JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2005; **18:** 193–209

Review Commentary

Tetrahedral intermediates in reactions of carboxylic acid derivatives with nucleophiles†

Martin Adler, Sandra Adler and Gernot Boche*

Fachbereich Chemie, Universität Marburg, D-35032 Marburg, Germany

Received 18 November 2003; revised 16 March 2004; accepted 17 March 2004

ABSTRACT: Transacylation reactions of carboxylic acids, carboxylic acid esters, carboxylic acid amides and other carboxylic acid derivatives are among the most widespread and most important reactions in chemistry and biochemistry. Already in 1887, Claisen suggested a tetrahedral intermediate in transformations of carboxylic acid derivatives with nucleophiles. A historical overview gives insight into the studies to detect possible tetrahedral intermediates in such reactions. However, only in recent years has detailed information concerning the structures of such species become available. In this review, neutral, cationic and anionic tetrahedral intermediates are described which serve as models for transacylations under neutral, acid-catalysed or basic conditions. The characteristically different structures correspond nicely with experimental experience with reactions of carboxylic acid derivatives and with quantum chemical model calculations on tetrahedral intermediates. Finally, by means of model calculations, an explanation is given for the fast reactions of Weinreb amides, $RC(O)N(CH_3)OCH_3$, with organolithium and even with Grignard reagents: the reactions are determined by comparatively stable chelate transition states. Copyright © 2004 John Wiley & Sons, Ltd.

Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/0894-3230/suppmat/

KEYWORDS: Tetrahedral intermediates; carboxylic acid derivatives; structures; reactions; calculations

INTRODUCTION

One of the most common and therefore most important reactions in organic chemistry is that of a carboxylic acid derivative **1**, bearing a leaving group X, with a nucleophile NuM (NuH) **2** to give **4** (Scheme 1).

This is a key reaction for a multitude of laboratory syntheses[1–57] and it is found in almost every biological system.[58–64] Esterification, ester hydrolysis, transesterification, formation and hydrolysis of amides and peptides, hydride reduction of such carbonyl compounds and aldehyde and ketone syntheses are among the most significant examples of this reaction type.

Most of these transformations proceed via a two-step addition–elimination mechanism.[1–64] Thereby the HOMO **2a** of the nucleophile **2** interacts with the π^* LUMO **1a** of the carbonyl compound **1** leading to a new σ-bond in the tetrahedral intermediate (**3a**) (Scheme 1). In the second step, the interaction of an oxygen lone pair n with the σ^* orbital of the C—X bond (**3b**) leads to a weakening of the C—X bond in **3** and finally to an elimination of the leaving group X(M, H) **5** to give the new carboxylic acid derivative **4**.

The nucleophilic attack of **2** on **1** and the elimination of the leaving group **5** from **3** proceed in a similar manner, namely along the Bürgi–Dunitz trajectory[56,65–74] (Scheme 2).

The angle $\alpha > 90°$ is due to a better orbital overlap between the HOMO of the nucleophile **2a** and the π^* LUMO of the C═O bond **1a** (Schemes 1 and 2).

The nature and the stability of a tetrahedral intermediate and also its reactivity depend strongly on the respective reagents. This is illustrated by the reaction of a carboxylic acid derivative **1** [R = H, alkyl, aryl; X = SR, OR, NR_2, (Hal)] with an organometallic species R′M **6**, (Scheme 3).[1–64]

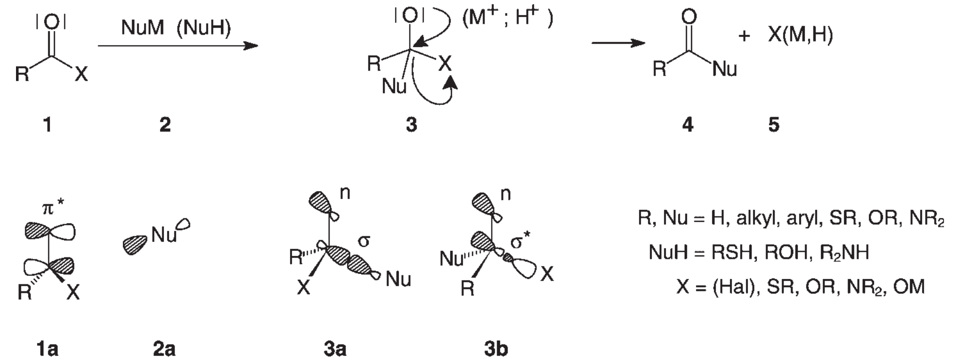
Pathway a: if in the tetrahedral intermediate **7**, X is an excellent leaving group, fast elimination of XM **8** gives the new carbonyl compound **9**, which reacts also with the nucleophile R′M **6** to give the alcoholate **10**. Protonation

---

**Correspondence to:* G. Boche, Fachbereich Chemie, Universität Marburg, D-35032 Marburg, Germany.
E-mail: boche@chemie.uni-marburg.de

†Dedicated to Professor Manfred T. Reetz and Professor Helmut Schwarz.

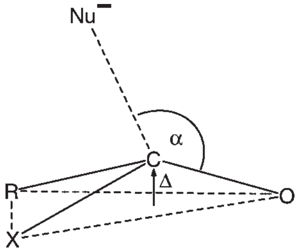
Contract/grant sponsors: Deutsche Forschungsgemeinschaft; Fonds der Chemischen Industrie.



Scheme 1. Addition–elimination reaction of a carboxylic acid derivative **1** with a nucleophile **2**; reaction scheme and orbital interactions

of **10** results in the alcohol **11**. Pathway b: there exists also the possibility that the alcoholate **10** is directly formed from **7** with **6**. Pathway c: if the tetrahedral intermediate **7** is stable towards elimination of **8** (pathway a) and substitution by **6** (pathway b), hydrolysis of **7** gives **9**.

Interestingly, a tetrahedral intermediate is not necessarily formed in reactions of carboxylic acid derivatives **1** with nucleophiles, as indicated from studies in solution,[1–5,58–61] in the gas phase[75–94] and from calculations.[57,95–131] Especially in the case of chloride or other excellent leaving groups X, a tetrahedral intermediate has never been proven clearly. Rather, an alternative, S_N2-like substitution mechanism is often highly probable.[95–131] The lack of certainty is mainly due to the high reactivity of, e.g., carboxylic acid chlorides with nucleophiles, preventing the identification of possibly formed tetrahedral intermediates. The very fast reaction of acid chlorides RC(O)Cl (R = alkyl, aryl) even with the less nucleophilic organometallic reagents R′M where M = Li, Mg, Ca, Mn, Fe, Co, Rh, Ni, Pd, Cu, Zn, Cd, Hg, Al, Ga, In, Tl, Si, Ge, Sn, Pb and Sb, together with the comparatively slow reaction of the first formed ketone with R′M, has thus led to ‘A banquet table of metals for ketone synthesis’, as a recent review article was entitled.[132–136]

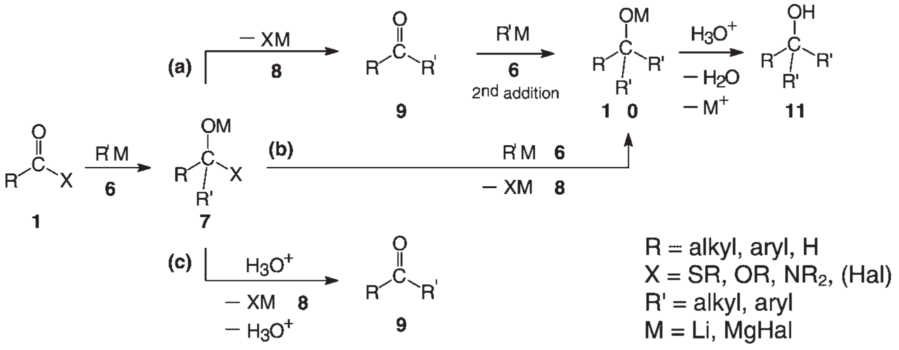


Scheme 2. Bürgi–Dunitz trajectory: in the reaction of Nu^- with a carbonyl compound [here RC(O)X], the distance Nu—C is shortened, C—O lengthened and Δ increased; the angle α is >90°

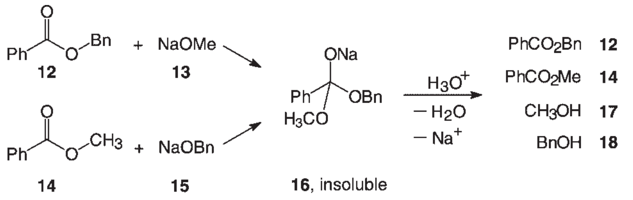
Before the nature of the tetrahedral intermediate in reactions of carboxylic acid derivatives with nucleophiles is discussed in more detail, which is the main purpose of this paper, a brief historical overview is given of tetrahedral intermediates of carboxylic acid derivatives.

HISTORICAL OVERVIEW OF TETRAHEDRAL ADDUCTS OF CARBOXYLIC ACID DERIVATIVES

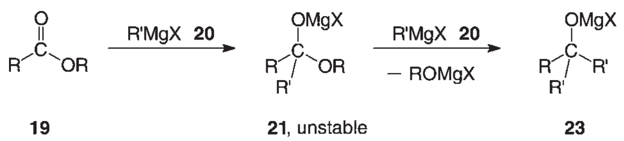
Already in 1887, Claisen discussed an intermediate in transformations of esters with nucleophiles[137–139] (Scheme 4). In the reaction of the benzyl benzoate **12**



Scheme 3. Alternative pathways for the reaction of a carboxylic acid derivative **1** with an organometallic nucleophile **6** via the tetrahedral adduct **7**



Scheme 4. Claisen's assumption of a tetrahedral intermediate (1887)



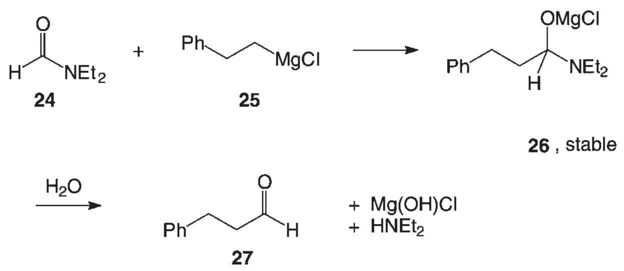
Scheme 5. Unstable tetrahedral intermediates in the reaction of esters with Grignard reagents (Grignard, 1901)

with sodium methanolate **13**, and in the reaction of methyl benzoate **14** with the sodium salt of benzyl alcohol **15**, he observed a white precipitate which, on treatment with acid, gave the same products benzyl benzoate **12**, methyl benzoate **14**, methanol **17** and benzyl alcohol **18**. He named the likely common intermediate **16** 'additionelle Verbindung' ('adduct').

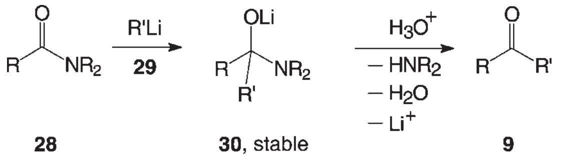
Reactions of esters **19** with organomagnesium reagents **20** giving tertiary alcoholates **23** led Grignard in 1901 to the assumption of a related unstable intermediate **21**.[140,141] The elimination of ROMgX **22** from **21** to give a ketone **9** (Scheme 3) was not suggested at first. Rather, **21** should react directly with a second R′MgX **20** to give **23** (Scheme 5).

Shortly afterwards (1904) a new synthesis of aldehydes was published by Bouveault[142–151] (Scheme 6).

The outcome of the reaction is determined by the stable metallated intermediate **26**, which is formed by the addition of the Grignard species phenylethylmagnesium chloride **25** to *N*,*N*-diethylformamide **24**. Hydrolysis of **26** yields the aldehyde **27**. The high stability of the amide adduct **26** is due to the low tendency for the elimination of Et_2NMgCl, which is in strong contrast to the facile elimination (substitution) of ROMgX **22** from the ester adduct **21** (Scheme 5). Interestingly, *excess* of a Grignard reagent RMgX such as **25** results in the substitution of $MgXO^-$ by a second RMgX to give a tertiary amine R_2CHNEt_2.[143,144] As we shall see in the following, the stability of amide adducts such as **26** has been used repeatedly in reactions involving tetrahedral intermediates.



Scheme 6. Aldehyde synthesis of Bouveault (1904)



Scheme 7. Ketone synthesis of Evans (1956)

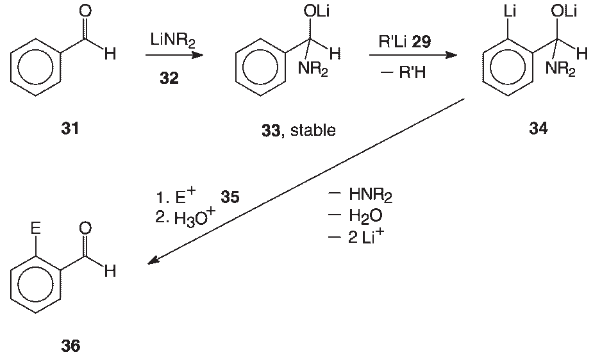
A further example was published by Evans (1956).[152,153] He used the reaction of carboxylic acid amides of the type **28** with R′Li compounds **29**, giving the stable intermediate **30**, for the synthesis of ketones **9** (Scheme 7).

Only organo*lithium* compounds can be used in this reaction; *Grignard reagents* do not lead to ketone formation. Adducts such as **30** are also used for further reactions such as orthometallation[154] (see also below).

