

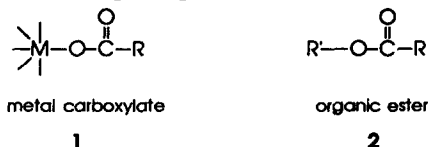
HIGH OXIDATION STATE TRANSITION METAL CARBOXYLATES AS ACYLATING AGENTS

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Summary: The formation of amide bonds from the reaction of metal carboxylates with amines was observed for the first time; complexes of titanium(IV), zirconium(IV) and tantalum(V) were investigated.

The observation that metal carboxylates (1) are formally analogous to organic esters (2) led us to consider if transition metal carboxylates could possibly be used as acylating agents. Although metal carboxylates have long occupied a central position in coordination chemistry,¹

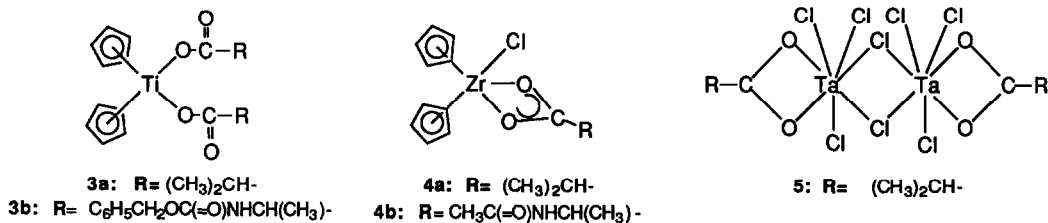


little is known about the occurrence of nucleophilic substitutions at the metal coordinated carbonyl function: A literature search revealed that only one system had specifically been investigated for the possible reactivity of the metal coordinated carbonyl function toward nucleophilic attack: Jordan and Taube² reported that the aqueous hydrolysis of cobalt(III)pentaamine trifluoroacetate proceeded under very basic conditions (concentrated NaOH) via attack at the carbonyl carbon.

Since the susceptibility of metal carboxylates toward nucleophilic substitutions had never been investigated in detail, we studied the reactivities of zirconium(IV), titanium(IV), and tantalum(V) carboxylates toward amines. We selected high oxidation state complexes as model compounds since we expected that the high positive charge on the metal should increase the reactivity of the carboxylate ligand toward nucleophiles. The isobutyrate moiety was selected as a model ligand. The metallocene isobutyrate complexes (3a and 4a³) were prepared in yields of 77% and 70% respectively, following conventional methods of metal carboxylate synthesis. The tantalum(V)tetrachlorocarboxylate dimer (5) was prepared by a modification of Viard's procedure.⁴

The ability of the metallocene isobutyrate (3a) and (4a) to act as acylating agents for amide bond formation was demonstrated by their reaction with various amines. Typically, a THF solution of the metallocene isobutyrate and the amine was allowed to reflux under argon

atmosphere. Water was then added to the reaction mixture to precipitate an insoluble metal product whose structure is presently under investigation. After purification (extraction with acid and base) the yield of analytically pure amides ranged from 42 to 85% (Table 1). Among a variety of common solvents, THF was found to afford the best yields.



Since an important application of amide bond formation is found in peptide synthesis⁵ we examined the applicability of metallocene carboxylates as reagents for peptide synthesis. We prepared the titanocene dicarboxylate complex of N-benzyloxycarbonyl-L-alanine (Z-Ala), **3b**, and the zirconocene monocarboxylate complex of N-acetyl-L-alanine (N-Ac-Ala) **4b** in yields of 80% and 65% respectively. This is the first reported synthesis of metallocene amino acid carboxylates. The structures of **3b** and **4b** were confirmed by IR spectroscopy. An alanine dipeptide was successfully synthesized in a yield of 45% by refluxing complex **3b** in a THF solution of alanine methyl ester hydrochloride and triethylamine (TEA).

Table 1: Model reactions of metallocene complexes with amines.

metal carboxylate	amine	product	yield (%)
3a	benzylamine	N-benzylisobutyramide	82
4a	benzylamine	N-benzylisobutyramide	85
3a	α -methylbenzylamine (MBA)	N-(MBA)isobutyramide	63
4b	α -methylbenzylamine (MBA)	N-Ac-Ala-MBA	42
3b	HCl·Ala-OMe/TEA	N-Z-Ala-Ala-OMe	45
5	benzylamine	N-benzylisobutyramide	87

The above results demonstrated the validity of the analogy of active esters with metal carboxylates; however, the reaction times and conditions required were far more severe than those required by current methods of amide bond formation. On the other hand, the reaction of tantalum(V)tetrachloroisobutyrate (**5**) with benzylamine occurred readily at room temperature. We followed the progress of this reaction by HPLC, using the internal standard technique for the quantitative analysis of the amount of benzylisobutyramide formed in the reaction mixture. Under optimized reaction conditions, about 50% of the expected amount of benzylisobutyramide was formed within 2 minutes and the reaction went to completion within 30 min. The HPLC results were confirmed when about 87% of the theoretically expected amount of benzylisobutyramide could be isolated from the reaction mixture in analytically pure form.

Our initial results revealed a number of examples in which a high oxidation state transition metal activated the coordinated carbonyl carbon toward nucleophilic attack. This mode of reactivity had not previously been observed in high oxidation state transition metal carboxylates. The oxidation state of the metal center is an important parameter in determining the degree of this reactivity. In the only previous example of this type of reaction, cobalt(III)pentaamine trifluoroacetate underwent nucleophilic attack at the carbonyl carbon only under the most forcing reaction conditions, i. e., when exposed to concentrated NaOH.² In comparison, the carboxylates coordinated to titanium(IV) and zirconium(IV) were found in this study to be fairly susceptible to nucleophilic attack by amines. Even more reactive was the tantalum(V) carboxylate, whose reaction rate toward benzylamine was orders of magnitude faster than the reaction rates of the metallo(IV)cene complexes (reaction times of several minutes at 22 °C *versus* several hours at 67 °C). In particular, the fast and virtually quantitative reaction between tantalum(V)tetrachloroisobutyrate (**5**) and benzylamine holds promise that further exploration of high oxidation state metal carboxylates will yield a new class of powerful acylating agents with many potential applications in organic synthesis.

