How Small Amounts of Impurities Are Sufficient to Catalyze the Interconversion of Carbonyl Compounds and Iminium Ions, or Is There a Metathesis through 1,3-Oxazetidinium Ions? Experiments, Speculations, and Calculations

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Dedicated – delayed but not less cordially – to Professor *Ken N. Houk* at the occasion of his 70th birthday, in recognition of his seminal theoretical contributions to synthetic organic chemistry

Under the 'best anhydrous' conditions, we were able to achieve, the bicyclic oxazolidinones derived from proline and pivalaldehyde (or cyclohexanone) equilibrate with added carbonyl compounds in (D_6)DMSO and in (D_6)benzene. With (^{18}O)cyclohexanone, no incorporation of the label into the 1,3-oxazolidinone ring was observed (*in-situ* NMR investigations; *Figs. 1*, *3*, and *4*). Since an iminium-carboxylate zwitterion might be involved in this process, we also studied the reaction of *N*-isopropylidene-pyrrolidinium perchlorate with cyclohexanone in anhydrous $CDCl_3$ (*Fig. 5*). We speculated that an interconversion between iminium and carbonyl species might occur in the absence of H_2O or other impurities, *i.e.*, formally a metathesis through 1,3-oxazetidinium ions (*Schemes 2* and *3*). A theoretical investigation with various DFT methods, ranging all the way to CCSD(T)/aug-cc-pVTZ//MP2/def2-QZVPP, shows (*Figs. 8–11*) that oxazetidinium ions are stable species (more or less equienergetic with the reactants iminium ion + carbonyl system), but that the transition states leading to these cations are too high in energy for a reaction taking place in the gas phase at room temperature. Further investigations are proposed to study the iminium–carbonyl interconversion mechanism.

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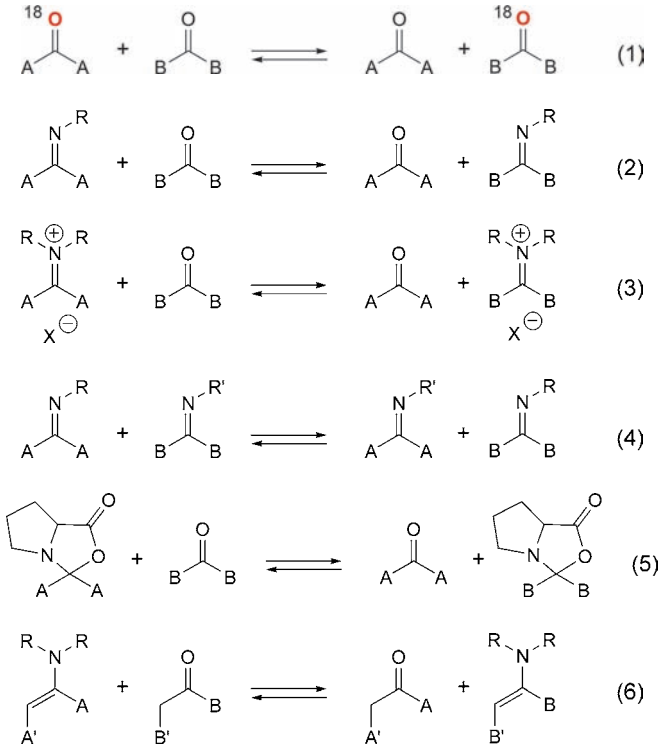
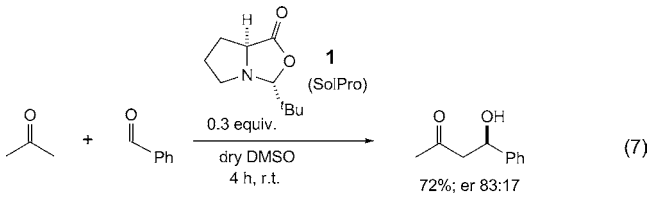
2) Ph.D. Student, financed by the *Gobierno de Chile* (studentship) and the *Spain Government* (grant CTQ2012-39230).

1. Introduction. – The interconversions between carbonyl compounds and their analogs constitute one of the few fundamental reactivity patterns of organic and biological chemistry. Besides the equilibrations between $^{16}O{=}CR_2$ and $^{18}O{=}CR'_2$ (*Eqn. 1*), or between $O{=}CR_2$ and $S{=}CR'_2$, the most important and most common interchanges of this type are those involving species with N=C bonds (*Eqns. 2–4*); these include not only imine and iminium ion but also oxime, hydrazone, nitrone, and nitronate derivatives. Furthermore, in the course of transacetalizations and related processes, such as the oxazolidinone/ketone interchange shown in *Eqn. 5*, as well as in the course of equilibrations between enamines and carbonyl compounds (*Eqn. 6*), interconversion steps of this kind are involved. Areas of current research, in which the interconversions outlined in *Eqns. 2–6* are of central importance, are *organocatalysis* (iminium and enamine reactive intermediates) [1], *dynamic covalent chemistry* (DCC) [2a] and *bioorthogonal reactions* [2b].



Everybody, who has successfully completed an introductory course of Organic Chemistry (see textbooks), is able to propose a mechanism for the six reactions shown in *Eqns. 1–6*, when they occur in the presence of (catalytic) trace amounts of H_2O, amine, and/or acid. When we had discovered that the proline-derived, ^{t}Bu-substituted oxazolidinone **1** (SolPro) (see *Eqn. 7*) catalyzes the aldol addition of acetone to benzaldehyde in *dry* DMSO much more efficiently than proline (1/10 reaction time, higher yield, identical enantioselectivity [3]), we wondered how the pivalaldehyde- and

the acetone-derived oxazolidinones could possibly undergo interconversions under *anhydrous* conditions. This process would be required to occur, since the acetone-derived oxazolidinone is a precursor or an intermediate on the way to the enamine responsible for the actual aldol addition step [4][3]). As a *non-hydrolytic* mechanism of



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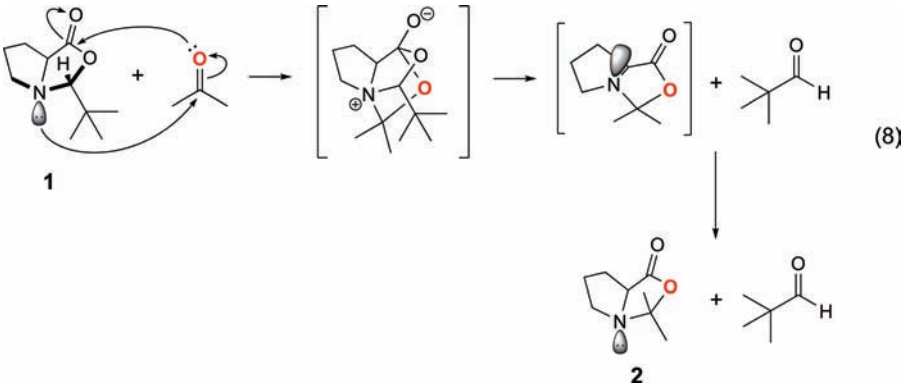
the observed [3] interconversion between oxazolidinones and aldehydes or ketones (*Eqn. 5*), the nucleophilic addition of the bridgehead N-atom to the C=O group with formation of a tricyclic intermediate was suggested, among other possibilities [3]: as can be seen in *Eqn. 8* this would lead to incorporation of the carbonyl O-atom, for instance, of acetone, into the oxazolidinone molecule (→**2**). To find out whether this is indeed the case, we have carried out experiments with ^{18}O-labeled cyclohexanone(s), and we have tested to which extent the involvement of traces of H_2O can be excluded.



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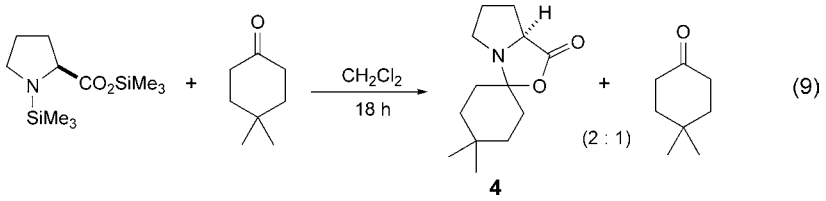
2. Investigation of the Equilibration between Oxazolidinones and Carbonyl Compounds. – ^{18}O-Labeled cyclohexanone [5a] was prepared by CF_3COOH (TFA)-catalyzed hydrolysis with $H_2{}^{18}O$ of the enamine *N*-(cyclohex-1-enyl)pyrrolidine in Et_2O. The freshly distilled, ^{18}O-labeled cyclohexanone (20 equiv.) and the, likewise freshly distilled, *t*Bu-substituted oxazolidinone **1** (1 equiv.) [6] were added (by syringe technique) to (D_6)DMSO or (D_6)benzene (C_6D_6) dried over 4-Å molecular sieves (MS; which had been heated under Ar with a heat gun) in an NMR tube (150° (oven-dried), with cooling in a desiccator over P_4O_{10}). After equilibration at room temperature, which took <3 h in both solvents, ^{1}H- and ^{13}C-NMR spectra were

[3]) For a comprehensive discussion of the mechanism of organocatalytic reactions, see the article by *A. Moyano*, '*Activation Modes in Asymmetric Organocatalysis*', in [1c].

recorded (*Fig. 1*). With an initial cyclohexanone/oxazolidinone **1** ratio of 20:1, the final equilibrium ratio of the two oxazolidinones **1**/**3** was close to 1:1. While both carbonyl compounds had approximately the same ^{18}O content, there were only single ^{13}C signals of the oxazolidinone carbonyl C-atoms indicating that there is no detectable ^{18}O incorporation into the oxazolidinone O-positions of **1** and **3**. The mechanistic proposal outlined in *Eqn. 8* is thus not confirmed by this labeling experiment.