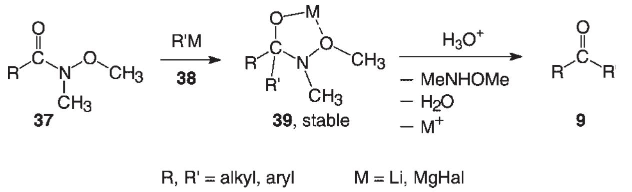
Comins and co-workers (1981) used the formation of adducts such as **33** for the protection of aldehydes (Scheme 8).[155–160]

Reaction of benzaldehyde **31** with a lithium amide **32** leads to **33**, which, like **26** and **30** (Schemes 6 and 7), is stable with respect to elimination of $LiNR_2$. Compound **33** is thus accessible for further reactions, e.g. orthometallation with R′Li **29** to give **34**. Reaction with an electrophile E^+ **35** followed by protonation gives the *ortho*-substituted aldehyde **36**.

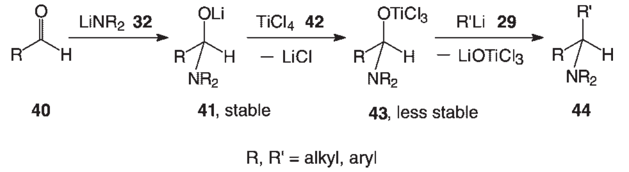
A more general synthesis of ketones **9** than outlined in Scheme 7 was published by Weinreb and co-workers (1981)[161–175] (Scheme 9). Here, *N*-methoxy-*N*-methylcarboxylic acid amides ('Weinreb amides') **37** are reacted with organometallic compounds R′M (M = Li, MgHal) **38** to give, on protonation, ketones **9**. It was concluded and generally accepted[161–175] that the high yields of ketones are due to the high stability of the five-membered ring-chelated intermediate **39**. The role of thermodynamics and kinetics in this reaction is elaborated by means of quantum chemical calculations later.



Scheme 8. Protection of aldehydes according to Comins and co-workers (1981)



Scheme 9. General synthesis of ketones with Weinreb amides (1981)



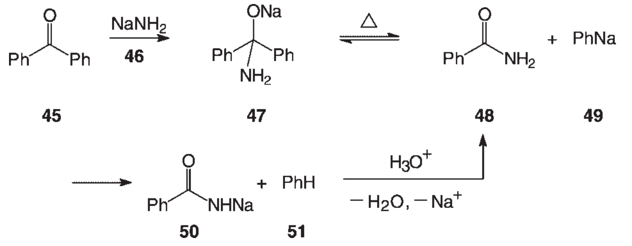
Scheme 10. Synthesis of tertiary amines by Seebach and co-workers (1983)

Seebach and co-workers (1983) used stable carboxylic acid amide adducts in a different manner (Scheme 10).[176–179]

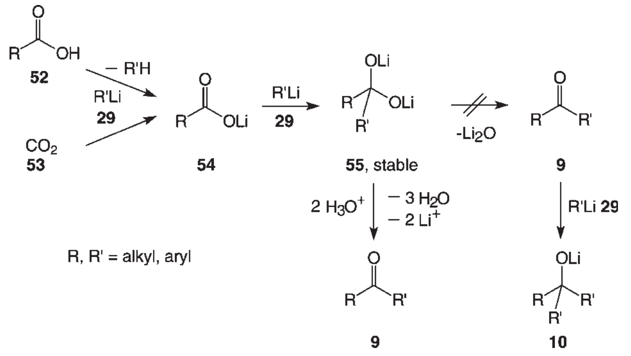
In that case the stable adduct **41** is formed from aldehydes **40** and disubstituted lithium amides **32**, as already outlined in Scheme 8. Then, in order to transform the comparatively poor leaving group LiO^- into a better one, **41** is reacted with $TiCl_4$ **42** to give the transmetallated adduct **43** with the better leaving group Cl_3TiO^-. Indeed, reaction of **43** with R′Li **29** removes the oxygen substituent to give the tertiary amine **44**. The *lithiated* adduct **41** is not a very favourable reagent for R′Li **29** as shown before. The formation of tertiary amines was observed earlier when Grignard adducts such as **26** were reacted with *excess* RMgX[143,144] (see in the context of Scheme 6).

The low tendency towards the elimination of metallated amines R_2NM from carboxylic acid amide adducts is again illustrated by the Haller–Bauer reaction (1908)[180,181] (Scheme 11).

When the authors reacted benzophenone **45** with sodium amide **46**, the adduct **47** was formed, which apparently is in equilibrium with a small amount of benzoic acid amide **48** and phenylsodium **49**. Thus, phenylsodium **49** competes successfully with sodium amide **46** for the elimination from **47**! Deprotonation of the amide **48** by **49** then leads to the metallated amide **50** and benzene **51**, which are thermodynamically more stable than **48** and **49**. Protonation of **50** results finally in the amide **48**. In addition to metallated aryl species such as PhNa **49**, other comparatively stable organometallic species RM are also observed as leaving groups in Haller–Bauer reactions. We shall come back to this interesting phenomenon of the competition of an organometallic species RM with a metallated amine R_2NM as leaving groups when we discuss the structures of tetrahedral intermediates in the next section.



Scheme 11. The Haller–Bauer reaction (1908)



Scheme 12. Ketone synthesis of Gilman and van Ess (1933)

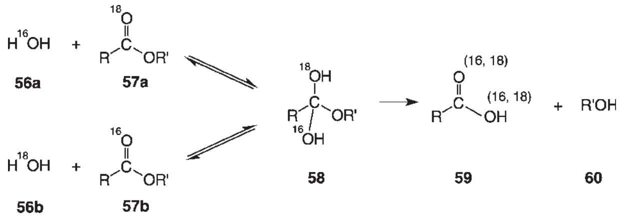
The related eliminations of metal hydrides HM, in general, however, not from tetrahedral adducts of *carboxylic acid* derivatives, to give carbonyl compounds are only briefly mentioned here: the Cannizzaro reaction,[182] the Meerwein–Ponndorf–Verley reduction,[183–185] the Oppenauer oxidation[186] and the oxidation of aldehydes to carboxylic acids.[187,188]

Yet another stable tetrahedral intermediate (**55**), formed from carboxylic acids **52** or carbon dioxide **53** with R′Li **29**, first to give the carboxylate **54** and then with a second R′Li **29** the adduct **55**, was discovered by Gilman and van Ess (1933) (Scheme 12).[189–194]

The reaction is also used in ketone synthesis, because elimination of Li_2O from the dilithiated hydrated ketone **55** to give the ketone **9**, which could react with further R′Li **29** to give the tertiary alcoholate **10**, does not take place. Rather, protonation of **55** gives the ketone **9**. This is in strong contrast to the fast elimination (substitution) of alcoholates ROM from *ester* adducts finally to give an alcoholate such as **11** (Scheme 3).

Although a tetrahedral intermediate in reactions of carboxylic acid derivatives with nucleophiles seems rather plausible, or even clear, from many of the examples given above, one should strongly emphasize that the definitive proof of its existence, or structural studies of the adduct, were performed only much later than many of the reactions which suggested their existence. Thus, it was only in 1951 that Bender was able to prove the existence of a tetrahedral intermediate in the reaction of esters with H_2O (Scheme 13)[195] (see also Refs 1–5 and 58–61).

When the ^{18}O-labelled ester **57a** was partially hydrolysed with $H^{16}OH$ **56a**, a certain amount of non-labelled ester **57b** was also detected, which requires formally the



Scheme 13. Bender's proof of the tetrahedral intermediate in reactions of esters with H_2O (1951)

breaking of the $C{=}^{18}O$ bond in **57a**, and therefore the existence of the tetrahedral intermediate **58** with a C—O single bond. Elimination of $H^{16}OH$ **56a** and $H^{18}OH$ **56b** from **58** gives **57a** and **57b**, respectively. Elimination of R′OH **60** from **58** leads to the partially labelled acid **59**. An S_N2-like substitution of the R′O group in the ester **57** by the HO group of **56** is excluded by these findings.

Following the studies of Bender, tetrahedral adducts in reactions of carboxylic acid derivatives with nucleophiles were intensively investigated. In the field of organic and bioorganic chemistry, many kinetic studies were performed, especially by the groups of Bender,[2,7,8,10,17,18,20] Bruice,[9,11,13,24,25,29,58] Fersht,[61] Guthrie[31,34,35,37] and Jencks.[4,12,14,15,19,21,23,28,30,32,33,36,59] Antibodies, which were selected to bind phosphate and phosphonate *tetrahedral transition state analogues*, turned out to be the first catalytic antibodies for the selective hydrolysis of carbonates or esters, as Lerner and co-workers[196,201] and Schultz and co-workers[197–199] revealed.[196–205]

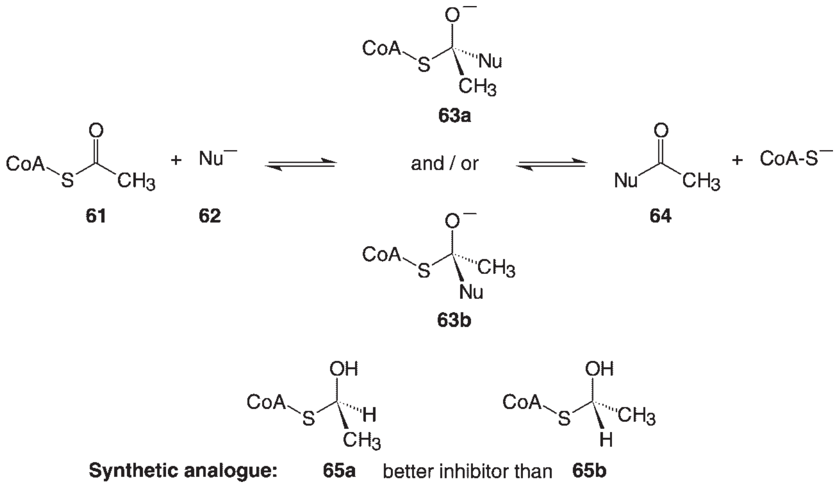
An interesting study by Schwarz and Drueckhammer (1996) concerning the stereochemistry of the tetrahedral intermediate in acetyl-CoA-promoted acyl transfer reactions is shown in Scheme 14.[206] The stereochemistry of such intermediates is of fundamental importance in enzyme catalysis.[58–61]

The acyl transfer from acetyl-CoA **61** to the nucleophile Nu^- **62** to give **64** could proceed through either one of the two intermediates with the stereochemistry as shown in **63a** or **63b**, or through both. Therefore, the authors synthesized the two enantiomeric alcohols **65a** and **65b** and studied their inhibitor strength in acetyl-CoA-dependent acyl transferase reactions: **65a** turned out to be the much stronger inhibitor, which indicated the tetrahedral intermediate **63a** to have the more favourable stereochemistry in the acyl transfer.

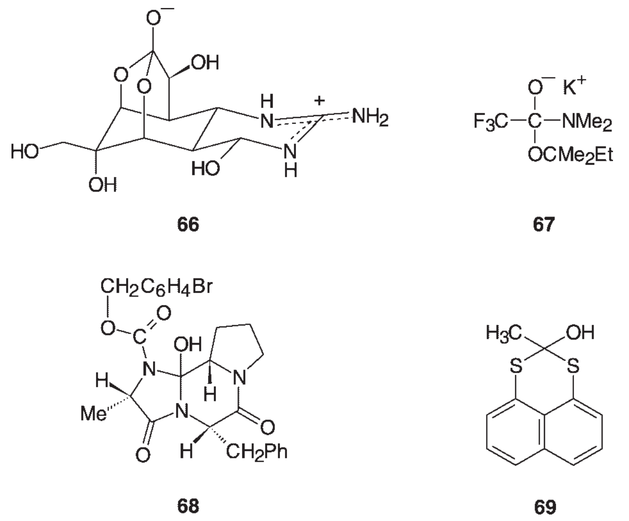
After this short review of significant historical examples of tetrahedral intermediates of carboxylic acid derivatives, we shall concentrate in the next section on structural investigations of intermediates formed from RC(O)X **1** and nucleophiles **2** (see Scheme 1). It will be of interest to see whether the structural details are in agreement with the Bürgi–Dunitz formulation of the approach of a nucleophile **2** to a carbonyl species RC(O)X **1** and with its removal from the tetrahedral intermediate **3**. What is the influence of the charge of the tetrahedral intermediate, neutral, cationic or anionic, on its structure? Do model calculations support the structural characteristics of such intermediates? A further point of interest is the question of whether the facile formation of a tetrahedral intermediate **3** is (always) due the thermodynamic stability of **3**, or whether kinetic reasons are also significant, at least in some cases (see later).

STRUCTURES OF NEUTRAL, CATIONIC AND ANIONIC TETRAHEDRAL ADDUCTS

At the beginning of the investigations of tetrahedral intermediates in transformations of carboxylic acid derivatives with nucleophiles, it was difficult to get hold of such species because of their instability; see, e.g., Scheme 13 and the situation described there. Stimulation for further efforts came from the discovery of the anomeric effect and its significance for structural details and reactivities of compounds bearing two or three



Scheme 14. Identification of the absolute stereochemistry of the tetrahedral intermediate in the reaction of acetyl-CoA with a nucleophile Nu^- by Schwartz and Drueckhammer (1996)



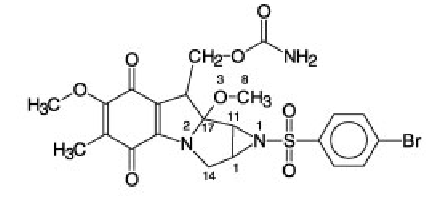
Scheme 15. Four types of stable tetrahedral adducts

heteroatoms with non-bonded electron pairs at the anomeric centre.[207–219] Initially compounds possessing special structural features were investigated (Scheme 15): (1) with bicyclic or polycyclic structures such as tetrodotoxin **66**;[220] (2) with a strong electron-withdrawing group, e.g. CF$_3$, attached to the (pro)acyl carbon (**67**[221]); (3) with a donor group with reduced conjugation with the potential carbonyl group (**68**[222,223]); and (4) with sulfur atoms bonded to the anomeric centre (**69**[224]).

