipiperidinium Bis(*N*-tosyl- α -alaninato)cuprate(II) Monohydrate Complexes

L. Antolini,^{1a} L. P. Battaglia,^{1b} A. Bonamartini Corradi,^{1b} G. Marcotrigiano,^{1c} L. Menabue,^{1a} and G. C. Pellacani^{*1a}

Contribution from Ministero della Pubblica Istruzione of Italy, Istituto di Chimica Generale e Inorganica, University of Modena, 41100 Modena, Istituto di Chimica Generale e Inorganica, Centro di Studio per la Strutturistica Diffratometrica del C.N.R., University of Parma, 43100 Parma, and Istituto di Chimica, Facoltà di Medicina-Veterinaria, University of Bari, 70126 Bari, Italy. Received March 28, 1984

Abstract: The interaction between *N*-tosyl- α - and *N*-tosyl- β -alanine and the copper(II) ion in aqueous solution at different pH gives rise to the formation of two types of compounds differing from each other by virtue of the presence on the amino acid of neutral (type 1) or deprotonated (type 2) NH group. Type 1 complexes are simple green complexes of formula $\text{Cu}(\text{Tsala})_2$ ($\text{Tsala}^- = N$ -tosylalaninate anion), which show physical properties indicating dimeric or polymeric structure like copper(II) acetates and their amine adducts of formula $\text{Cu}(\text{Tsala})_2\text{B}_2$ ($\text{B} =$ imidazole (ImH), *N*-methylimidazole (MeImH), piperidine (PipdH), and morpholine (MorfH), and $\text{Tsala}^- = N$ -tosyl- β -alaninate anion; $\text{B} =$ ImH and MeImH, and $\text{Tsala}^- = N$ -tosyl- α -alaninate anion), which present physical properties similar to those of $\text{Cu}(\text{Ts-}\beta\text{-ala})_2(\text{ImH})_2$, the crystal structure of which has also been determined. The $\text{Cu}(\text{Ts-}\beta\text{-ala})_2(\text{ImH})_2$ complex crystallizes in monoclinic $P2_1/n$ space group with $a = 14.287$ (2) Å, $b = 7.169$ (1) Å, $c = 16.363$ (2) Å, $\beta = 110.6$ (1)°, $Z = 2$. Coordination around the copper, lying on the center of symmetry, is square planar and involves two centrosymmetric carboxylic oxygens of two amino acids and two imidazole molecules. Type 2 complexes contain only compounds of *N*-tosyl- α -alanine which present a coordinative behavior, strictly dependent on the pH of the solution, separating at $\text{pH} \geq 5$ a blue compound of formula $\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala}) \cdot 3\text{H}_2\text{O}$ ($\text{Ts-}\alpha\text{-H}_1\text{ala}^{2-} = N$ -tosyl- α -alaninate dianion; the NH group is also deprotonated) and at $\text{pH} > 7$ compounds of formula $\text{A}_2[\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala})_2]$ ($\text{A} = \text{K}^+$, piperidinium (PipdH_2^+), morpholinium (MorfH_2^+) cations). The crystals of $[\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala})(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$ are orthorhombic, space group *Pbca* with $a = 27.198$ (3) Å, $b = 9.001$ (1) Å, $c = 11.908$ (1) Å, and $Z = 8$. The structure consists of polymeric $[\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala})(\text{H}_2\text{O})_2]_n$ units, in which each copper atom is five-coordinated in a distorted square pyramid involving, at the base, the deprotonated amide nitrogen, one carboxylic oxygen, and two water molecules. The apex of the pyramid is occupied by a second carboxylate oxygen belonging to an adjacent amino acid molecule. The $[\text{PipdH}_2]_2[\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala})_2] \cdot \text{H}_2\text{O}$ complex crystallizes in monoclinic *C2/c* space group with $a = 19.407$ (2) Å, $b = 9.950$ (1) Å, $c = 18.930$ (2) Å, $\beta = 99.35$ (1)°, and $Z = 4$. The structure consists of piperidinium cations and $[\text{Cu}(\text{Ts-}\alpha\text{-H}_1\text{ala})_2]^{2-}$ anions. Coordination around the copper involves two centrosymmetric amino acid molecules coordinating via deprotonated sulfonamide nitrogen and one carboxylate oxygen in a square-planar arrangement. Magnetic and spectroscopic (EPR, IR, and vis) properties of all the complexes are reported. The ability of α - and β -carboxylic groups to behave as primary ligating groups is discussed.

It is known that the metal ion substitution of amide proton is a very difficult process as it suffers from competition from the metal ion hydrolysis reaction. Only the presence of a primary ligating site (or anchor) or the ligand molecule favoring a 5- or 6-membered chelate ring formation, permits pH regions to be

reached where substitution of a metal ion for an amide hydrogen may occur.²

In particular, the COO^- group is commonly believed to be ineffective as primary ligating group in promoting ionization of

(1) (a) University of Modena. (b) University of Parma. (c) University of Bari.

(2) Sigel, H.; Martin, R. B. *Chem. Rev.* 1982, 82, 385 and references therein.