To have equilibrating components of comparable stability, we have also studied ^{18}O exchange between cyclohexanone, 4,4-dimethylcyclohexanone, and the corresponding oxazolidinones **3** and **4**, respectively. The oxazolidinone **4** was prepared from doubly silylated L-proline [4][7] and 4,4-dimethylcyclohexanone (*Eqn. 9*); the reaction did not proceed to completion and furnished a 2:1 mixture of the tricyclic compound **4** and the



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ketone precursor. The subsequent interconversion experiments were carried out in the non-polar, non-hygroscopic solvent benzene rather than in DMSO (*cf. Fig. 1*). As evident from *Fig. 2*, there is no ^{13}C-NMR-detectable ^{18}O exchange between the two ketones (in the presence of H_2O) unless acid is added. On the other hand, there was ^{18}O-interchange when the oxazolidinone **4**, 4,4-dimethylcyclohexanone, and ^{18}O-labeled cyclohexanone were mixed in C_6D_6 under *anhydrous* conditions. As expected from the mixing ratio and from the comparable stabilities of the components, a *ca.* 1:1:2:2 ratio of the two oxazolidinones and the two ketones was observed after completed equilibration (see the ^1H- and ^{13}C-NMR analyses[4]) of the mixture shown in *Fig. 3*). Qualitatively, the degree of ^{18}O incorporation in the ketones suggests that there cannot be much ^{18}O labeling in the oxazolidinones. From this experiment, the conclusion might be drawn that an oxazolidinone, such as **4**, mediates or *catalyzes* the $^{16}O/^{18}O$-exchange reaction between the cyclohexanones in *dry* benzene, a reaction that did not take place under 'aqueous' conditions in the *absence* of oxazolidinone (*cf. Fig. 2*). Concerning this conclusion, a *caveat* is necessary: the oxazolidinone **4** used in this experiment was not rigorously purified (see *Exper. Part*); from its mode of preparation, the sample could have contained traces of disilylated proline or of other trace impurities that could possibly have acted as catalysts.

3. The Role of Traces of H_2O in Oxazolidinone and Iminium Ion Equilibrations. – In the previous *Sect.* we have highlighted the terms *anhydrous, non-hydrolytic*, and *dry* in italics to indicate that comments on them are required. Here are some of them: *i*) the DMSO and (D_6)DMSO, as well as C_6D_6, used as solvents were dried over molecular

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[4]) The ^{13}C-NMR signal of the carbonyl C-atom in the unsubstituted cyclohexanone appears at higher field than the corresponding signal of the dimethyl derivative by *ca.* 0.4 ppm (*Figs. 2* and *3*; [8a]: 0.6 ppm).

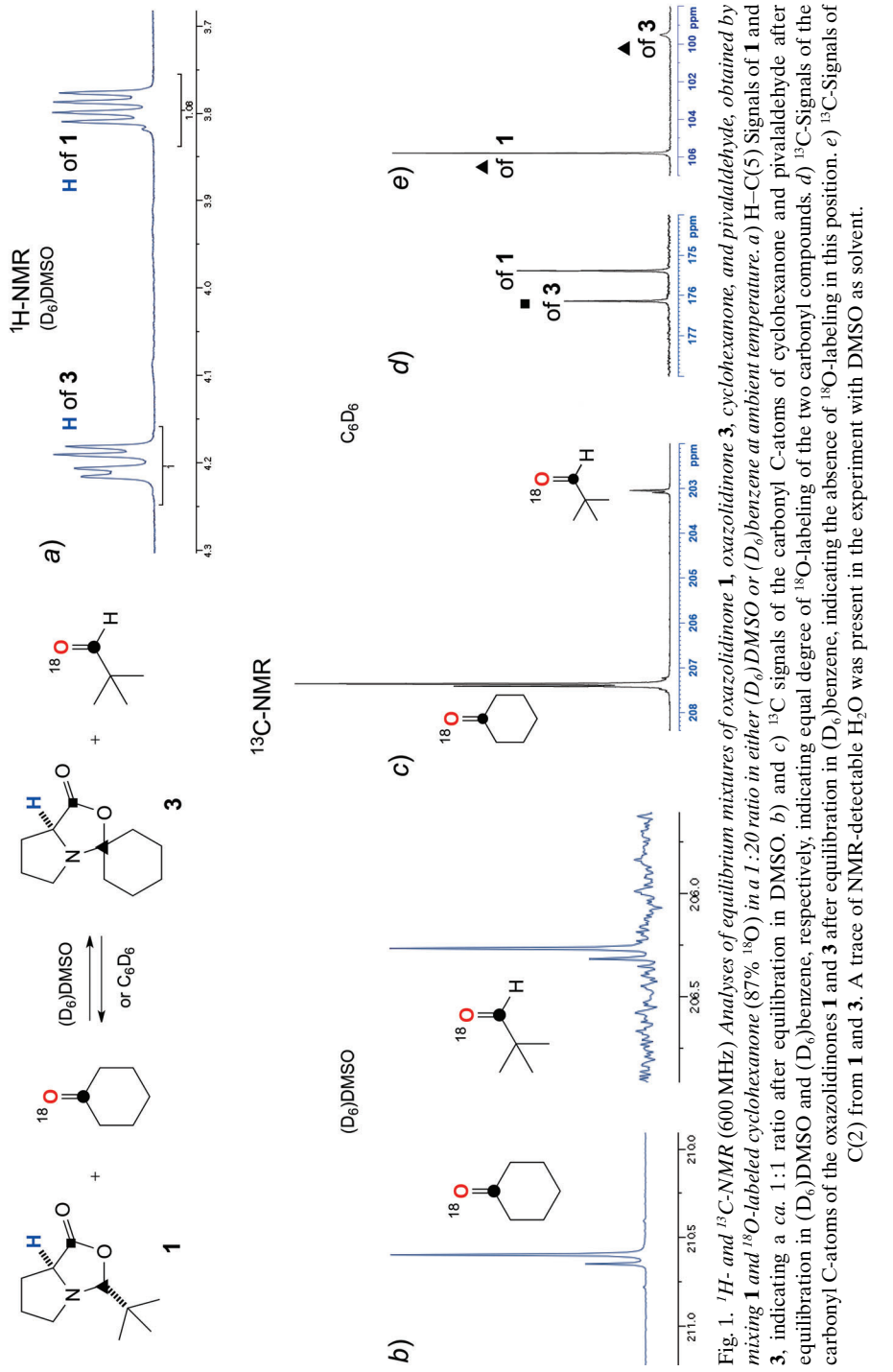

Fig. 1. *^{1}H- and ^{13}C-NMR* (600 MHz) *Analyses of equilibrium mixtures of oxazolidinone* **1**, *oxazolidinone* **3**, *cyclohexanone, and pivalaldehyde, obtained by mixing* **1** *and* ^{18}*O-labeled cyclohexanone* (87% ^{18}O) *in a 1 : 20 ratio in either* (D_6)*DMSO or* (D_6)*benzene at ambient temperature. a)* H–C(5) Signals of **1** and **3**, indicating a *ca.* 1 : 1 ratio after equilibration in DMSO. *b)* and *c)* ^{13}C signals of the carbonyl C-atoms of cyclohexanone and pivalaldehyde after equilibration in (D_6)DMSO and (D_6)benzene, respectively, indicating equal degree of ^{18}O-labeling of the two carbonyl compounds. *d)* ^{13}C-Signals of the carbonyl C-atoms of the oxazolidinones **1** and **3** after equilibration in (D_6)benzene, indicating the absence of ^{18}O-labeling in this position. *e)* ^{13}C-Signals of C(2) from **1** and **3**. A trace of NMR-detectable H_2O was present in the experiment with DMSO as solvent.