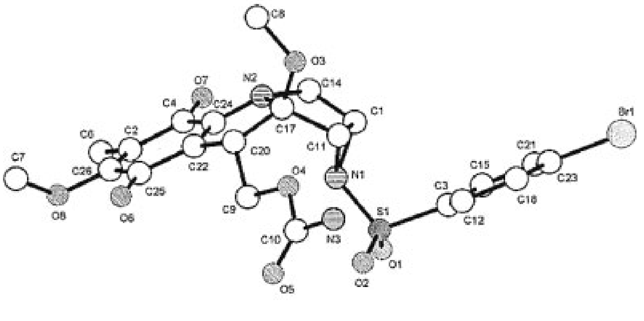
Such compounds, and also simpler ones, were used to study kinetically their decomposition into the respective carbonyl species and to measure the IR, UV and NMR spectra in order to show the existence of an adduct with a tetrahedral carbon atom.[225–238] More recently, NMR investigations were performed on **70** and **71** (Scheme 16).[239,240]

Detailed insight into the structures of tetrahedral adducts, however, was only provided by x-ray crystal structure determinations. Interestingly, among the first structures were two of biochemical origin: Blow and co-workers (1974) investigated the crystal structure of the complex of porcine trypsin with soybean trypsin inhibitor (at 260 pm resolution),[241] whereas Huber and co-workers (1973) were interested in the related complex of basic pancreatic trypsin inhibitor with bovine trypsin.[242] The interatomic distances at the active site of the first-mentioned complex[241] show the complex to be in the form of a tetrahedral adduct of the scissile bond to the active serine. The strong binding energy of the inhibitor and the stabilization of the tetrahedral form result from the nature of the active site of the enzyme, which is designed to stabilize the transition state of peptide hydrolysis. However, because of the resolution mentioned above, the authors unfortunately 'have no evidence whether the bond lengths around the tetrahedral carbon are abnormal. The evidence that the crystal structure shows a tetrahedral adduct is strong, but indirect.'[241]

Scheme 16. Tetrahedral adduct structures confirmed by NMR spectroscopy



72

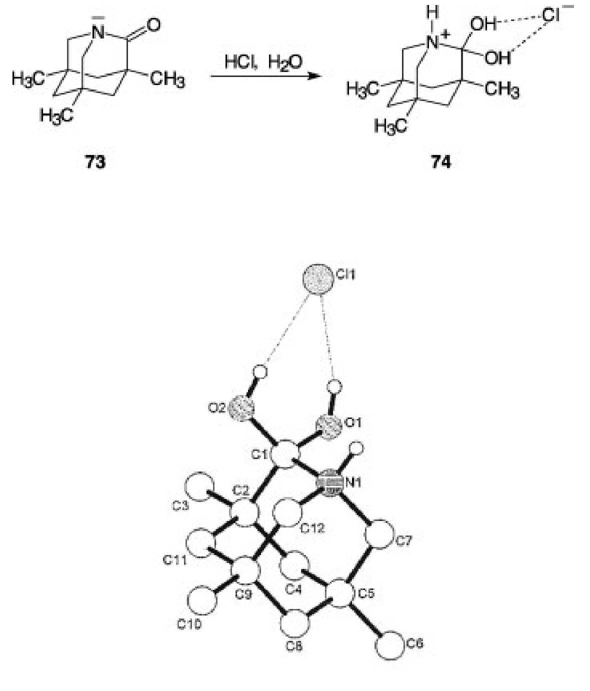


72

Scheme 17. X-ray crystal structure determination of *N*-brosylmitomycin A **72**. Important bond lengths (pm) and angles (°): C17—O3 136.54, C17—N2 149.06, C8—O3 142.31, N1—C1 148.75, N1—C11 147.85, C14—N2—C17—O3 85.82, C24—N2—C17—O3 −129.27, C8—O3—C17—N2 48.22. Reprinted with permission from Ref. 243. Copyright (1967) American Chemical Society

More insight into the structure of a tetrahedral adduct is available from the early crystal structure determination of *N*-brosylmitomycin A **72**[243] (1967) (Scheme 17).

The C17—O3 bond involving the tetrahedral carbon atom C17 amounts to 136.54 pm, which is shorter than C8—O3 (142.31 pm). In contrast, C17—N2 (149.06 pm) is slightly longer than the two aziridine bonds N1—C1 (148.75 pm) and N1—C11 (147.85 pm). From the above-mentioned torsion angles (Scheme 17) a torsion angle between the nitrogen lone pair (lp) and the C17—O3 bond [N$_{\mathrm{lp}}$—(C17—O3)] of ~16° is derived, which is not favourable for an N$_{\mathrm{lp}}$–$\sigma^*_{\mathrm{C—O}}$ interaction. On the other hand, there exists an essentially antiperiplanar orientation (~170°) of an oxygen lone pair at O3 with the C17—N2 bond, which is optimal for an O$_{\mathrm{lp}}$–$\sigma^*_{\mathrm{C—N}}$ interaction, and which is in agreement with the bond lengths at the tetrahedral carbon atom C17 in the *neutral* **72**. Overall, **72** is not a good model for a tetrahedral intermediate in an acyl transfer reaction, however, because the tetrahedral



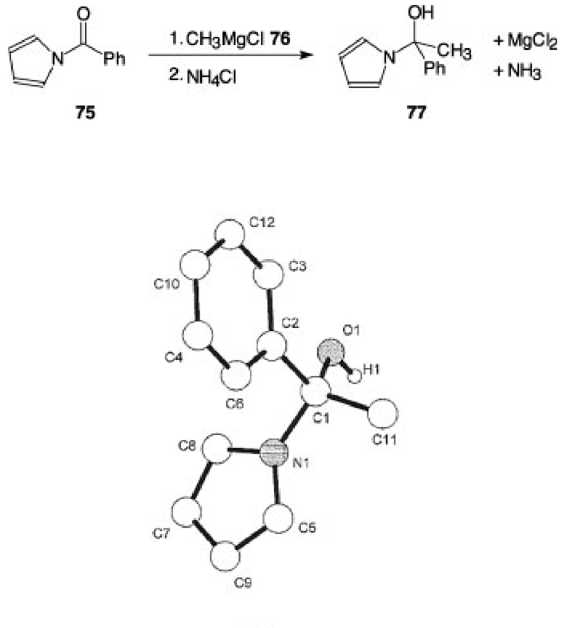
74

Scheme 18. Formation of **74** from **73** and x-ray crystal structure determination of **74**. Important bond lengths (pm) and angles (°): C1—N1 155.2(4), C1—O1 138.2(4), C1—O2 138.2(4), C7—N1 150.3(4), C1—C2 153.3(4), C7—N1—C1—O1 −58.4(3), C12—N1—C1—O1 178.6(2), C7—N1—C1—O2 179.1(2), C12—N1—C1—O2 56.1(3). Reprinted with permission from Ref. 244. Copyright (1998) American Chemical Society

carbon atom C17 is forced into a tetracyclic skeleton. Furthermore, O3 is methylated. In a good model for a tetrahedral intermediate, the oxygen atom should be part of an HO group, bear a negative charge, or the nitrogen atom should be transformed by protonation into an ammonium cation. This latter example, a model for a *cationic* tetrahedral intermediate, is shown next.

When 1-aza-3,5,7-trimethyladamantan-2-one **73** was dissolved at pH 3.3 in H_2O, the *N*-protonated hydrate of the orthoamide **74** was formed, which allowed a more recent x-ray crystal structure determination (1998) (Scheme 18).[244]

The situation at the tetrahedral carbon atom is mainly characterized by a rather long C1—N1 bond [155.2(4) pm] and by shortened C1—O1(2) bonds [138.2(4) pm]: the protonated nitrogen atom N1 becomes an excellent amine leaving group, especially since the electron pairs of the two hydroxy groups support the formation of a carbenium ion at C1. Although the torsion angles which include the O1(O2)—H bonds are not mentioned in the publication, which would allow one to estimate the torsion angles of the oxygen lone pairs with the C—N bond, one can conclude from the above-mentioned bond lengths that they result from antiperiplanar (app) orientations of oxygen lone pairs with the $\sigma^*_{\text{C—N}}$ orbital



77

Scheme 19. Structure of **77** in the crystal. Important bond lengths (pm) and angles (°): C1—N1 147.84(14), C1—O1 141.15(13), C1—C2 152.75(15), C1—C11 152.16(17), C5-N1—C1—O1 141.51(11), C8—N1—C1—O1 −48.10(14). Reproduced from Ref. 245 with permission from *Angewandte Chemie*

(app O_{lp}–$\sigma^*_{\text{C—N}}$). The structure of **74** is thus an excellent example of the structure of a tetrahedral intermediate in which the cleavage of the C—N bond is supported by acid catalysis. The situation described here is in perfect agreement with theoretical studies of the 'Stereoelectronic control in acid and basic catalysis of amide hydrolysis', published by Lehn and Wipff in 1980.[215] Especially in the case of acid catalysis (protonated nitrogen atom), the anomeric effect, lengthening *specifically* the C—N bond, is of great significance.

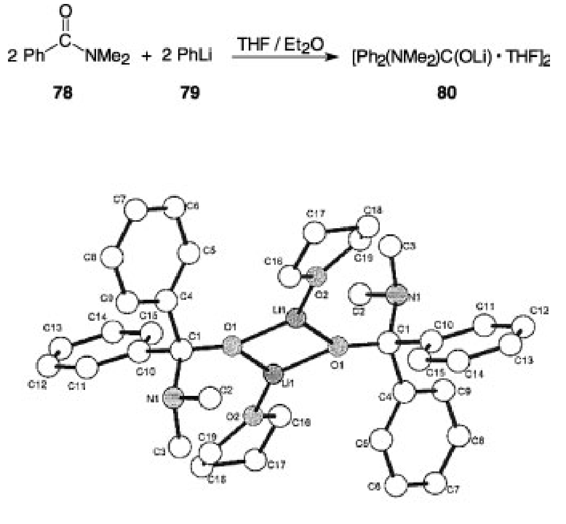
Remarkably stable *neutral* tetrahedral intermediates were recently (2002) observed in the reaction of *N*-acylpyrroles such as **75** with organometallic compounds such as **76** followed by protonation with ammonium chloride (NH_4Cl) to give carbinols such as **77**.[245] The result of the x-ray crystal structure determination of **77** is shown in Scheme 19.

The C1—N1 bond [147.84(14) pm] is longer than C_{sp^3}—$N_{pyrrole}$ bonds, which range from 141.2 to 145.8 pm. Conversely, the C1—O1 bond (141.15(13) pm) is shorter than average C_{sp^3}—OH bonds (143.2 pm). The C1—C11 bond [152.16(17) pm] is slightly shorter than average C_{sp^3}—C_{sp^3} bonds (153.0 pm). In contrast, the C1—C2 bond [152.75(15) pm] is somewhat longer than average C_{sp^2}—C_{aryl} bonds (151.3 pm). The shortened C1—O1 bond and the elongated C1—N1 bond are explained with an anomeric effect resulting from the interaction of the oxygen lone pairs with the $\sigma^*_{\text{C—N}}$ orbital. A similar interaction of an oxygen lone pair with the $\sigma^*_{\text{C—C}}$ orbital should be responsible for the slightly lengthened C1—C2 bond. From the torsion angles mentioned in Scheme 19, one calculates an angle N_{lp}—(C1—O1) of ~47°. The lone pair at N1 therefore does not adopt an antiperiplanar conformation with C1—O1, although the pyrrole substituent could in principle rotate freely around the C1—N1 bond. Apparently an app N_{lp}–$\sigma^*_{C—O}$ interaction is not very profitable for **77**.

Compound **77** is therefore a good model for a *neutral* tetrahedral intermediate in an acyl transfer reaction. If one compares its structure with that of the *N*-protonated tetrahedral intermediate **74** (Scheme 18), which is a model for an intermediate in an *acid-catalysed* reaction, one recognizes immediately the difference: in the *N*-protonated **74** the reaction path—cleavage of the C1—N1 bond—is clearly indicated, which is much less so in the case of the neutral **77**, again in agreement with theoretical studies:[215] there is no *specific* lengthening of one bond at the tetrahedral carbon atom C1 of a neutral model adduct. The results, of course, also fit the experimental experience: transacylations are normally not performed at pH 7. Rather, they are acid-catalysed, or performed in a basic medium.

This latter condition leads to the next question: what are the structural features of tetrahedral intermediates of the type discussed here with a negative charge at the oxygen atom? The following examples are models for that case.

The tetrahedral lithiated adduct **80** formed from benzoic acid *N*,*N*-dimethylamide **78** and phenyllithium **79** crystallizes as the tetrahydrofuran solvated dimer (Scheme 20).[246] It was the first *anionic* tetrahedral adduct which was analysed with respect to its bond lengths and angles at the tetrahedral carbon atom.