Experimental Procedures:

All reactions were performed under an atmosphere of dry nitrogen or argon. All solvents were dried and degassed by standard techniques.

Representative procedure for the preparation of titanocene and zirconocene carboxylates (3) and (4): Cp₂TiCl₂ (1 mmol) or Cp₂ZrCl₂ (2 mmol; Cp = η⁵-C₅H₅) was added to a solution of 2 mmol of triethylamine and 2 mmol of acid in tetrahydrofuran (THF). After 12 h, the Et₃NHCl precipitate was removed by filtration and the clear filtrates were evaporated to dryness. After recrystallization of the crude products (**3a** and **4a** from benzene/pentane, **3b** from THF/hexane, **4b** from chloroform/pentane) pure titanocene and zirconocene carboxylates were obtained in yields of about 70%. (**3a**), ν_{max} (KBr pellet, cm⁻¹) 1633 (ν_{COO} asym), 1468 (ν_{COO} sym), 1445 (Cp ring). (**3a**), ¹H NMR (CDCl₃, δ) 6.44 (10 H, s, cp), 2.46 (1 H, m, CH), 1.15 (6 H, d, CH₃); (**4a**) ν_{max} (KBr pellet, cm⁻¹) 1510 (ν_{COO} asym), 1476 (ν_{COO} sym), 1442 (Cp ring). (**4a**), ¹H NMR (CDCl₃, δ) 6.25 (10 H, s, cp), 2.45 (1 H, m, CH), 1.18 (6 H, d, CH₃). (**4b**), ν_{max} (KBr pellet, cm⁻¹) 3339 (ν_{NH}), 1667 (ν_{C(=O)Me}), 1536 (ν_{COO} asym), 1487 (ν_{COO} sym), 1445 (Cp ring). (**4b**), ¹H NMR (CDCl₃, δ) 6.27 (10 H, s, cp), 4.35 (1 H, m, CH), 2.03 (3 H, s, C(=O)Me), 1.42 (3 H, d, CH₃).

Preparation of tantalum(V)tetrachloroisobutyrate (5): TaCl₅ (10.2 g, 28.5 mmol) was suspended in 125 mL of benzene. With stirring, isobutyric acid (2.5 mL, 27 mmol) was slowly added. After 1 h, the solvent was evaporated and the residue was taken up in 15 mL of toluene. This suspension was filtered and the clear filtrate was cooled to -20 °C, yielding pale yellow crystals (8.0 g, 72%), m. p. 109-112 °C (dec.). ν_{max} (KBr pellet, cm⁻¹) 1541 (br), 1363. ¹H NMR (C₆D₆, δ) 2.52 (1 H, septet, (CH₃)₂CHCO₂, ³J_{H-H} = 6.9 Hz), 0.91 (6 H, d, (CH₃)₂CHCO₂, ³J_{H-H} = 6.9 Hz). Calcd. for C₄H₇Cl₄O₂Ta: C, 11.73; H, 1.72%. Found: C, 11.92; H, 1.72%.

Reaction of titanocene (3) and zirconocene carboxylates (4) with amines: The metal complex (0.4 mmole/mL) was refluxed in THF for 24 h with a stoichiometric amount of an amine. The reaction was terminated by the addition of 5% (v/v) of water, resulting in a metal containing precipitate which was removed by filtration. The clear filtrate was redissolved in ethyl acetate and extracted repeatedly with 1 M HCl and 1 M NaCO₃. Evaporation of the ethyl acetate solution yielded analytically pure amides.

Reaction of tantalum(V)tetrachloroisobutyrate dimer (5) with amines: Benzylamine (0.57 mL, 5.2 mmol) was added with stirring to a solution of 5 (1.0 g, 2.4 mmol) in benzene (25 mL). A precipitate of benzylamine hydrochloride formed immediately. The reaction was stirred at room temperature for 30 min. and then terminated by the addition of aqueous HCl (0.1 M, 50 mL). Stirring was continued for an additional 15 min to allow the dissolution of all benzylamine hydrochloride and the complete formation of a tantalum-containing precipitate. The mixture was filtered and the filtrate was separated into an aqueous phase and an organic phase which was repeatedly extracted with 1 M HCl and 1 M NaCO₃. The organic phase was then evaporated to yield analytically pure benzylisobutyramide (87%).

References

1. For example, see: C. Oldham in *Comprehensive Coordination Chemistry*; Pergamon Press: Oxford, 1987, pp. 435-459.
2. R. B. Jordan, H. Taube, *J. Am. Chem. Soc.* **1966**, *88*, 4406. It is noteworthy that the kinetic studies of this work indicate that OH⁻ is not sufficiently nucleophilic to complete the reaction with the trifluorocarboxylate group; a second hydroxide ion is required to form a transition state of the configuration (NH₃)₅Co[O₂(CF₃)C...OH...OH].
3. A single crystal X-ray structure of 4a revealed the bidentate configuration of the isobutyrate ligand: H. Schugar, J. Potenza, A. Goldman, and J. Kohn, to be submitted for publication.
4. B. Viard, M. Poulain, D. Grandjean, J. Amaudrut, *J. Chem. Res.* **1983**, (S) 84, or *J. Chem. Res.* **1983**, (M) 0853.
5. For example, see: M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag, Berlin, 1984.

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