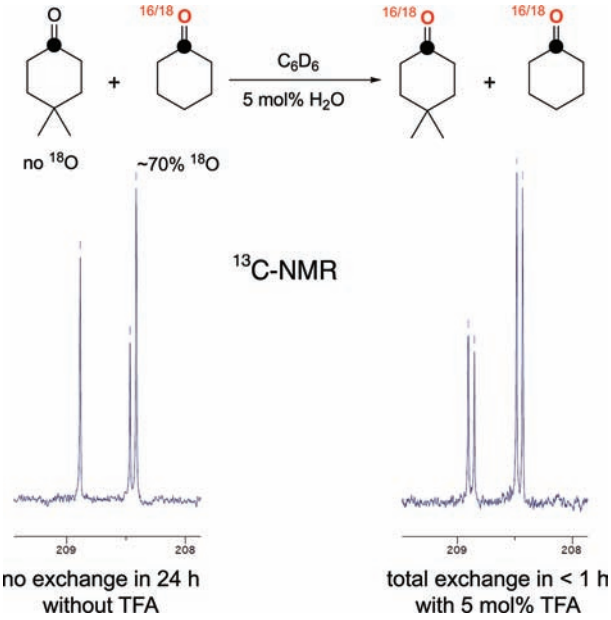

Fig. 2. *^{18}O-Exchange between ^{18}O-cyclohexanone and 4,4-dimethylcyclohexanone in C_6D_6 in the presence of H_2O without* (left) *and with* (right) *addition of CF_3CO_2H.* The ^{18}O-content of cyclohexanone and of 4,4-dimethylcyclohexanone is approximately the same. It is known that, in the absence of acid, there is no incorporation of ^{18}O into acetone from excess ^{18}O-labeled H_2O in 24 h at 25° [5b].

sieves (3- or 4-Å MS powders, depending on the compounds studied), which had been dried by heating with a heat gun in *vacuo*; *ii*) DMSO is hygroscopic; MS are expected to remove H_2O from DMSO less effectively than from C_6H_6; *iii*) H_2O-saturated benzene contains $3.4 \cdot 10^{-2}$ mmol H_2O/ml and H_2O-saturated $CHCl_3$ contains 0.081% H_2O; *iv*) the humidity of Zürich air in the summer/winter time can be estimated to be *ca.* 5 and 10 mg/l, respectively; *v*) oxazolidinones react spontaneously with H_2O, forming proline that is insoluble in benzene[5]); in our handling techniques for preparing NMR solutions, we did not see any evidence for this, *vi*) in a glove box filled with dry Ar, containing 1 ppm of H_2O, there are still *ca.* 10^{17} H_2O molecules in 22 l of gas.

To find evidence for the role of H_2O in the interchange between the oxazolidinone **1** and cyclohexanone with oxazolidinone **3** and pivalaldehyde in C_6D_6, we have carried out NMR-sample preparations by syringe techniques *a*) in a glove box (6 ppm H_2O)[6]), *b*) in the laboratory atmosphere, and *c*) with addition of a drop of H_2O-saturated C_6D_6. The reaction was followed by recording NMR spectra at certain time intervals for 12 h (see *Fig. 4*). Clearly, equilibrium was reached in *ca.* 4 h in the presence of H_2O and in *ca.* 12 h *in the absence of H_2O*, with a rather insignificant difference between the samples prepared outside and inside the glove box.

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5) When the stopper is removed from a flask containing **1**, the surface of the liquid was immediately covered by a white film (of precipitated proline); the same was observed for a benzene solution.

6) We thank Prof. *Franziska Schönebeck* for allowing us to use the glove box of her group. For previous *anhydrous* handling of oxazolidinones in a dry box, see [4].

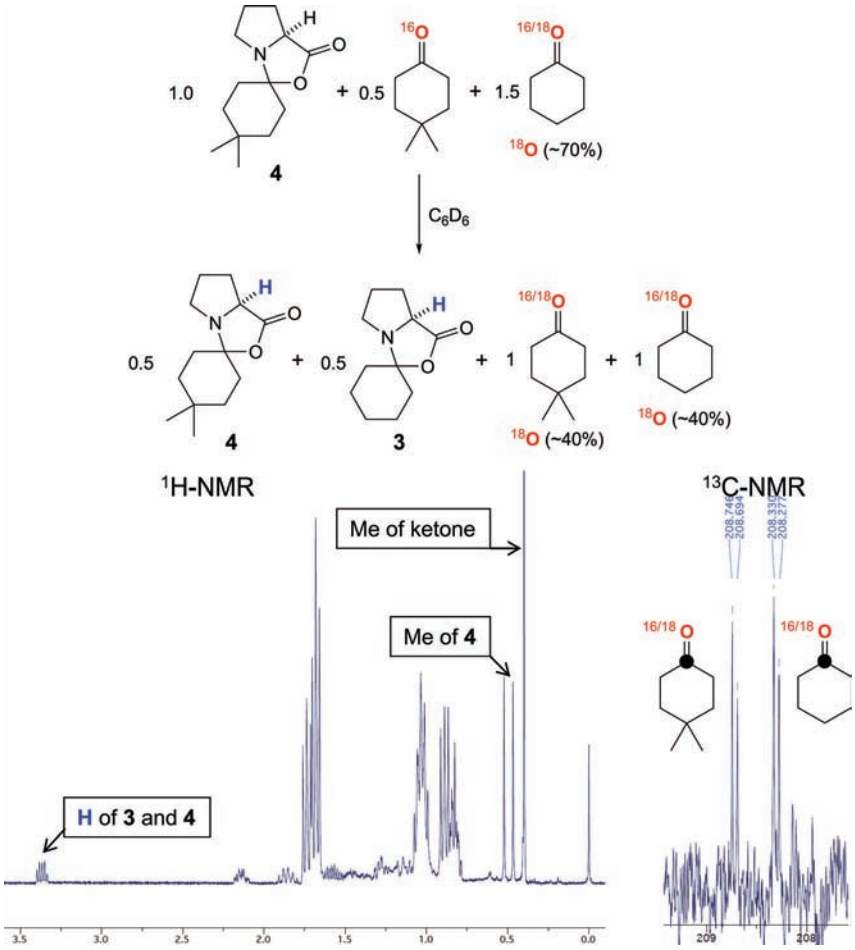

Fig. 3. *NMR Analysis of the equilibrium mixture formed by addition of* ^{18}*O-cyclohexanone* (*ca.* 70% ^{18}O) *to the benzene solution of 4,4-dimethylcyclohexanone and its oxazolidinone derivative* **4** (ratio 1.5 : 0.5 : 1.0) *under* anhydrous *conditions.* See specification in the accompanying text and details in the *Exper. Part*. After equilibration, the ^{18}O-content of the two ketones is approximately the same.

Since a zwitterionic iminium carboxylate (see *Sect. 4*) could be involved in the interconversion of oxazolidinones (*Figs. 3* and *4*), we have also tested the interconversion of simple iminium ions with the corresponding carbonyl compounds. To this end, we prepared the known [8b] crystalline iminium perchlorate from acetone and pyrrolidine in analytically pure form[7])[8]). A solution of the iminium salt

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[7]) We also used the method of *Leonard* and *Paukstelis* [8b] for the preparation of iminium salts from imidazolidinones (*MacMillan* catalysts) [9a][9b][9d–9f] or diarylprolinol trimethylsilyl ethers (*Jørgensen–Hayashi* catalysts) [9a][9c], and cinnamaldehyde.

[8]) To compare the NMR spectra (*cf. Fig. 5*) we have also prepared the *N*-cyclohexylidenepyrrolidinium perchlorate (see *Fig. 6*, *Exper. Part* and [8b]).