80

Scheme 20. Structure of **80** in the crystal. Important bond lengths (pm) and angles (°): C1—O1 137.1(2), C1—N1 150.0(3), C1—C4 154.8(3), C1—C10 154.9(3), Li1—N1 375.1(4), Li1—N1A 373.7(4), O1—C1—N1-C2 −58.4(2), O1—C1—N1—C3 63.8(2), C4—C1—N1—C2 65.3(2), C10—C1—N1—C3 −60.8(2). Reproduced from Ref. 246 with permission from *Angewandte Chemie*

Table 1. Comparison of the C—O, C—N and C—C bond lengths in the *N*-protonated **74**, the neutral **77** and the anionic tetrahedral adduct **80**

Compound	C—O (pm)	C—N (pm)	C—C (pm)
74 (cationic)	138.2(4)	155.2(4)	153.3(4) (C—C_{alk})
77 (neutral)	141.15(13)	147.84(14)	152.75(15) (C—C_{aryl})
80 (anionic)	137.1(2)	150.0(3)	154.8(3), 154.9(3) (C—C_{aryl})

In the dimer structure **80**, two lithium cations (Li1 and Li1A) are bonded to each of the anionic O atoms O1 and O1A and to one O atom of a THF molecule (O2 and O2A, respectively), leading to rarely observed three-coordinated lithium cations. C1—O1 is 137.1(2) pm long. In $(CH_3)_3C$—OLi the C—O bond measures 139.2 pm.[247] In amides such as **78**, the C=O bond is 123.1 pm long,[248] and in aromatic ketones 123.0 pm.[248] C1—N1 amounts to 150.0(3) pm. The mean value for C_{sp^3}—N bonds is 146.9 pm.[248] In carboxylic acid amides the C—N bonds are much shorter (134.6 pm).[248] The bonds from C1 to the phenyl-C atoms measure 154.8(3) (C4) and 154.9(3) pm (C10). The mean value of C_{sp^3}—C_{arom} bonds is 151.3 pm.[248] In conclusion, the bonds of C1 to N1, C4 and C10 are all elongated, whereas the C1—O1 bond is shortened.

Table 1 shows a comparison of the C—O, C—N and C—C bond lengths in the *N*-protonated **74** (Scheme 18), the neutral **77** (Scheme 19) and the anionic tetrahedral adduct **80** (Scheme 20).

In the anionic **80** the C—O bond is shorter (better oxygen donor) than in the neutral **77**. Correspondingly, the C—N and C—C bonds in the anionic **80** are longer than in the neutral **77**. In both cases the lengthening of bonds is *not selective*. This is totally different in the cationic **74**, in which both C—O bonds are shortened and *only the C—N bond* is strongly elongated. Hence, the cationic **74**, the neutral **77** and the anionic **80** are good models for the differences in the structures of the tetrahedral adducts in proton-catalysed, neutral and base-induced transacylations. The experimental results are nicely supported by model calculations on $HC(OH)_2NH_3^+$, $HC(OH)_2NH_2$ and $HC(OH)(O^-)NH_2$.[215]

The lengthening of both the C1—N1 and the C1—C4 (C10) bonds in the anionic adduct **80** is in agreement with the experimental observation that it is not only the C—N bond which may be cleaved if an anionic oxygen atom is present, but also the C—C bond; see the Haller–Bauer reaction[180,181] in Scheme 11: in this example, phenylsodium **49** eliminates from the anionic adduct $Ph_2C(NH_2)(ONa)$ **47**.

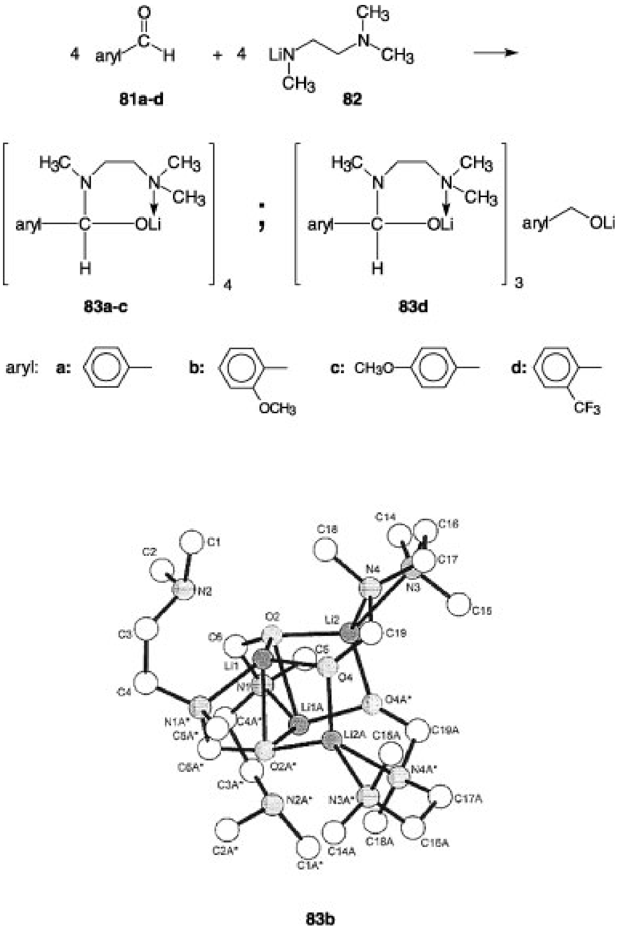
With regard to the elongated C1—N1 and the shortened C1—O1 bond in the anionic adduct **80**, it was checked whether the data fit the considerations of Bürgi and Dunitz[65–74] concerning the geometry of the approach of a nucleophile to a carbonyl group, and to the reverse reaction (see Scheme 2). The angles between the C1—C4—C10 plane and the vectors C1—N1 (60.3°) and C1—O1 (52.8°) in **80** indeed reflect the beginning of the elimination of $LiNMe_2$ from the adduct **80**: N1 'eliminates' along the trajectory C1—N1, whereas O1 moves towards the C1—C4—C10 plane.

Concerning the structure of **80** in the crystal, it is interesting to hint at the bonding situation of the dimethylamino group. Normally, the N atoms of such groups are bonded to Li cations, especially if these are only three-coordinated as is the case here. The distances Li1—N1 375.1(4) pm and Li1—N1A 373.7(4) pm are, however, far beyond normal Li—N bond lengths of ~220 pm.[249] In order to establish an Li–N interaction in **80**, the two dimethylamino groups had to rotate around the C1—N1 (C1A—N1A) bonds. From the torsion angles given in Scheme 20, a torsion angle N_{lp}—(C—O) of ~180° is calculated for **80**. A totally different conformation around the C—N bond, which is necessary for of an Li—O—C—N four-membered ring, is observed in the following anionic adducts.

Independently of the investigation of **80**,[246] Wheatley, Snaith and co-workers studied solid-state structures of related species.[250–253] Reaction of the aromatic aldehydes **81a–d** with lithium *N*,*N*,*N′*-trimethylethylenediamide, $LiN(CH_3)CH_2CH_2N(CH_3)_2$ **82**, led to the respective tetrameric adducts **83a–c**. In the case of the *o*-CF_3-substituted compound **83d**, one benzyl alkoxide reduction product replaces one tetrahedral adduct (Scheme 21).

Wheatley, Snaith and co-workers were exclusively interested in Li–N and Li–O interactions. The bonding situation at the tetrahedral carbon atoms of the adducts **83a–d** is not mentioned in their publications. Since it is not of significance to discuss the details of the pseudo-cubane or 'open' pseudo-cubane tetrameric structures in the context of this paper, only the bond lengths and torsion angles relevant for the subject outlined here are summarized in Table 2, together with those of **80**.

Although the data within the series **83a–d** are rather similar, some characteristic differences are observed. (1) In the *o*-OCH_3-substituted tetramer **83b**, two tetrahedral adducts have anionic oxygen atoms bonded to two Li^+ and the other two to three Li^+. Each additional Li^+ reduces the donor qualities of the anionic O atom: in **83b** ($2Li^+$) the C—O bond is shorter than in **83b** ($3Li^+$) because **83b** contains the better oxygen donor. Correspondingly, the C—N and C—C_{aryl} bonds are longer in **83b** ($2Li^+$) than in **83b** ($3Li^+$). This effect is nicely supported by model calculations (B3LYP/6–311 + G**): $H_2(H_2N)C—O^-$, C—O 132.1 pm, C—N 193.9 pm; $H_2(H_2N)C—OLi$, C—O 137.7 pm, C—N 146.7 pm (see Acknowledgements). (2) In the *o*-CF_3-substituted **83d** the C—C_{aryl} bonds are comparatively long because $C_6H_4(o\text{-}CF_3)Li$ is a better leaving group than C_6H_5Li (from **83a**) or $C_6H_4(o\text{-}OCH_3)Li$ and $C_6H_4(p\text{-}OCH_3)Li$ (from **83b** and **83c**, respectively). Correspondingly, the C—N bond in **83d** is somewhat shorter.



Scheme 21. Preparation of the tetrahedral adducts **83a–d** and structure of **83b** in the crystal. For important bond lengths of **83b**, see Table 2; torsion angles (°): C18—N4—C19—O4 71.7(4), C17—N4—C19—O4 −158.9(3), C4—N1—C6—O2 154.9(4), C5—N1—C6—O2 −73.9(4). Aryl groups have been omitted for clarity. Reproduced from Ref. 250 by permission of the Royal Society of Chemistry

If one compares the tetrahedral adduct **80** crystallizing as a dimer with the structures of the tetramers **83a–d**, one notices rather similar C—O, C—N and C—C_{aryl} bond lengths (see Table 2). A striking difference exists in the torsion angles N_{lp}—(C—O): in **80** with Li^+ not being bonded to the nitrogen atoms of the dimethylamino groups it amounts to ~180°, whereas it is $43 \pm 11°$ in **83a–d** (and not ~0°, which reduces steric interactions along the C—N bonds in the Li—O—C—N four-membered rings of these adducts). Qualitatively one would expect in the anionic adduct **80**, in addition to the O_{lp}–$\sigma^*_{C—N}$ and O_{lp}–$\sigma^*_{C—C_{aryl}}$ interactions, which also exist in **83a–d**, an N_{lp}–$\sigma^*_{C—O}$ interaction because of the favourable antiperiplanar orientation of these orbitals.[215] This should lead to a comparatively shorter C—N and a longer C—O bond in **80**, which, however, is not the case (see

Table 2. C—O, C—N and C—C$_{aryl}$ bond lengths (pm) at the tetrahedral carbon atoms and torsion angles N$_{lp}$—(C—O) (°) in the adducts **83a–d** compared to those of **80**[a]

Compound	C—O (pm)	C—N (pm)	C—C$_{aryl}$ (pm)	Torsion angle N$_{lp}$—(C—O) (°)
80	137.1(1)	150.0(3)	154.8(3)	~180
83a	135.7(4)	150.1(5)	152.2(5)	~38
83b* (2Li$^+$)	136.2(6)	150.0(6)	152.2(6)	~44
(3Li$^+$)	137.7(6)	149.7(6)	151.1(6)	~41
83c	135.1(3)	151.0(4)	151.7(3)	~42
	136.4(3)	149.7(3)	152.9(4)	~32
	135.7(3)	150.1(4)	153.3(3)	~39
	135.5(3)	149.1(4)	152.8(4)	~33
83d	137.6(4)	149.1(4)	154.0(5)	~54
	137.7(4)	149.0(4)	153.6(4)	~53
	137.8(4)	148.9(4)	153.8(4)	~52

83b* (2Li$^+$), two Li cations bonded to the anionic O atom; (3Li$^+$), three Li cations bonded to the anionic O atom. The torsion angles N$_{lp}$—(C—O) are calculated from the torsion angles O—C—N—R^1 and O—C—N—R^2. For the torsion angles of **83a**, **83c** and **83d**, see the original publications.

Table 2). Quantum chemical model calculations on **84**–**86A** and **B** support the expectation (see Table 3).[246]

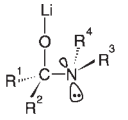
In the highly substituted **84**, isomer **A** is more favourable than **B**. In **A** the C—O bond is longer and the C—N bond is shorter than in isomer **B**. Although the calculated torsion angles N$_{lp}$—(C—O) in isomers **A** and **B** correspond to those found experimentally in the crystal structures of **80** and **83a–d**, respectively, the same agreement does not exist for the C—O and C—N bond lengths (see Tables 2 and 3). For **85A** and **B**, a similar situation is calculated as for **84A** and **B** (see Table 3). In the less sterically hindered **86A** and **B** the result is comparable to that for **83** and **84** except that conformer **B** is now more stable than **A**. That it is not simply the kind of crystallization which is responsible for the difference between experimental and calculated bond lengths is indicated by the adduct of *p*-methoxybenzaldehyde **81c** with lithium *N*-methylpiperazide crystallizing as a hexamer:[253] the bond lengths C8—N1 = 150.74 pm and C8—O1 = 137.68 pm and the torsion angle N$_{lp}$—(C—O) ≈ 45° agree well with those of **83a–d** in Table 2. We have no explanation for the discrepancy between the calculated bond lengths of isomers **A** and **B** (Table 3) and the experimental values for **80** and **83a–d**, respectively (Table 2) (see Acknowledgements). Further structure determinations of anionic tetrahedral adducts comparable to those of **80** and **83a–d** could shed more light on this problem.

A corroboration of the structural features of anionic tetrahedral intermediates comes from the dimeric solid-state structure **87** shown in Scheme 22.[254]

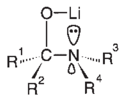
The C8—O1 bond in **87** is extremely short (compare with Table 2), which should be due to K$^+$ being the gegenion instead of Li$^+$ in **80** and **83a–d**: K$^+$ is a much weaker Lewis acid than Li$^+$. The C8—N1 bond length is 151.7(3) pm, which is greater than the C—N bond lengths in **80** and **83a–d** (see Table 2). The C8—C9 bond [155.4(5) pm] is the longest C—C$_{aryl}$ bond so far observed in an anionic tetrahedral adduct (see Table 2). The reason is also in the case of **87** the non-selective electron donation of the anionic oxygen atom, the good qualities as a leaving group of *p*-BrC$_6$H$_4$K and the excellent stabilization of a (developing) positive charge at C8 by the two nitrogen substituents. Again, the Haller–Bauer reaction[180,181] is 'on its way' (see the discussion of **80** and Scheme 11).