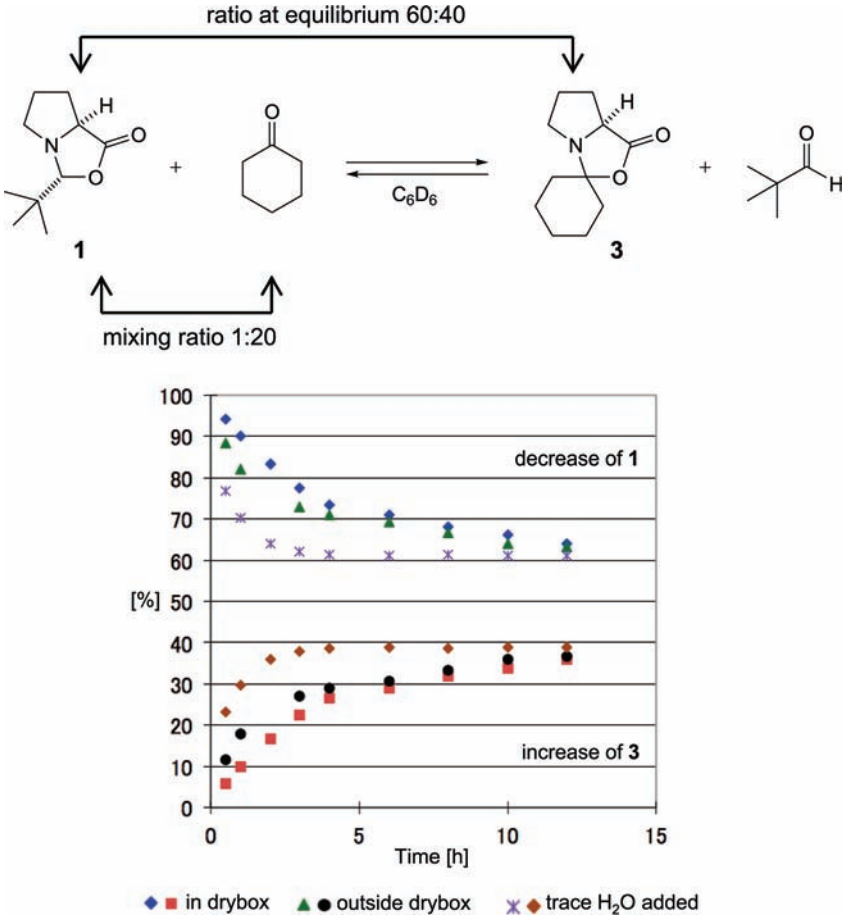


Fig. 4. *Equilibration* (by NMR analysis) *of oxazolidinones* **1** *and* **3**, *pivalaldehyde, and cyclohexanone* (C_6D_6, room temperature) *with various degrees of exclusion of* H_2O. The rate of equilibration increases in the presence of *ca.* 10 mol-% H_2O; for details see accompanying text and *Exper. Part*.

and cyclohexanone (ratio 1:25) was prepared (in $CDCl_3$; dried over basic Al_2O_3, activity I) in an NMR tube (dried at 150°) outside or inside the glove box, or with some added H_2O, and the spectra were recorded at various time intervals for 24 h (*Fig. 5*). Under the *driest* conditions, there was a slow interconversion leveling off with a *ca.* 85:15 ratio of the isopropylidene- and cyclohexylidene iminium ions (*Fig. 5, a*). When the solution was prepared outside the dry box, the equilibration occurred somewhat faster, with a final ratio *ca.* 70:30 (*Fig. 5, b*). The product of hydrolysis (pyrrolidinium salt) was not detected under these two sets of conditions. In the presence of H_2O, the reaction was fastest and reached an almost 1:1 ratio of the two iminium ions, with simultaneous formation of the hydrolysis product, the pyrrolidinium perchlorate (*Fig. 5, c*). We have no clue, as to why the final

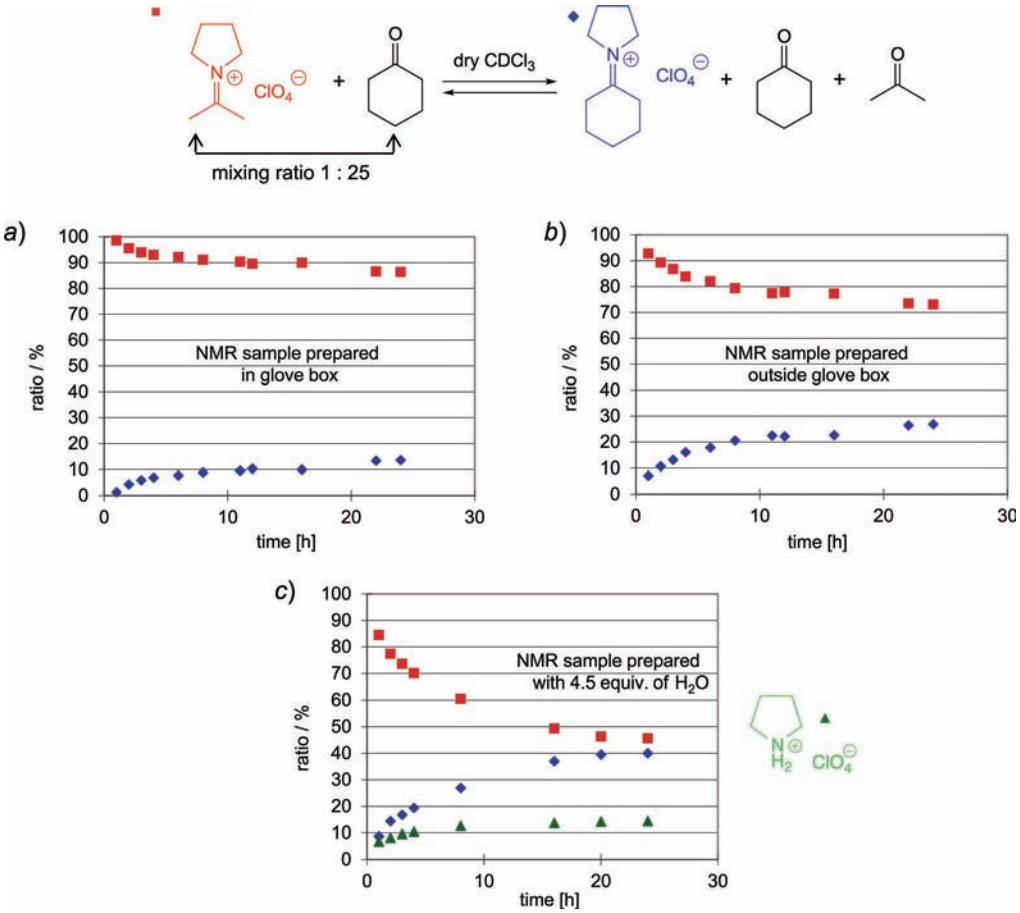


Fig. 5. *Interchange* (followed by NMR analysis) *between the pyrrolidinium ions derived from acetone and cyclohexanone under various conditions* (*a*) very dry, *b*) dry, *c*) 'aqueous', in $CDCl_3$). For details, see accompanying text and *Exper. Part*.

(thermodynamic?) ratios differ under the three sets of conditions, which is in sharp contrast to the result of the experiment with the oxazolidinones (compare *Fig. 4* with *Fig. 5*), where the same final ratio was observed under the same three sets of conditions for the sample preparation. If we assume that the *ca.* 1:1 ratio of the two iminium ions observed in the 'deliberate' presence of H_2O is the thermodynamic ratio (*Fig. 5, c*), it appears as if under the *dry* conditions (*Fig. 5, a* and *b*) the conversion of the acetone-derived iminium ion to the cyclohexanone-derived one comes to a halt before equilibrium is reached, *i.e,.* as if a catalyst of the reaction is being removed, or an inhibitor is being generated. The product of hydrolysis with traces of H_2O will be traces of ammonium salt (pyrrolidinium perchlorate; see *Figs. 5, c*, and *6*); this salt should act as an acid catalyst for the interconversion

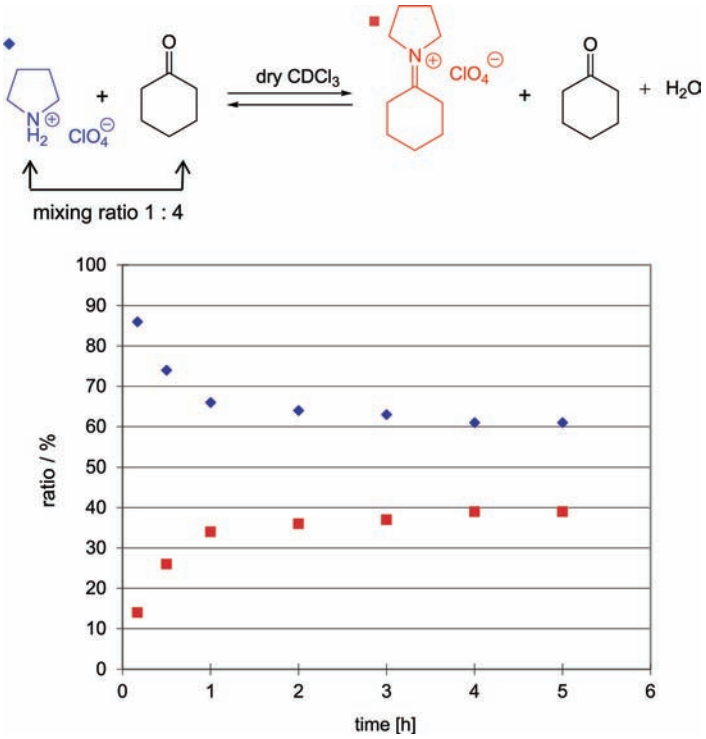
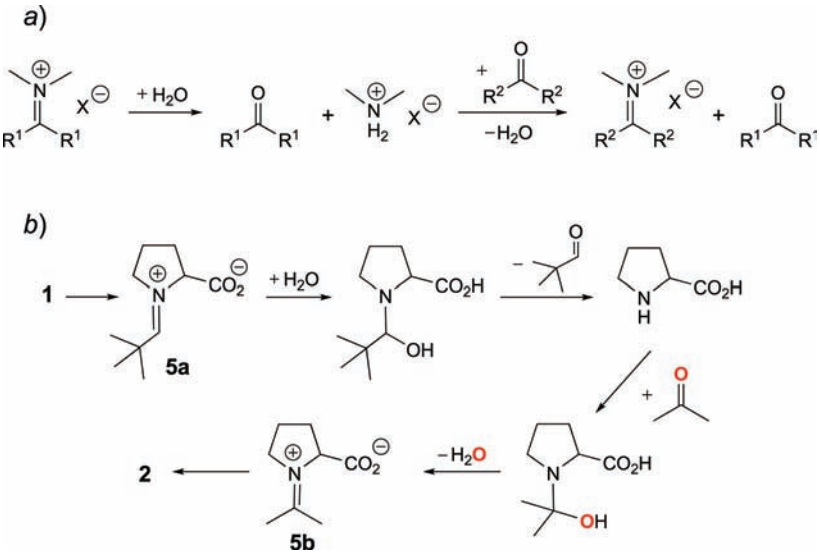