In summary, although there have so far been only a few crystal structure determinations of tetrahedral adducts which can serve as models for intermediates in the

Table 3. Bond lengths (pm), torsion angles (°) and relative energies (kcal mol^{-1}) of the conformers **A** and **B** of the tetrahedral adducts **84–86** (RHF/3–21G//PM3)[a]



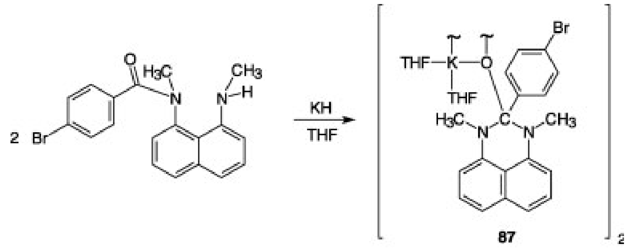
A

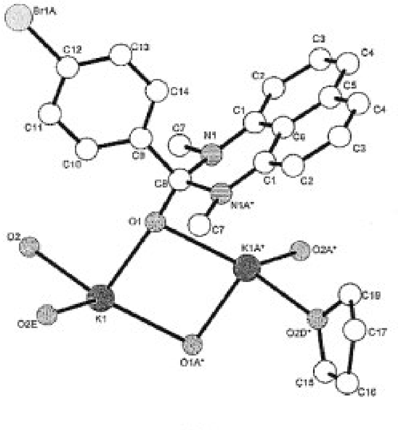


B

Compound	R^1	R^2	R^3	R^4	C—O (pm)	C—N (pm)	Torsion angle N$_{lp}$—(C—O) (°)	E_{rel} (kcal mol^{-1})
84A	Ph	Ph	CH$_3$	CH$_3$	137.0	153.2	~174	0.0
84B	Ph	Ph	CH$_3$	CH$_3$	135.9	159.0	~43	8.0
85A	Ph	H	CH$_3$	CH$_3$	136.7	152.0	~174	0.0
85B	Ph	H	CH$_3$	CH$_3$	135.4	157.2	~30	4.6
86A	CH$_3$	CH$_3$	H	H	138.3 (139.3)	150.4 (147.1)	~180 (~180)	0.0 (0.0)
86B	CH$_3$	CH$_3$	H	H	136.2 (137.3)	155.9 (154.8)	~5 (~9)	−4.5 (−6.0)

[a] MP2/6–31 + G* values of **86** in parentheses. The torsion angles N$_{lp}$—(C—O) are calculated from the torsion angles O—C—N—R^3 and O—C—N—R^4. 1 kcal = 4.184 kJ.





87

Scheme 22. Structure of **87** in the crystal. Important bond lengths (pm) and torsion angles (°): C8—O1 131.5(5), C8—N1 151.7(3), C8—C9 155.4(5), C1—N1—C8—O1 155.7(2), C7—N1—C8—O1 −53.0(2). The second part of the dimer is omitted. Reprinted with permission from Ref. 254. Copyright (1999) American Chemical Society

reactions of carboxylic acid derivatives with nucleophiles, they provide a consistent picture: the neutral, cationic and anionic models of such tetrahedral intermediates are characteristically different from each other, in agreement with experimental observations and theoretical calculations.

MODEL CALCULATIONS OF THE REACTIONS OF HC(O)X, X = NH_2 AND NHOH, WITH THE NUCLEOPHILES LIH AND FMgH

Whereas tetrahedral intermediates in the reactions of carboxylic acid chlorides with nucleophiles have never been detected, and those of carboxylic acid esters never isolated, even at low temperatures (see earlier), it is shown in the previous two sections that tetrahedral intermediates derived from carboxylic acid amides are stable and useful for further syntheses. However, there are remarkable differences between different carboxylic acid amides concerning their reactivity with nucleophiles: 'normal' amides $RC(O)NR_2$ **28** react with organo*lithium* species R′Li **29** to give adducts $RR'CNR_2(OLi)$ **30**, which, on hydrolysis, give ketones RR′C(O) **9**; however, *Grignard reagents* R′MgX do not lead to adducts and finally ketone formation (see Scheme 7). In contrast, reaction of *Weinreb amides* $RC(O)N(CH_3)$-OCH_3 **37** give ketones **9** with both organo*lithium* as well as with *Grignard reagents* (see Scheme 9). In order to find out whether it is the particular thermodynamic stability of Weinreb amide adducts **39** (Scheme 9) which is responsible for this synthetically significant difference, as generally assumed,[161–175] or whether the kinetics of the reactions are also significant, model calculations were performed by optimization of the stationary points along the reaction path of the gas-phase reactions of $HC(O)NH_2$ **88** (model for normal amides) and HC(O)NHOH **89** (model for Weinreb amides) with LiH **90** and with FMgH **91** at the MP2/6–31 + G*//MP2/6–31G* level.[255] Energies are corrected for zero point energies (ZPE), and all stationary points were characterized by vibrational analysis showing zero imaginary frequencies for the ground states and exactly one imaginary frequency for the transition states. If necessary, the trajectory was proved by calculation of the intrinsic reaction coordinate (IRC). Hydrides such as LiH **90** and FMgH **91** have been used as simple models for organolithium and Grignard reagents before.[256,257] As shown below, the calculated reaction intermediates and transition states provide an overall picture which leads to a consistent explanation of the experimental facts.

The LUMO energies $\pi^*_{C=O}$ of the amide models **88** and **89** and the HOMO energies of the nucleophiles LiH **90** and FMgX **91** are listed in Table 4.

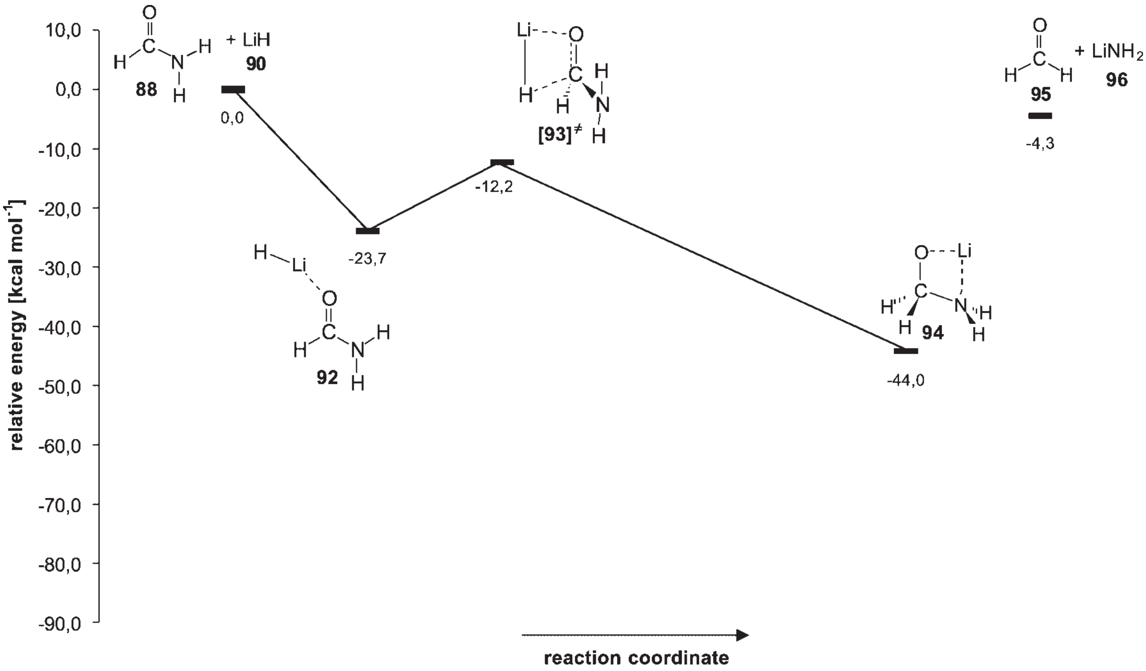
Not unexpectedly, the model for Weinreb amides **89** has essentially the same LUMO energy (0.179 a.u.) as the model for 'normal' amides **88** (0.177 a.u.). The higher HOMO energy is found in the case of LiH **90** (−0.298 a.u.) as compared with the 'Grignard reagent' **91** (−0.410 a.u.), which corresponds to the higher nucleophilicity of RLi compounds.

For reasons of simplicity, reactions involving dimers of LiH **90** and FMgH **91** were not calculated. Similarly, solvation of LiH **90** and FMgH **91** with model solvent molecules such as H_2O or NH_3 was not considered.[256,257]

In Scheme 23, the reaction of $HC(O)NH_2$ **88** with LiH **90** is shown.

Table 4. MP2/6–31 + G*//MP2/6–31 + G* LUMO energies (a.u.) of **88** and **89** and HOMO energies (a.u.) of **90** and **91**

Compound	LUMO energy $\pi^*_{C=O}$ (a.u.)	Compound	HOMO energy (a.u.)
$HC(O)NH_2$ **88**	0.177	LiH **90**	−0.298
HC(O)NH—OH **89**	0.179	FMgH **91**	−0.410

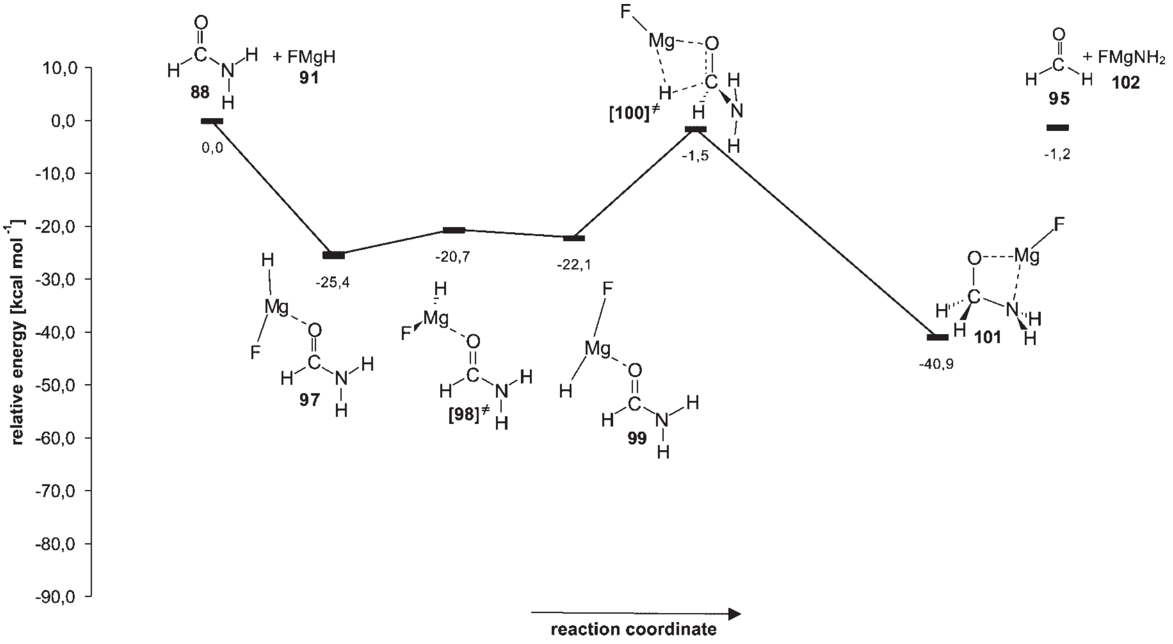


Scheme 23. HC(O)NH$_2$ **88** and LiH **90**: calculated reaction intermediates and transition states [MP2/6–31 + G*//MP2/6–31G* + ZPE (kcal mol^{-1})]

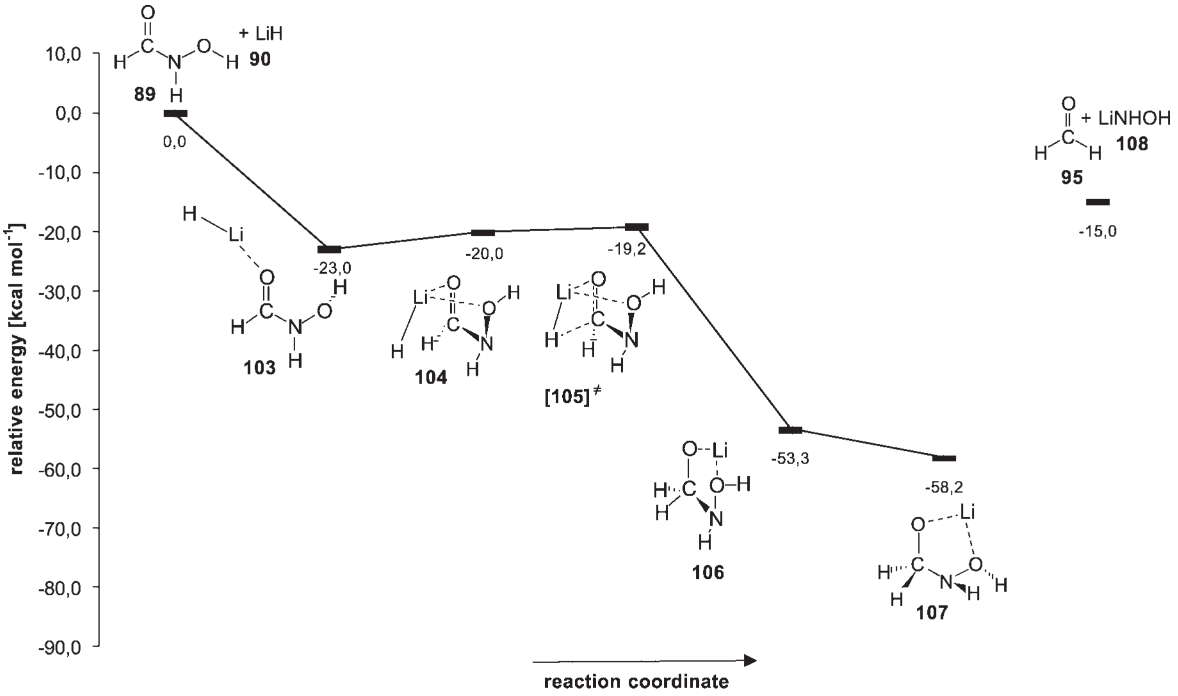
The reaction starts with the complexation of HC(O)NH$_2$ **88** and LiH **90** to give **92**, which reacts via the transiton state [**93**]‡ to the tetrahedral intermediate **94**. **94** is 20.3 kcal mol^{-1} more stable than **92**. The activation energy for the formation of **94** amounts to 11.5 kcal mol^{-1}. Transformation of **94** into H$_2$C=O **95** and LiNH$_2$ **96** requires 39.7 kcal mol^{-1}. Hence, in agreement with the experimental results outlined earlier, the tetrahedral adduct **94** is formed easily and it is fairly stable.

The reaction of HC(O)NH$_2$ **88** with FMgH **91** is shown in Scheme 24.

As in the case of **88** and **90**, HC(O)NH$_2$ **88** and FMgH **91** react first to give a complex **97**, which is transformed via [**98**]‡ into the reactive complex **99** and then via the transition state [**100**]‡ into the tetrahedral adduct **101**. Compound **101** is 15.5 kcal mol^{-1} more stable than **97** and 39.7 kcal mol^{-1} more stable than H$_2$C=O **95** and FMgNH$_2$ **102**. Hence the tetrahedral adduct **101**, if



Scheme 24. HC(O)NH$_2$ **88** and FMgH **91**: calculated reaction intermediates and transition states [MP2/6–31 + G*//MP2/6–31G* + ZPE (kcal mol^{-1})]



Scheme 25. HC(O)NHOH **89** and LiH **90**: calculated reaction intermediates and transition states [MP2/6–31 + G*//MP2/6–31G* + ZPE (kcal mol^{-1})]

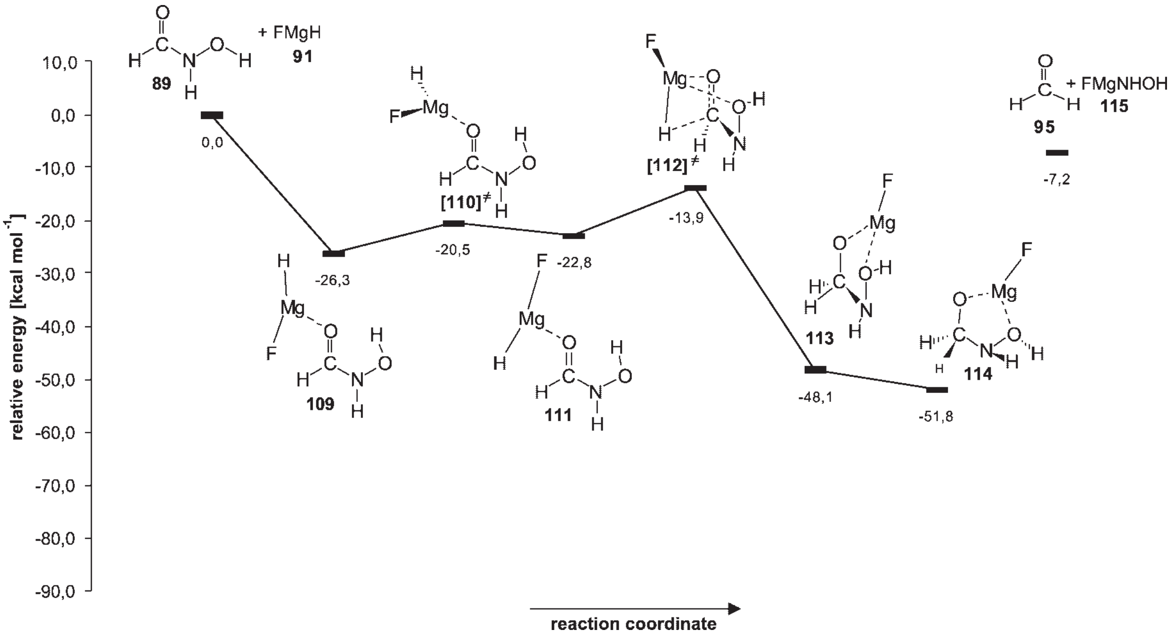
formed, should also be fairly stable. The activation energy for the formation of **101** from **97** (23.9 kcal mol^{-1}), however, is much higher than in the case outlined in Scheme 23 with LiH **88** being the nucleophile (11.5 kcal mol^{-1}), which agrees nicely with the reluctant reactivity of Grignard reagents with carboxylic acid amides.

The reaction of HC(O)NHOH **89**, the model for Weinreb amides, with LiH **90** is shown in Scheme 25.

As before, the starting materials **89** and **90** first form a complex (**103**, −23.0 kcal mol^{-1}), in which LiH **90** is attached to the carbonyl oxygen atom of **89**. Via the chelate complex with the lithium cation being bonded to both oxygen atoms (**104**), the chelate transition state [**105**]‡ is reached very easily (3.8 kcal mol^{-1}), leading to the tetrahedral chelate adducts **106** and **107**. Compound **107** is 35.2 kcal mol^{-1} more stable than **103** and 43.2 kcal mol^{-1} more stable than $H_2C{=}O$ **95** and LiNHOH **108**, which is in agreement with the detection of such adducts by NMR spectroscopy.[258] Most significant, however, is the very low activation energy **103** → [**105**]‡ of 3.8 kcal mol^{-1}. For the reaction of the 'normal amide' $HC(O)NH_2$ **88** with LiH **90**, an activation energy of 11.5 kcal mol^{-1} was calculated (Scheme 23). The reaction of HC(O)OH (model for esters) with LiH **90** requires 7.6 kcal mol^{-1} [255] (for details see the Supplementary material, available in Wiley Interscience). The activation energy for the reaction of the Weinreb amide model **89** with LiH **90** (3.8 kcal mol^{-1}) comes even close to that calculated for the reaction of HC(O)Cl with LiH **90** (2.7 kcal mol^{-1} [255] (see also Refs. 71, 100, 103, 106, 108, 109, 111 and 113); for details see the Supplementary material). The very facile reaction of Weinreb amides with organolithium reagents, which even tolerates the presence of ester functionalities,[165] therefore results from the chelate stabilization in the tetrahedral adduct **107** and, most importantly, in the transition state [**105**]‡. A strong stabilization of the transition state is also described for the ortholithiation of aromatic ethers such as methyl phenyl ether.[256]

The reaction of the Weinreb amide model HC(O)NHOH **89** with the Grignard model FMgH **91** is shown in Scheme 26.

The starting materials **89** and **91** first form the complexes **109** and **111**, which are connected with each other via the transition state [**110**]‡. A complex with FMgH **91** binding to both oxygen atoms of HC(O)NHOH **89** was not found. Then **111** transforms via the chelate transition state [**112**]‡ into the tetrahedral adducts **113** and **114**. Compound **114** is 25.5 kcal mol^{-1} more stable than **109**; formation of $H_2C{=}O$ **95** and FMgNHOH **115** from **114** requires 44.6 kcal mol^{-1}, which documents the stability of the chelate adduct **114**. Related to these numbers is the comparatively low activation energy (12.4 kcal mol^{-1}) from **109** to the chelate transition state [**112**]‡, which is in agreement with the reaction of Weinreb amides also with Grignard reagents.[161–175] For the reaction of the 'normal' amide $HC(O)NH_2$ **88** with FMgH **91** an activation energy of 20.6 kcal mol^{-1} was calculated (see Scheme 24). Correspondingly, this reaction was never observed.



Scheme 26. HC(O)NHOH **89** and FMgH **91**: calculated reaction intermediates and transition states [MP2/6–31 + G*//MP2/6–31G* + ZPE (kcal mol^{-1})]

The model calculations outlined above provide the following results. (1) '*Normal*' carboxylic acid amides react well with organolithium reagents because the activation energy of the reaction is comparatively low, but the reaction with Grignard reagents is very sluggish owing to a much higher activation energy. (2) In the case of *Weinreb amides*, more stable chelate tetrahedral intermediates are related to more favourable chelate transition states for their formation. This leads to high chemoselectivity owing to very high reactivity in the case of organolithium species—ester groups present in the reaction are not attacked—and to reaction also with Grignard reagents. A similar situation should hold for related ketone syntheses.[259–264]

CONCLUSIONS

Transacylation reactions of carboxylic acids, carboxylic acid esters, carboxylic acid amides and other carboxylic acid derivatives are among the most important reactions in chemistry and biochemistry. However, only in recent years has information concerning the structural details of possible tetrahedral intermediates become available. In this review, tetrahedral intermediates are discussed which serve as models for acid-catalysed reactions, neutral reactions and reactions under basic conditions. The structural features correspond nicely with experimental experience and, in general, to quantum chemical model calculations. Furthermore, by means of model calculations, an explanation is given for the fast reactions of Weinreb amides with organolithium compounds and even with Grignard reagents: they are due to low-energy chelate transition states for the formation of the fairly stable chelate tetrahedral intermediates.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 260) and the Fonds der Chemischen Industrie is gratefully acknowledged. The authors also thank Professor Paul von Ragué Schleyer, Dr John Lohrenz, and Michael Marsch for their support. We are very grateful to Professor Paul von Ragué Schleyer for the calculations of the bond lengths in $H_2(H_2N)C—O^-$ and $H_2(H_2N)C—OLi$ and also for discussions concerning experimental and calculated bond lengths in the anionic tetrahedral adducts.

REFERENCES

1. Hammett LP. *Physical Organic Chemistry*. McGraw-Hill: New York, 1940.
2. Bender ML. *Chem. Rev.* 1960; **60**: 53–112.
3. Johnson SL. *Adv. Phys. Org. Chem.* 1967; **5**: 237–330.
4. Jencks WP. *Chem. Rev.* 1972; **72**: 705–719.
5. McClelland RA, Santry LJ. *Acc. Chem. Res.* 1983; **16**: 394–399.
6. Hauser CR, Hudson BE Jr. *Org. React. 1* 1942; 266–292.
7. Bender ML, Ginger RD, Kemp KC. *J. Am. Chem. Soc.* 1954; **76**: 3350–3351.
8. Bender ML, Ginger RD. *J. Am. Chem. Soc.* 1955; **77**: 348–351.
9. Bruice TC, Schmir GL. *J. Am. Chem. Soc.* 1957; **79**: 1663–1667.
10. Bender ML, Ginger RD, Unik JP. *J. Am. Chem. Soc.* 1958; **80**: 1044–1048.
11. Bruice TC, Lapinski R. *J. Am. Chem. Soc.* 1958; **80**: 2265–2267.
12. Jencks WP, Carriuolo J. *J. J. Biol. Chem.* 1959; **234**: 1280–1285.
13. Bruice TC, Mayahi MF. *J. Am. Chem. Soc.* 1960; **82**: 3067–3071.
14. Jencks WP, Carriuolo J. *J. Am. Chem. Soc.* 1960; **82**: 675–681.