Fig. 6. *Course of iminium salt formation from pyrrolidinium perchlorate and cyclohexanone in $CDCl_3$.* For details, see *Exper. Part.*

reaction, rather than as an inhibitor. From the experiments described in *Fig. 5* the following extrapolation could be made: the *less H_2O* the slower the reaction – *no H_2O* no reaction.

In conclusion, we have demonstrated that, under the best conditions for exclusion of H_2O, we were able to achieve, various oxazolidinones and iminium ions interconvert with each other and with the corresponding carbonyl compounds (*Figs. 3–5*). Furthermore, an ^{18}O label introduced with the carbonyl compound remains in the pool of carbonyl O-atoms upon interchange with oxazolidinones, *i.e.*, no ^{18}O was detected in the heterocyclic rings (*Figs. 1* and *3*). These processes were observed to occur not only in the aprotic dipolar solvent (D_6)DMSO (*Fig. 1*), but also in the less polar solvent $CDCl_3$ (*Fig. 5*) and in the nonpolar solvent C_6D_6 (*Figs. 3* and *4*). Neglecting other possible impurities, which may act as mediators or catalysts in the solutions of the interconverting species, and remembering that there is no way of *absolutely* excluding H_2O, the following two questions can be asked: *i*) how little H_2O may suffice to mediate these reactions *via* routes such as, for instance, those outlined in *Scheme 1*, and *ii*) are there conceivable alternative mechanisms, by which the interconversions might occur *without* involvement of any 'mediators'?

Scheme 1. *Possible H_2O-Mediated Mechanisms of the Observed Interconversion between Iminium Salts and Carbonyl Compounds, and between Oxazolidinones and Carbonyl Compounds. a*) Hydrolysis of an iminium ion providing the carbonyl compound R^1_2CO and an ammonium salt, which, in turn, reacts with a second carbonyl compound R^2_2CO to form the derived new iminium ion. *b*) Opening of the oxazolidinone **1** to an iminium carboxylate (zwitterion **5a**) [4], hydrolysis of which leads to proline and pivalaldehyde; subsequent reversal of this sequence with acetone (→ **5b**), the O-atom of which winds up in a H_2O molecule that eventually will become the carbonyl O-atom of pivalaldehyde, with no ^{18}O-incorporation into the oxazolidinone **2**. For the sake of simplicity, we have used single reaction arrows herein, although all steps are, of course, reversible.



While we feel unable to answer the first question on the basis of the experimental data presented[9]), we could not resist the temptation to speculate about the second question and put the results of the speculation to the test of state-of-the-art theory, as described in the following two *Sections*.

4. Is there a Carbonyl–Iminium Metathesis? Organic Chemists' Analysis. – 4.1. *Speculative Discussion of a Four-Membered Ring Intermediate and a [1.3]-Sigmatropic Transition State.* For the interchange reaction between two different oxazolidinones and the corresponding two carbonyl compounds without incorporation of the carbonyl O-atom into the heterobicyclic system (*Eqn. 5*, and *Figs. 1*, *3*, and *4*) in the *absence of H_2O*, we should like to discuss two routes with an oxazetidinium ion of type **7** as a common intermediate (*Scheme 2*). In the first proposal (*Scheme 2,a*), the bridgehead N-atom of the oxazolidinone (*cf.* **1**) adds to the C=O group of a ketone (*cf.* acetone) to form an ammonium alkoxide; this zwitterion[10]) undergoes cyclization by substitution of the

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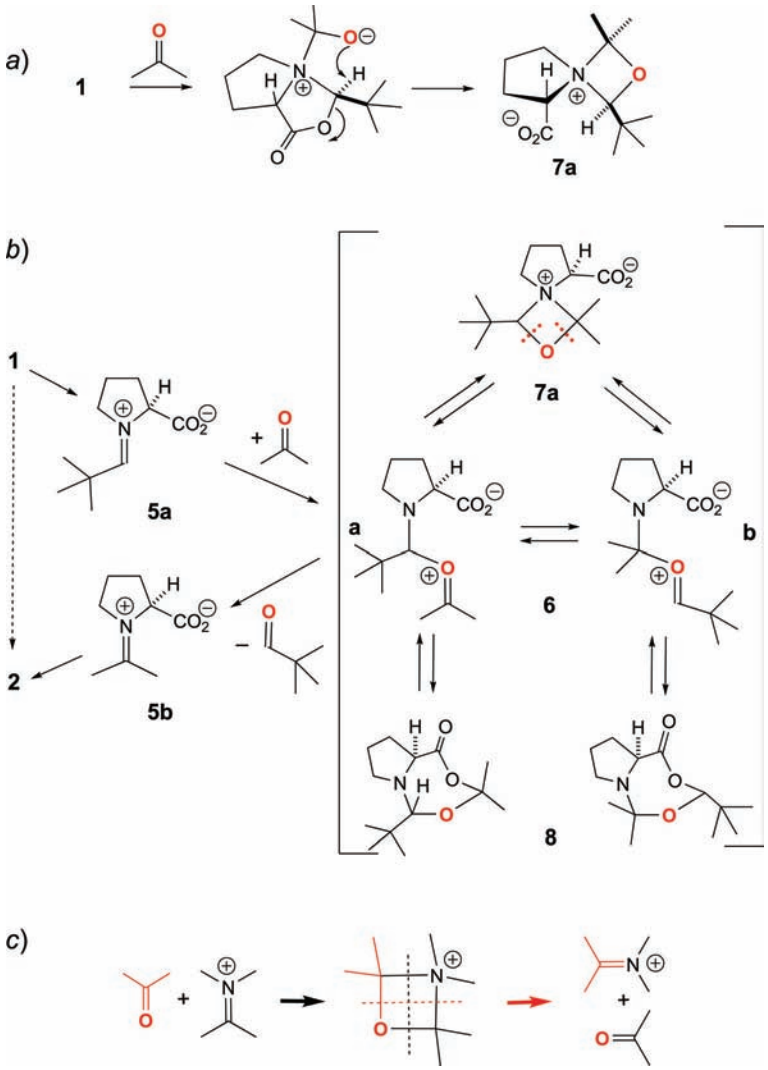
9) They neither definitely prove nor definitely disprove that such processes can occur in the *absence* of impurities (H_2O, acid, amine)!

10) The carbonyl compound would have to approach the bridgehead N-atom '*cis*' to the bulky *t*Bu group of **1**!

Scheme 2. *Speculations about Interconversions of Oxazolidinones* (*cf.* **1**–**4**) *with Aldehydes or Ketones* (without loss of ^{18}O-Label from the carbonyl pool), *and about a C=N/C=O Metathesis Process through an Oxazetidinium Intermediate* **7**. *a*) Formation of a spiro-iminium carboxylate **7a** through an ammonium alkoxide; formation of the 4-membered ring would, at the same time, be a favorable four-exocyclic and an unfavorable 7-endocyclic intramolecular S_N2-type substitution [29a]. *b*) Formation of the intermediate **7a** *via* iminium carboxylates **5** and oxenium carboxylates **6**; alternative collapse of **6** to the heterobicyclic structures **8**. *c*) Formal overall iminium/carbonyl metathesis through an intermediate 1,3-oxazetidinium cation **7** (generic formula).



carboxylate group at the *N*,*O*-acetal center to give oxazetidinium carboxylate **7a**. In the second proposal, an oxazolidinone (*cf.* **1**–**4**) opens up to an iminium carboxylate (**5** in *Schemes 1,b* and *2,b*)[11])[12]), the C=N bond of which undergoes nucleophilic addition by the O-atom of a carbonyl compound; the resulting oxenium carboxylate (zwitterion of type **6**) can collapse to the same four-membered ring derivative **7a**, invoked in the first proposal; otherwise, the zwitterion **6** could also collapse to the hetero-bicyclic structures **8** (*Scheme 2, b*). If there is equilibrium between the involved species, mechanistic routes would be available not only for the interchanges between oxazolidinones and carbonyl compounds (without loss of ^{18}O label in the latter), but also for the simple iminium ion/carbonyl interchanges. The species of central importance, zwitterion **7** or a simple oxazetidinium ion, become the intermediates of a metathesis process as indicated in *Scheme 2, c*[13]).

During a discussion with *Albert Eschenmoser*, it occurred to us that, instead of an intermediate of type **7**, a formally allowed [12][14]) [1.3]-sigmatropic shift through a four-membered cyclic transition state **TS** could lead to an interchange of the positions of the R_2N group in oxenium cations **6** (*Scheme 3*), and thus cause the overall metathesis transformation.

We realize that, in the speculative conversions presented in the previous paragraphs, we have addressed neither the role of counterions (proline-derived iminium ions have a built-in CO_2^- counterion)[15]), nor the steric hindrance in an up to hexasubstituted four-membered ring, nor the ring strain, nor possible precedents in the literature.

4.2. *Four-Membered Rings with Two Heteroatoms – A Brief Literature Survey.* According to the *Woodward–Hofmann* rules [12], the concerted formation of a four-membered ring from and its dissociation to two double bond-containing species is '*formally forbidden*'. This means that such processes should either occur stepwise through 1,4-diradicals or 1,4-zwitterions[16])[17]), or by photochemical processes involving

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[11]) In *anhydrous* solutions of proline-derived oxazolidinones in MeOH, PhOH, HFIP (=1,1,1,3,3,3-hexafluoropropan-2-ol), AcOH, or TFA, or in THF/LiBr, the zwitterion or the corresponding carboxy-iminium salt can actually be the only species detectable by NMR analysis. In DMSO, the prevailing species is the oxazolidinone and in the presence of certain bases the enamino-carboxylate is observed, see Sect. 5 in [4], and [10].

[12]) Zwitterions of this type, derived from proline and other amino acids, undergo decarboxylation at elevated temperatures to form azomethine ylides, which can be trapped with dipolarophiles or are hydrolyzed when generated in H_2O. The latter process has been discovered 150 years ago by *Curtius* and *Strecker* (see the discussion in Sect. 2 and the references in Footnotes 14–16 of [4]).

[13]) The interconversion between an enamine and a carbonyl compound in *dry* DMSO [11] could also be formulated with an intermediate of type **6**: reversible enamine protonation would generate an iminium ion, the precursor of amino-oxenium ions of type **6**.

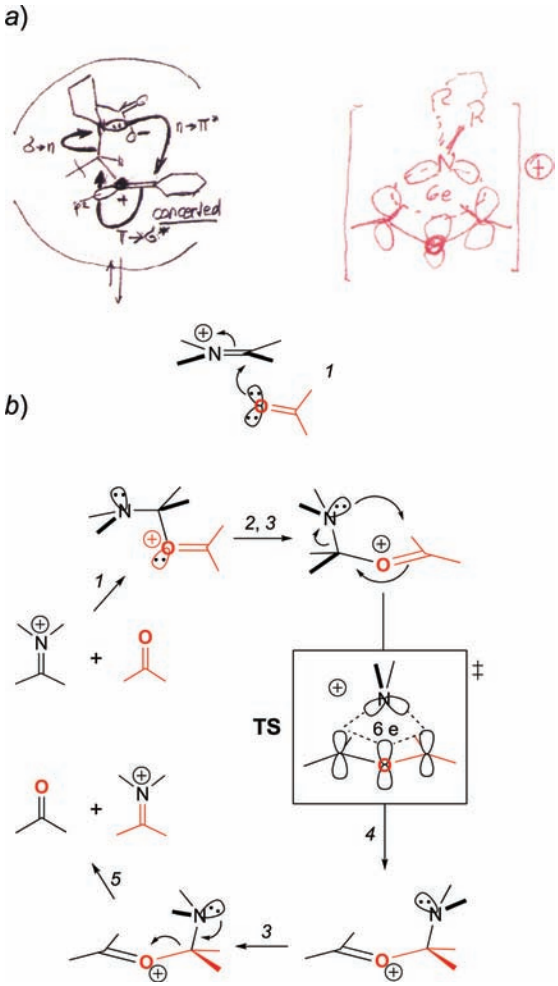
[14]) For an early review on orbital-symmetry controlled reactions in German, see [12b].

[15]) For an investigation of the interaction between iminium ions and their counterions, see [13]. For electrophilicity parameters *E* of iminium ions visit: http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

[16]) For two scholarly articles on this subject by *R. Huisgen*, see [14] and ref. cit. therein.

[17]) For theoretical and experimental investigations of zwitterion 'collapse' to cyclobutanes, oxetanes, and azetidines, of interest in connection with organocatalysis, see [15].

Scheme 3. *1.3-Sigmatropic Shift of the R_2N-Group in an Oxenium Ion of Type* **6**. *a*) The first idea by *A. Eschenmoser* and *D. S. b*) The steps leading to an overall metathesis: *1*) nucleophilic addition of the carbonyl O-atom to the C=N bond; *2*) rotation around the *O–C* bond; *3*) rotation around the *N–C* bond or inversion on N-atom; *4*) 1,3-sigmatropic shift of R_2N; *5*) β-elimination.

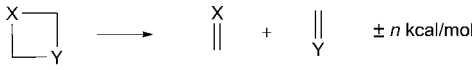


excited states[18])[19]). For the parent system, the hydrocarbon cyclobutane, the activation energy of ring opening to a 1,4-diradical has been determined to be 60 kcal/mol [18]. Using standard average, 'generic' bond energies and the strain energy of a four-

[18]) Photoexcitation to a singlet excited state and singlet–triplet intersystem crossing usually lead to diradical intermediates; for a comprehensive review on synthetically useful [2 + 2] cycloadditions, including the *Paterno–Büchi* reaction (C=C + C=O → oxetanes), see [16].

[19]) A 1,2-dioxetane and a 1,3-oxazetidinone intermediate have actually been proposed to be responsible for bioluminescence (when they undergo *retro*-cycloaddition to two carbonyl moieties or to CO_2 + an imino derivative) [17].

membered ring[20]), the cycloreversion of cyclobutane, 1,3-dioxetane, 1,3-diazetidine, and 1,3-oxazetidine to ethylene, formaldehyde or its imine, respectively, are endothermic for the hydrocarbon and highly exothermic for the heterocycles (*Eqn. 10*)[21]). Still, not only cyclobutanes are stable compounds: there are many reports on four-membered ring heterocycles[22]) with RN, O, PR_3, and/or S in 1,2- or 1,3-position[23]), which have either been isolated or detected, or proposed as intermediates. For a few



(10)

n [kcal/mol]	−13	+33	+25	+29
X	CH_2	O	NR	O
Y	CH_2	O	NR	NR

selected examples related to the overall metathesis process[24]) shown in *Scheme 2,c* see *Fig. 7*. Interestingly, a spiro-1,3-oxazetidinium zwitterion of type **7** (*Scheme 2*) has been previously suggested (**v** in *Fig. 7*) as intermediate of an oxazolidinone-catalyzed reaction (*cf.* SolPro (**1**) in *Eqns. 7* and *8*): to explain the release of product from its iminium-carboxylate precursor (*in the absence of* H_2O), with concomitant regeneration of enamine, *McQuade* and co-workers. proposed [28] a cycloaddition of the C=O groups of the aldehyde starting material to the $R_2N{=}C^+$ group (→ **v**), with subsequent elimination/fragmentation [29b][25]).

Thus, the literature survey indicates that an oxazetidinium ion of type **7** might indeed exist. The next step of our investigation was the search for structures of this type

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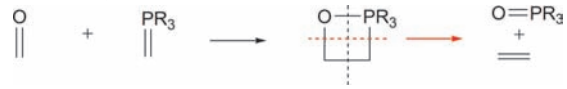
[20]) The following values were used for the calculations to obtain the endo- and exothermicities shown in *Eqn. 10* and in *Footnote 21:* 84 (C–C), 148 (C=C), 87 (C–O), 177 (C=O), 72 (C–N), 143 (C=N), 45 (O–O), 27 (ring strain) kcal/mol.