15. Jencks WP, Carriuolo J. *J. Am. Chem. Soc.* 1960; **82**: 1778–1786.
16. Bunnett JF, Davis GT. *J. Am. Chem. Soc.* 1960; **82**: 665–674.
17. Bender ML, Thomas RJ. *J. Am. Chem. Soc.* 1961; **83**: 4189–4193.
18. Bender ML, Matsui H, Thomas RJ, Tobey SW. *J. Am. Chem. Soc.* 1961; **83**: 4193–4196.
19. Jencks WP, Carriuolo J. *J. Am. Chem. Soc.* 1961; **83**: 1743–1750.
20. Zerner B, Bender ML. *J. Am. Chem. Soc.* 1961; **83**: 2267–2274.
21. Hand ES, Jencks WP. *J. Am. Chem. Soc.* 1962; **84**: 3505–3514.
22. Johnson SL. *J. Am. Chem. Soc.* 1964; **86**: 3819–3824.
23. Jencks WP, Gilchrist M. *J. Am. Chem. Soc.* 1964; **86**: 5616–5620.
24. Fedor LR, Bruice TC. *J. Am. Chem. Soc.* 1964; **86**: 5697–5698.
25. Fedor LR, Bruice TC. *J. Am. Chem. Soc.* 1965; **87**: 4138–4147.
26. Schowen RL, Jayaraman H, Kershner L. *J. Am. Chem. Soc.* 1966; **88**: 3373–3375.
27. Greenzaid P, Luz Z, Samuel D. *J. Am. Chem. Soc.* 1967; **89**: 756–759.
28. Blackburn GM, Jencks WP. *J. Am. Chem. Soc.* 1968; **90**: 2638–2645.
29. Maugh T, Bruice TC. *Chem. Commun.* 1969; 1056–1057.
30. Jencks WP, Salvesen K. *J. Am. Chem. Soc.* 1971; **93**: 1419–1427.
31. Guthrie JP. *J. Am. Chem. Soc.* 1973; **95**: 6999–7002.
32. Satterthwait AC, Jencks WP. *J. Am. Chem. Soc.* 1974; **96**: 7018–7031.
33. Satterthwait AC, Jencks WP. *J. Am. Chem. Soc.* 1974; **96**: 7031–7044.
34. Guthrie JP. *J. Am. Chem. Soc.* 1974; **96**: 3608–3615.
35. Guthrie JP. *Can. J. Chem.* 1976; **54**: 202–209.
36. Hupe DJ, Jencks WP. *J. Am. Chem. Soc.* 1977; **99**: 451–464.
37. Guthrie JP. *J. Am. Chem. Soc.* 1991; **113**: 3941–3949.
38. Kellogg BA, Tse JE, Brown RS. *J. Am. Chem. Soc.* 1995; **117**: 1731–1735.
39. Kellogg BA, Neverov AA, Aman AM, Brown RS. *J. Am. Chem. Soc.* 1996; **118**: 10829–10837.
40. Colthurst MJ, Williams A. *J. Chem. Soc., Perkin Trans. 2* 1997; 1493–1497.
41. Oh HK, Woo SY, Shin CH, Park YS, Lee I. *J. Org. Chem.* 1997; **62**: 5780–5784.
42. Marlier JF, Haptonstall BA, Johnson AJ, Sacksteder KA. *J. Am. Chem. Soc.* 1997; **119**: 8838–8842.
43. Cacciapaglia R, di Stefano S, Kelderman E, Mandolini L, Spadola F. *J. Org. Chem.* 1998; **63**: 6476–6479.
44. Koh HJ, Shin CH, Lee HW, Lee I. *J. Chem. Soc., Perkin Trans. 2* 1998; 1329–1332.
45. Hall CD, Le VT. *J. Chem. Soc., Perkin Trans. 2* 1998; 1483–1488.
46. Venkatasubban KS, Bush M, Ross E, Schultz M, Garza O. *J. Org. Chem.* 1998; **63**: 6115–6118.
47. Hubbard P, Brittain WJ. *J. Org. Chem.* 1998; **63**: 677–683.
48. Hess RA, Hengge AC, Cleland WW. *J. Am. Chem. Soc.* 1998; **120**: 2703–2709.
49. Castro EA, Leandro L, Milán P, Santos JG. *J. Org. Chem.* 1999; **64**: 1953–1957.
50. Koh HJ, Han KL, Lee I. *J. Org. Chem.* 1999; **64**: 4783–4789.
51. Castro EA, Ruiz MG, Salinas S, Santos JG. *J. Org. Chem.* 1999; **64**: 4817–4820.
52. Castro EA, Pavez P, Santos JG. *J. Org. Chem.* 1999; **64**: 2310–2313.
53. Marlier JF, Dopke NC, Johnstone KR, Wirdzig TJ. *J. Am. Chem. Soc.* 1999; **121**: 4356–4363.
54. Fife TH, Chauffe L. *J. Org. Chem.* 2000; **65**: 3579–3586.
55. Castro EA, Garcia P, Leandro L, Quesieh N, Rebolledo A, Santos JG. *J. Org. Chem.* 2000; **65**: 9047–9053.
56. Singleton DA, Merrigan SR. *J. Am. Chem. Soc.* 2000; **122**: 11035–11036.
57. Lee HW, Yun YS, Lee BS, Koh HJ, Lee I. *J. Chem. Soc., Perkin Trans. 2* 2000; 2302–2305.
58. Bruice TC, Benkovic S. *Bioorganic Mechanisms*. Benjamin: New York, 1966.
59. Jencks WP. *Catalysis in Chemistry and Enzymology*. McGraw-Hill: New York, 1969.
60. Blow DM. *Acc. Chem. Res.* 1976; **9**: 145–152.
61. Fersht A. *Enzyme Structure and Mechanism*. Freeman: New York, 1985.
62. Rodriguez EJ, Angeles TS, Meek TD. *Biochemistry* 1993; **32**: 12380–12385.
63. Lee H, Darden TA, Pedersen LG. *J. Am. Chem. Soc.* 1996; **118**: 3946–3950.
64. Page MI, Laws AP. *Chem. Commun.* 1998; 1609–1617.
65. Allen FH, Kennard O, Taylor R. *Acc. Chem. Res.* 1983; **16**: 146–153.
66. Bürgi HB, Dunitz JD. *Acc. Chem. Res.* 1983; **16**: 153–161.
67. Bürgi HB, Dunitz JD, Shefter E. *J. Am. Chem. Soc.* 1973; **95**: 5065–5067.
68. Bürgi HB, Dunitz JD, Shefter E. *Acta Crystallogr., Sect. B* 1974; **30**: 1517–1527.
69. Bürgi HB, Dunitz JD, Lehn JM, Wipff G. *Tetrahedron* 1974; **30**: 1563–1572.
70. Bürgi HB, Lehn JM, Wipff G. *J. Am. Chem. Soc.* 1974; **96**: 1956–1957.
71. Scheiner S, Lipscomb WN, Kleier DA. *J. Am. Chem. Soc.* 1976; **98**: 4770–4777.
72. Cieplak AS. *J. Am. Chem. Soc.* 1981; **103**: 4540–4552.
73. Frenking G, Köhler KF, Reetz MT. *Angew. Chem.* 1991; **103**: 1167–1170; *Angew. Chem., Int. Ed. Engl.* 1991; **30**: 1146–1149.
74. Tomoda S, Senju T. *Chem. Commun.* 1999; 423–424.
75. Riveros JM, José SM, Takashima K. *Adv. Phys. Org. Chem.* 1983; **21**: 222–227.
76. Bowie JH, Williams BD. *Aust. J. Chem.* 1974; **27**: 1923–1927.
77. Asubiojo OI, Blair LK, Brauman JI. *J. Am. Chem. Soc.* 1975; **97**: 6685–6688.
78. Comisarow M. *Can. J. Chem.* 1977; **55**: 171–173.
79. Takashima K, Riveros JM. *J. Am. Chem. Soc.* 1978; **100**: 6128–6132.
80. Asubiojo OI, Brauman JI. *J. Am. Chem. Soc.* 1979; **101**: 3715–3724.
81. Bohme DK, Mackay GI, Tanner SD. *J. Am. Chem. Soc.* 1980; **102**: 407–409.
82. Bartmess JE, Hays RL, Caldwell G. *J. Am. Chem. Soc.* 1981; **103**: 1338–1344.
83. Tanner SD, Mackay GI, Bohme DK. *Can. J. Chem.* 1981; **59**: 1615–1621.
84. Klass G, Sheldon JC, Bowie JH. *Aust. J. Chem.* 1982; **35**: 2471–2481.
85. McDonald RN, Chowdhury AK. *J. Am. Chem. Soc.*1982; **104**: 901–902.
86. McDonald RN, Chowdhury AK. *J. Am. Chem. Soc.*1983; **105**: 7267–7271.
87. Takashima K, José SM, do Amaral AT, Riveros JM. *Chem. Commun.* 1983; 1255–1256.
88. Sheldon JC, Bowie JH, Hayes RN. *Nouv. J. Chim.* 1984; **8**: 79–85.
89. Johlman CL, Wilkins CL. *J. Am. Chem. Soc.* 1985; **107**: 327–332.
90. Han CC, Brauman JI. *J. Am. Chem. Soc.* 1987; **109**: 589–590.
91. Han CC, Brauman JI. *J. Am. Chem. Soc.* 1990; **112**: 7835.
92. Wilbur JL, Brauman JI. *J. Am. Chem. Soc.* 1994; **116**: 5839–5846.
93. Zhong M, Brauman JI. *J. Am. Chem. Soc.* 1999; **121**: 2508–2515.
94. Bakhtiar R, Hop CECA. *J. Phys. Org. Chem.* 1999; **12**: 523.
95. Dewar MJS. *The Electronic Theory of Organic Chemistry*. Oxford University Press: London, 1949; 117–123.
96. Alagona G, Scrocco E, Tomasi J. *J. Am. Chem. Soc.* 1975; **97**: 6976–6983.
97. Williams IH, Maggiora GM, Schowen RL. *J. Am. Chem. Soc.* 1980; **102**: 7831–7839.
98. Sheldon JC. *Aust. J. Chem.* 1981; **34**: 1189–1193.
99. Oie T, Loew GH, Burt SK, Binkley JS, MacElroy RD. *J. Am. Chem. Soc.* 1982; **104**: 6169–6174.
100. Yamabe S, Minato T. *J. Org. Chem.* 1983; **48**: 2972–2975.
101. Oie T, Loew GH, Burt SK, MacElroy RD. *J. Am. Chem. Soc.* 1983; **105**: 2221–2227.
102. Williams IH, Spangler D, Femec DA, Maggiora GM, Schowen RL. *J. Am. Chem. Soc.* 1983; **105**: 31–40.
103. Williams IH, Spangler D, Maggiora GM, Schowen RL. *J. Am. Chem. Soc.* 1985; **107**: 7717–7723.
104. Dewar MJS, Storch DM. *Chem. Commun.* 1985; 94–96.
105. Weiner SJ, Singh UC, Kollman PA. *J. Am. Chem. Soc.* 1985; **107**: 2219–2229.
106. Yamataka H, Nagase S, Ando T, Hanafusa T. *J. Am. Chem. Soc.* 1986; **108**: 601–606.