[21]) The highest exothermicity results for 1,2-dioxetane → 2 $H_2C{=}O$ + 78 kcal/mol. Trimethyl- and tetramethyl-1,2-dioxetane are isolable compounds [19], and the dimer of CO_2 [O–CO–CO–O] has been shown to be involved in the light-emitting reaction between oxalyl chloride and H_2O_2 [20] (*cf.* 'glowsticks').

[22]) For a review covering the literature up to 1985, see [21].

[23]) A *SciFinder* search in November 2013 produced 211 hits for 1,3-oxazetidines (61 hits with 0 references, 123 hits with 1 reference). More than 50 of the structures are oxazetidinones of the type shown as **iv** in *Fig. 7*.

[24]) The transition-metal catalyzed metathesis reaction (*cf.* 2 R–CH=CH_2 → R–CH=CH–R + $CH_2{=}CH_2$) does not proceed through cyclobutane intermediates [22]. A well-known metathesis occurring through a four-membered ring containing an O- and a P-atom in 1,2-position is the (*cis*-selective) *Wittig* reaction carried out in the absence of salts [23]. For a mechanistic discussion, see also Tab. 2 (Entries 2 and 3) and **A** in Footnote 10 of [23d].



[25]) Unfortunately, the formula **v** shown in [28] is wrong; see the correction in *Fig. 7*. For a DFT calculation of an oxazetidinium carboxylate of type **7** by the *McQuade* group [28], see also *Footnote 27*, below.

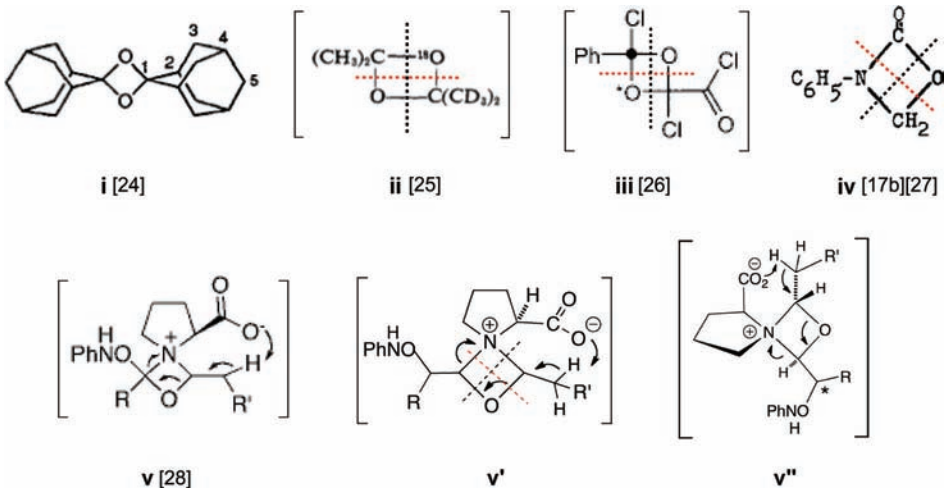


Fig. 7. *Stable compounds,* **i** *and* **iv***, and proposed intermediates,* **ii**, **iii** *and* **v***, of 1,3-dioxetane and 1,3-oxazetidine structures.* **i**: The dimer of adamantanone, formed, together with the corresponding 1,2-dioxetane (*cf.* other derivatives of this heterocycle [17a][19][20] and *Footnote* 21, above), by γ-radiolysis; interestingly, E_a for decomposition of **i** (26 kcal/mol) is much lower than that of the peroxide isomer (34 kcal/mol). **ii**: Intermediate of irradiation with scrambling of labeled acetones, *i.e.*, $^{18}O{=}C(CH_3)_2 + O{=}C(CD_3)_2 \rightleftharpoons O{=}C(CH_3)_2 + {}^{18}O{=}C(CD_3)_2]$ (wavelength 313 nm, neat liquid); in this case, polymer formation, $HO{-}[C(CH_3)_2{-}{}^{18}O{-}C(CD_3)_2{-}O{-}]_n{-}H$ could also explain the result. **iii**: Proposed intermediate of $^{18}O/^{16}O$-scrambling between ^{18}O-labeled PhCOCl and $(COCl)_2$. **iv**: First 1,3-oxazetidine derivative (an oxa-β-lactam, prepared in gram amounts in 1967, from $Ph{-}N{=}C{=}O + H_2C{=}O$); retrocycloaddition to $Ph{-}N{=}CH_2 + CO_2$: $E_a = 30.8$ kcal/mol [17b]. **v**: Spiro-oxazetidinium carboxylate of type **7** proposed as intermediate of the proline-catalyzed α-aminoxylation of aldehydes; the published formula, **v**, is incorrect and must be replaced by **v′**. **v″**: Possible geometry around the spiro center for the process, **v′**, (a fragmentative elimination), to take place. The formulae **i** – **v** are taken from [24] – [28].

and for the corresponding mechanisms of their formation, including transition states, by state-of-the-art computational methods.

5. Theoretical Chemists' Analysis of a Possible Carbonyl/Iminium Metathesis. – We have investigated the reactions of iminium ions with carbonyl compounds, using density-functional and *ab initio* methods in combination with different basis sets. In this theoretical approach, we employed density functional theory (DFT) and the *ab initio* method *Møller–Plesset* perturbation theory to second order (MP2), in order to assess the reliability of the results obtained. To investigate the internal consistency of the DFT results, we chose different types of density functionals, namely the popular BP86, B3LYP, and M06-2X functionals as representatives of different rungs of *Jacob*'s ladder. If results obtained with different functionals are similar, we consider the electronic structures to be insensitive to the approximations inherent in the functional.

The iminium ions included the proline-derived iminium carboxylates of type **5**, the isopropylidene-pyrrolidinium ion, the *N*,*N*-dimethyl-isopropylidene-iminium ion, and the protonated formaldehyde imine. As carbonyl components, we used formaldehyde,

acetone, and cyclohexanone. We describe herein only the results obtained for the isolated species, thus resembling the gas phase (*absolutely no H_2O!*); calculations including solvents modeled as dielectric media (applying dielectric constants of DMSO, $CHCl_3$, H_2O) were also performed and gave *qualitatively* similar results[26]). The thermodynamic data are differences in total electronic energies (approximate relative enthalpy values) in kcal/mol, *i.e.*, no temperature and entropy effects were considered[27]).

The relative energies of oxazolidinones and the corresponding iminium carboxylates are given in *Fig. 8, a*; the ring opening process is endothermic by 20–27 kcal/mol. From the data in *Fig. 8, b*, we would have to conclude that the spiro-ammonium carboxylate lies almost 30 kcal/mol[28]) above the oxazolidinone **1** + acetone, while the bicyclo[5.3.0] structures, **8**, are close in energy to the oxazolidinones[29]). Obviously, in the gas phase the collapse of an oxenium carboxylate of type **6**, if it existed (*cf. Scheme 2*), to a neutral seven-membered ring derivative **8** would be far more favorable than the cyclization to a zwitterionic four-membered ring derivative **7**.

Thus, the energy of the proposed intermediate **7** (without solvent and entropy effects, in the gas phase!) is too high to be reached at room temperature, especially when we consider that there will be an additional activation energy (*cf. Figs. 9* and *10*)!

To investigate whether the substitution pattern and the charge separation in the proline-derived oxazetidinium zwitterions are 'responsible' for the prohibitively high energy, we have calculated the energies, including activation barriers, for the reactions of $(CH_2)_4N{=}C(CH_3)_2^+$ with acetone and with cyclohexanone using various methods; the results are shown in *Figs. 9* and *10*. As can be seen from the reaction profiles, the 'primary-adduct' formation is exothermic (*ca.* −15 kcal/mol, with no barrier of activation); it is followed by a high-energy transition state, **TS**, to give the four-

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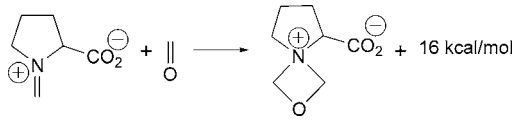
[26]) This is also true for a calculation ($Me_2C{=}O + (CH_2)_4N^+{=}CMe_2$), in which the BF_4^- counterion was included.