107. Madura JD, Jorgensen WL. *J. Am. Chem. Soc.* 1986; **108**: 2517–2527.
108. Blake JF, Jorgensen WL. *J. Am. Chem. Soc.* 1987; **109**: 3856–3861.
109. Taira K, Gorenstein DG. *Bull. Chem. Soc. Jpn.* 1987; **60**: 3625–3632.
110. Howard AE, Kollman PA. *J. Am. Chem. Soc.* 1988; **110**: 7195–7200.
111. Yamabe S, Koyama T, Minato T, Inagaki S. *Bull. Chem. Soc. Jpn.* 1990; **63**: 1684–1690.
112. Jensen JH, Baldridge KK, Gordon MS. *J. Phys. Chem.* 1992; **96**: 8340–8351.
113. Francisco JS, Williams IH. *J. Am. Chem. Soc.* 1993; **115**: 3746–3751.
114. Francisco JS, Williams IH. *J. Am. Chem. Soc.* 1993; **115**: 3746–3751.
115. Antonczak S, Ruiz-López MF, Rivail JL. *J. Am. Chem. Soc.* 1994; **116**: 3912–3921.
116. Pranata J. *J. Phys. Chem.* 1994; **98**: 1180–1184.
117. O'Brien JF, Pranata J. *J. Phys. Chem.* 1995; **99**: 12759–12763.
118. Hori K, Kamimura A, Ando K, Mizumura M, Ihara Y. *Tetrahedron* 1997; **53**: 4317–4330.
119. Lightstone FC, Bruice TC. *J. Am. Chem. Soc.* 1997; **119**: 9103–9113.
120. Venturini A, López-Ortiz F, Alvarez JA, González J. *J. Am. Chem. Soc.* 1998; **120**: 1110–1111.
121. Meijer WJ, Sprik M. *J. Am. Chem. Soc.* 1998; **120**: 6345–6355.
122. Adalsteinsson H, Bruice TC. *J. Am. Chem. Soc.* 1998; **120**: 3440–3447.
123. Kallies B, Mitzner R. *J. Mol. Model.* 1998; **4**: 183–196.
124. Luzhkov V, Åqvist J. *J. Am. Chem. Soc.* 1998; **120**: 6131–6137.
125. Bakowies D, Kollman PA. *J. Am. Chem. Soc.* 1999; **121**: 5712–5726.
126. Guthrie JP. *J. Am. Chem. Soc.* 2000; **112**: 5529–5538.
127. Hæffner F, Sun C, Williard PG. *J. Am. Chem. Soc.* 2000; **122**: 12542–12546.
128. Lee I, Kim CK, Li HG, Sohn CK, Kim CK, Lee HW, Lee BS. *J. Am. Chem. Soc.* 2000; **122**: 11162–11172.
129. Yang W, Drueckhammer DG. *Org. Lett.* 2000; **2**: 4133–4136.
130. Zhan CG, Landry DW. *J. Phys. Chem.* 2001; **105**: 1296–1301.
131. Pliego JR Jr, Riveros JM. *Chem. Eur. J.* 2001; **7**: 169–175.
132. Dieter RK. *Tetrahedron* 1999; **55**: 4177–4236.
133. Entemann CE, Johnson JR Jr. *J. Am. Chem. Soc.* 1933; **55**: 2900–2903.
134. Shirley DA. *Org. React.* 1954; **8**: 28–58.
135. Kharash MS, Reinmuth O. *Grignard Reactions of Nonmetallic Substances*. Prentice-Hall: New York, 1954.
136. Sato F, Inoue M, Oguro K, Sato M. *Tetrahedron Lett.* 1979; **20**: 4303–4306.
137. Claisen L. *Chem. Ber.* 1887; **20**: 646–650.
138. Wislicenus W. *Liebigs Ann. Chem.* 1888; **246**: 306–329.
139. Adickes F. *Chem. Ber.* 1925; **58**: 1992–1999.
140. Grignard V. *C. R. Acad. Sci.* 1901; **132**: 336–338.
141. Grignard V. *Ann. Chim. Phys.* 1901; **24**: 433–490.
142. Bouveault ML. *Bull. Soc. Chim. Fr.* 1904; **31**: 1322–1327.
143. Maxim N, Mavrodineanu R. *Bull. Soc. Chim. Fr.* 1935; **2**: 591–600.
144. Maxim N, Mavrodineanu R. *Bull. Soc. Chim. Fr.* 1936; **3**: 1084–1093.
145. Barger G, Easson APT. *J. Chem. Soc.* 1938; 2100–2104.
146. Smith LI, Bayliss M. *J. Org. Chem.* 1941; **6**: 437–442.
147. Sicé J. *J. Am. Chem. Soc.* 1953; **75**: 3697–3700.
148. Heyns K, Pyrus W. *Chem. Ber.* 1955; **88**: 678–683.
149. Jones ERH, Skatterbøl L, Whiting MC. *J. Chem. Soc.* 1958; 1054–1059.
150. Michael U, Gronowitz S. *Acta. Chem. Scand.* 1968; **22**: 1353–1355.
151. Olah GA, Arvanaghi M. *Angew. Chem.* 1981; **93**: 925–926; *Angew. Chem., Int. Ed. Engl.* 1981; **20**: 878–879.
152. Evans EA. *J. Chem. Soc.* 1956; 4691–4692.
153. Evans EA. *Chem. Ind. (London)* 1957; 1596–1597.
154. Gschwend HW, Rodriguez HR. *Org. React.* 1979; **26**: 52–53.
155. Comins DL, Brown JD. *Tetrahedron Lett.* 1981; **22**: 4213–4216.
156. Comins DL, Brown JD, Mantlo NB. *Tetrahedron Lett.* 1982; **23**: 3979–3982.
157. Comins DL, Brown JD. *J. Org. Chem.* 1984; **49**: 1078–1083.
158. Comins DL, Killpack MO. *J. Org. Chem.* 1987; **52**: 104–109.
159. Comins DL, Brown JD. *J. Org. Chem.* 1989; **54**: 3730–3732.
160. Comins DL. *Synlett* 1992; 615–625.
161. Sibi MP. *Org. Prep. Proced. Int.* 1993; **25**: 15–40.
162. Mentzel M, Hoffmann HMR. *J. Prakt. Chem.* 1997; **339**: 517–524.
163. Singh J, Satyamurthi N, Aidhen IS. *J. Prakt. Chem.* 2000; **342**: 340–347.
164. Nahm S, Weinreb SM. *Tetrahedron Lett.* 1981; **22**: 3815–3818.
165. Theisen PD, Heathcock CH. *J. Org. Chem.* 1988; **53**: 2374–2378.
166. Hanamoto T, Hiyama T. *Tetrahedron Lett.* 1988; **29**: 6467–6471.
167. Turner JA, Jacks WS. *J. Org. Chem.* 1989; **54**: 4229–4231.
168. Graham SL, Scholz TH. *Tetrahedron Lett.* 1990; **31**: 6269–6272.
169. Bergmann R, Nilsson B, Wickberg B. *Tetrahedron Lett.* 1990; **31**: 2783–2786.
170. Whipple WL, Reich HJ. *J. Org. Chem.* 1991; **56**: 2911–2912.
171. Guingant A. *Tetrahedrons Asym.* 1991; **2**: 415–418.
172. Oster TA, Harris TM. *Tetrahedron Lett.* 1993; **34**: 1851–1854.
173. Tillyer R, Frey LF, Tschaen DM, Dolling UH. *Synlett* 1996; 225–226.
174. Nicolaou KC, Sorensen EJ. *Classics in Total Synthesis*. VCH: Weinheim, 1996; 494.
175. Paris M, Pothion C, Heitz A, Martinez J, Fehrentz JA. *Tetrahedron Lett.* 1998; **39**: 1341–1344.
176. Seebach D, Beck AK, Schiess M, Widler L, Wonnacott A. *Pure Appl. Chem.* 1983; **55**: 1807–1822.
177. Seebach D, Weber T. *Tetrahedron Lett.* 1983; **24**: 3315–3318.
178. Seebach D, Weber T. *Helv. Chim. Acta* 1984; **67**: 1650–1661.
179. Betschart C, Seebach D. *Helv. Chim. Acta* 1987; **70**: 2215–2231.
180. Haller A, Bauer E. *C. R. Acad. Sci.* 1908; **147**: 824.
181. Hamlin KE, Weston AW. *Org. React.* 1957; **9**: 1–36.
182. Cannizzaro S. *Liebigs Ann. Chem.* 1853; **12**: 129–130.
183. Meerwein H, Schmidt R. *Liebigs Ann. Chem.* 1925; **444**: 221–238.
184. Verley A. *Bull. Soc. Chim. Fr.* 1925; **37**: 537–542.
185. Ponndorf W. *Angew. Chem.* 1926; **39**: 138–143.
186. Oppenauer RV. *Recl. Trav. Chim. Pays-Bas* 1937; **56**: 137–144.
187. Babler JH, Invergo BJ. *Tetrahedron Lett.* 1981; **22**: 621–622.
188. Screttas CG, Steele BR. *J. Org. Chem.* 1988; **53**: 5151–5153.
189. Jorgenson MJ. *Org. React.* 1970; **18**: 1–97.
190. Gilman H, van Ess PR. *J. Am. Chem. Soc.* 1933; **55**: 1258–1261.
191. Wittig G. *Angew. Chem.* 1941; **53**: 241–247.
192. Tegnér C. *Acta Chem. Scand.* 1952; **6**: 782–790.
193. Bluhm HF, Donn HV, Zook HD. *J. Am. Chem. Soc.* 1955; **77**: 4406–4407.
194. Alonso F, Lorenzo E, Yus M. *J. Org. Chem.* 1996; **61**: 6058–6059.
195. Bender ML. *J. Am. Chem. Soc.* 1951; **73**: 1626–1627.
196. Tramontano A, Janda KD, Lerner RA. *Science* 1986; **234**: 1566–1570.
197. Pollack SJ, Jacobs JW, Schultz PG. *Science* 1986; **234**: 1570–1573.
198. Jacobs J, Schultz PG. *J. Am. Chem. Soc.* 1987; **109**: 2174–2176.
199. Schultz PG. *Angew. Chem.* 1989; **101**: 1336–1348; *Angew. Chem., Int. Ed. Engl.* 1989; **28**: 1283–1295.
200. Kirby AJ. *Angew. Chem.* 1996; **108**: 770–790; *Angew. Chem., Int. Ed. Engl.* 1996; **35**: 705–724.
201. Keinan E, Lerner RA. *Isr. J. Chem.* 1996; **36**: 113–119.
202. Anderson GT, Alexander MD, Taylor SD, Smithrud DB, Benkovic SJ, Weinreb SM. *J. Org. Chem.* 1996; **61**: 125–132.
203. Teraishi K, Saito M, Fujii I, Nakamura H. *Tetrahedron Lett.* 1992; **33**: 7153–7156.
204. Na J, Houk KN. *J. Am. Chem. Soc.* 1996; **118**: 9204–9205.
205. Tantillo DJ, Houk KN. *J. Org. Chem.* 1999; **64**: 3066–3076.
206. Schwartz B, Drueckhammer DG. *J. Am. Chem. Soc.* 1996; **118**: 9826–9830.
207. Deslongchamps P. *Pure Appl. Chem.* 1975; **43**: 351–378.
208. Deslongchamps P. *Stereoelectronic Effects in Organic Chemistry.* Pergamon Press: Oxford, 1983.
209. Wolfe S, Rauk A, Tel LM, Csizmadia IG. *J. Chem. Soc.* 1971; **93**: 136–145.
210. Lehn JM, Wipff G. *J. Am. Chem. Soc.* 1974; **96**: 4048–4050.
211. Lehn JM, Wipff G, Bürgi HB. *Helv. Chim. Acta* 1974; **57**: 493–496.
212. Wipff G. *Tetrahedron Lett.* 1978; **19**: 3269–3270.
213. Jeffrey GA, Yates JH. *J. Am. Chem. Soc.* 1979; **101**: 820–825.

214. Jones PG, Kirby AJ. *Chem. Commun.* 1979; 288–289.
215. Lehn JM, Wipff G. *J. Am. Chem. Soc.* 1980; **102**: 1347–1354.
216. Briggs AJ, Glenn R, Jones PG, Kirby AJ, Ramaswamy P. *J. Am. Chem. Soc.* 1984; **106**: 6200–6206.
217. Taira K, Gorenstein DG. *Bull. Chem. Soc. Jpn.* 1987; **60**: 3625–3632.
218. Salzner U, Schleyer PvR. *J. Org. Chem.* 1994; **59**: 2138–2155.
219. Schreiner PR. *Angew. Chem.* 2002; **114**: 3729–3731; *Angew. Chem., Int. Ed.* 2002; **41**: 3579–3582.
220. Woodward RB, Gougoutas JZ. *J. Am. Chem. Soc.* 1964; **86**: 5030.
221. Fraenkel G, Watson D. *J. Am. Chem. Soc.* 1975; **97**: 231–232.
222. Lucente G, Romeo A. *Chem. Commun.* 1971; 1605.
223. Cerrini S, Fedeli W, Mazza F. *Chem. Commun.* 1971; 1607.
224. Tagaki M, Ishahara R, Matsudu T. *Bull. Chem. Soc. Jpn.* 1977; **50**: 2193.
225. Capon B, Ghosh AK, Grieve DMcLA. *Acc. Chem. Res.* 1981; **14**: 306–312.
226. Capon B, Dosunmu MI, Sanchez MdeNdeM. *Adv. Phys. Org. Chem.* 1985; **21**: 37–98.
227. Bender ML. *J. Am. Chem. Soc.* 1953; **75**: 5986–5990.
228. Zaugg HE, Papendick V, Michaels RJ. *J. Am. Chem. Soc.* 1964; **86**: 1399–1402.
229. Robinson DR. *Tetrahedron Lett.* 1968; **9**: 5007–5010.
230. Robinson DR. *J. Am. Chem. Soc.* 1970; **92**: 3138–3146.
231. Fodor G, Letourneau F, Mandava N. *Can. J. Chem.* 1970; **48**: 1465–1471.
232. Rogers GA, Bruice TC. *J. Am. Chem. Soc.* 1973; **95**: 4452–4453.
233. Hine J, Ricard D, Perez R. *J. Org. Chem.* 1973; **38**: 110–112.
234. Guthrie JP. *J. Am. Chem. Soc.* 1974; **96**: 588–590.
235. Rogers GA, Bruice TC. *J. Am. Chem. Soc.* 1974; **96**: 2481–2488.
236. Capon B, Gall JH, Grieve DMcLA. *Chem. Commun.* 1976; 1034–1035.
237. Capon B, Grieve DMcLA. *J. Chem. Soc., Perkin Trans. 2* 1980; 300–305.
238. Capon B, Ghosh AK. *J. Am. Chem. Soc.* 1981; **103**: 1765–1768.
239. Nudelman NS, Schulz H, Liñares GG, Bonatti A, Boche G. *Organometallics* 1998; **17**: 146–150.
240. Nudelman NS, Liñares GEG. *J. Org. Chem.* 2000; **65**: 1629–1635.
241. Sweet RM, Wright HT, Chothia CH, Blow DM. *Biochemistry* 1974; **13**: 4212–4228.
242. Rühlmann A, Kukla D, Schwager P, Bartels K, Huber R. *J. Mol. Biol.* 1973; **77**: 417.
243. Tulinsky A, van den Hende JH. *J. Am. Chem. Soc.* 1967; **89**: 2905–2911.
244. Kirby AJ, Komarov IV, Feeder N. *J. Am. Chem. Soc.* 1998; **120**: 7101–7102.
245. Evans DA, Borg G, Scheidt KA. *Angew. Chem.* 2002; **114**: 3320–3323; *Angew. Chem., Int. Ed.* 2002; **41**: 3188–3191.
246. Adler M, Marsch M, Nudelman NS, Boche G. *Angew. Chem.* 1999; **111**: 1345–1347; *Angew. Chem., Int. Ed.* 1999; **38**: 1261–1263.
247. Hvoslef J, Hope H, Murray BD, Power PP. *Chem. Commun.* 1983; 1438–1439.
248. Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R. In *International Tables for Crystallography, C.* Wilson AJC (ed). Kluwer Academic Publishers: Dordrecht, 1992; 685–706.
249. Williard PG, Salvino JM. *J. Org. Chem.* 1993; **58**: 1.
250. Davies JE, Raithby PR, Snaith R, Wheatley AEH. *Chem. Commun.* 1997; 1721–1722.
251. Clegg W, Liddle ST, Snaith R, Wheatley AEH. *New. J. Chem.* 1998; **22**: 1323–1326.
252. Armstrong DR, Davies JE, Davies RP, Raithby PR, Snaith R, Wheatley AEH. *New. J. Chem.* 1999; **23**: 35–41.
253. Armstrong DR, Davies JE, Raithby PR, Snaith R, Wheatley AEH. *New. J. Chem.* 1999; **23**: 499–507.
254. Cox C, Wack H, Lectka T. *J. Am. Chem. Soc.* 1999; **121**: 7963–7964.
255. Adler M. *Dissertation*, Philipps-Universität Marburg, 2001.
256. van E. Hommes NJR, Schleyer PvR. *Angew. Chem.* 1992; **6**: 768–771; *Angew. Chem., Int. Ed. Engl.* 1992; **31**: 755–758.
257. Kaufmann E, Schleyer PvR. *J. Am. Chem. Soc.* 1985; **107**: 5560–5562.
258. Adler S. *Dissertation*, Philipps-Universität Marburg, 2001.
259. Staab HA, Jost E. *Liebigs Ann. Chem.* 1962; **655**: 90–94.
260. Mukaiyama T, Araki M, Takei H. *J. Am. Chem. Soc.* 1973; **95**: 4763–4765.
261. Araki M, Sakata S, Takei H, Mukaiyama T. *Bull. Chem. Soc. Jpn.* 1974; **47**: 1777–1780.
262. Comins D, Meyers AI. *Synthesis* 1978; 403–404.
263. Knapp S, Toby BH, Sebastian M, Krogh-Jespersen K, Potenza JA. *J. Org. Chem.* 1981; **46**: 2490–2497.
264. Mattson MN, Rapoport H. *J. Org. Chem.* 1996; **61**: 6071–6074.