[27]) In the Supplementary Material of the paper by *McQuade* and co-workers [28], who have first proposed an oxazetidinium ion (**v** in *Fig. 7*), the result of a low-level DFT calculation (B3LYP with the inappropriate 3-21G basis set) was reported for the following isodesmic equation (copied from Supplementary Material of [28]):



The reaction of the proline-derived formaldehyde iminium carboxylate with formaldehyde is exothermic by this method! We have recalculated the energy of reaction for this process with the following methods and obtained values ranging from +8.3 to −9.8 kcal/mol: BP86/def2-TZVP: +7.4 kcal/mol, B3LYP/def2-TZVP: +8.3 kcal/mol, MP2/def2-QZVPP//BP86/def2-TZVP: −9.8 kcal/mol, BP86-D3/def2-TZVP: +1.7 kcal/mol. This is interesting because the MP2 value differs drastically from the BP86 and B3LYP values, indicating that there are appreciable long-range dispersion contributions of the interaction energy, which are overestimated by MP2, and totally missing in BP86 and B3LYP. Indeed, with added *Grimme*'s D3 dispersion correction the transformation becomes essentially thermoneutral.

[28]) Approximately 27 kcal/mol for **1** → (*E*)-**5a** plus 2.1 kcal/mol for (*E*)-**5a** + acetone → **7**.

[29]) The energies of structures **8** are *ca.* 30 kcal/mol lower than those of the iminium carboxylates **5**, which, in turn, are *ca.* 20–27 kcal/mol higher in energy than those of the oxazolidinones.

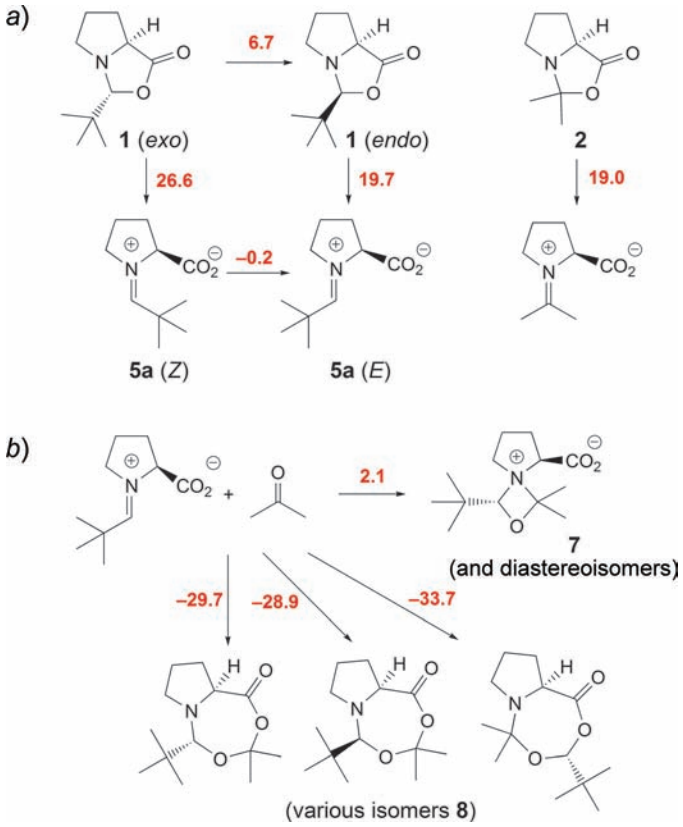


Fig. 8. *Calculated energy differences* [kcal/mol] (gas phase), a) *for the proline-derived oxazolidinones* **1** *and* **2**, *and for the iminium carboxylates* **5a**; b) *for the oxazetidinium ions* **7** *and 1-aza-3,5-dioxabicyclo[5.3.0]decan-6-ones of type* **8**. Method for the neutral species: M06-2X/6-311 + G(d,p)// B3LYP/6-31G(d); method for the zwitterionic species: M06-2X/6-311 + G(d,p)//B3LYP/6-31 + G(d). Inclusion of a DMSO solvent effect lowers the relative energies of zwitterionic species with respect to the bicyclic precursors by 12 – 19 kcal/mol (see *Supplementary Material* and compare with the experimental results alluded to in *Footnotes 11* and *12*, above).

membered ring intermediates of type **7**, which are almost equi-energetic with the separated reactants. The stable structures for the system shown in *Fig. 9* have been fully re-optimized with MP2/def2-QZVPP (no core shells frozen), which confirmed the qualitative picture[30]). However, the optimized educt complex is then by – 15.5 kcal/mol more stable than the separated educts (this is a – 0.3 kcal/mol more exothermic value than the one obtained with MP2/6-311 + G(d,p)). The four-membered ring structure is even more stabilized, namely by – 2.9 kcal/mol with the better-basis-set

[30]) For these calculations we used the *Turbomole* 6.4 suite of programs as described in the *Exper. Part*; computational details are also described in our previous paper [15e] (Sect. 2.1.5.3, Computational methodology, p. 817/818).

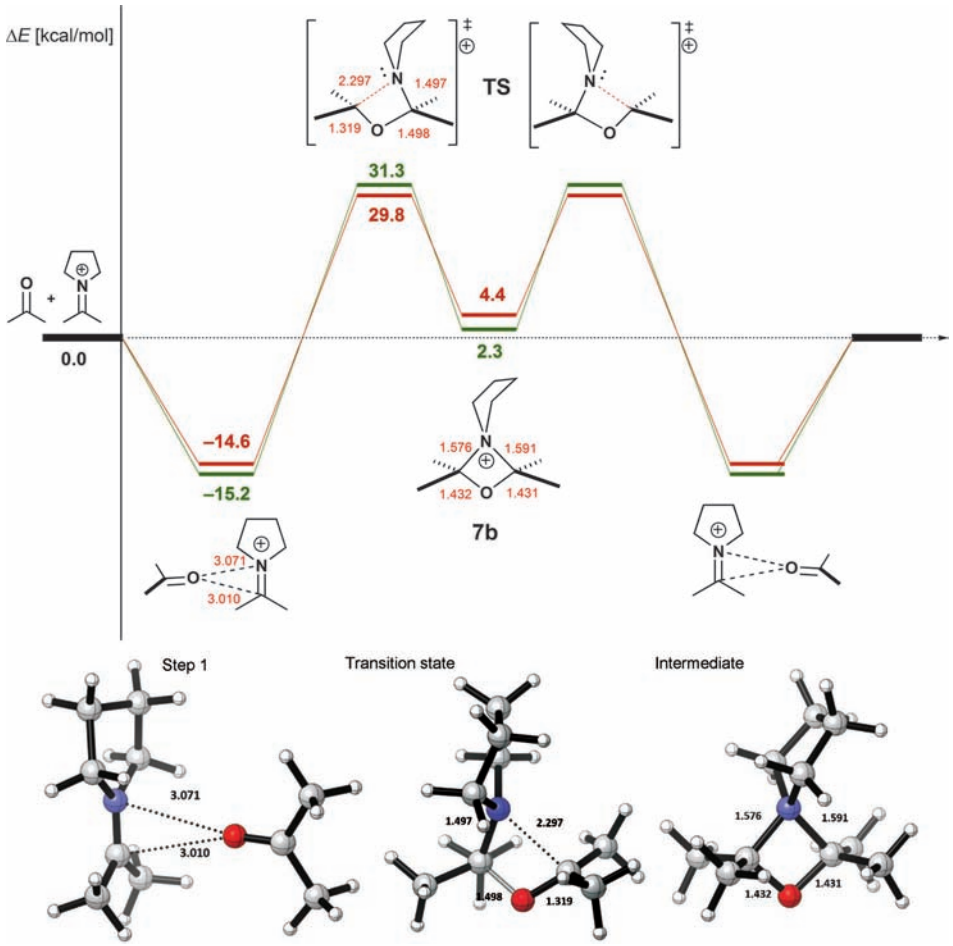


Fig. 9. *Relative energies* [kcal/mol], *obtained with the M06-2X/6-311 + G(d,p)//B3LYP/6-31 + G(d) method* (red) *and with the MP2/6-311 + G(d,p)//B3LYP/6-31 + G(d) method* (green), *for the primary adduct species formed from acetone and isopropylidene-pyrrolidinium ion and for the corresponding spiro-oxazetidinium ion* **7b**, *as well as for the transition state leading to* **7b**. The small numbers in red next to bonds and dotted interaction lines are distances in Å.

MP2/def2-QZVPP calculation when compared to the MP2/6-311 + G(d,p) result. Hence, MP2 puts the four-ring intermediate − 0.6 kcal/mol lower than the two separated educt structures, which is to be compared to the + 4.4 kcal/mol obtained with the M06-2X functional. We consider the MP2/def2-QZVPP results most reliable, although MP2 is known to overestimate dispersion effects[27]). In MP2 and M06-2X calculations, both oxazetidinium ions have nearly the same energy (− 0.6 to 4.4 kcal/mol) as the starting materials (ketone + iminium ion); still, the energies of the transition states leading from the primary adducts to the oxazetidinium ions of type **7** are very high (*ca.* 40 – 45 kcal/mol). Thus, from the point of view of stability these four-

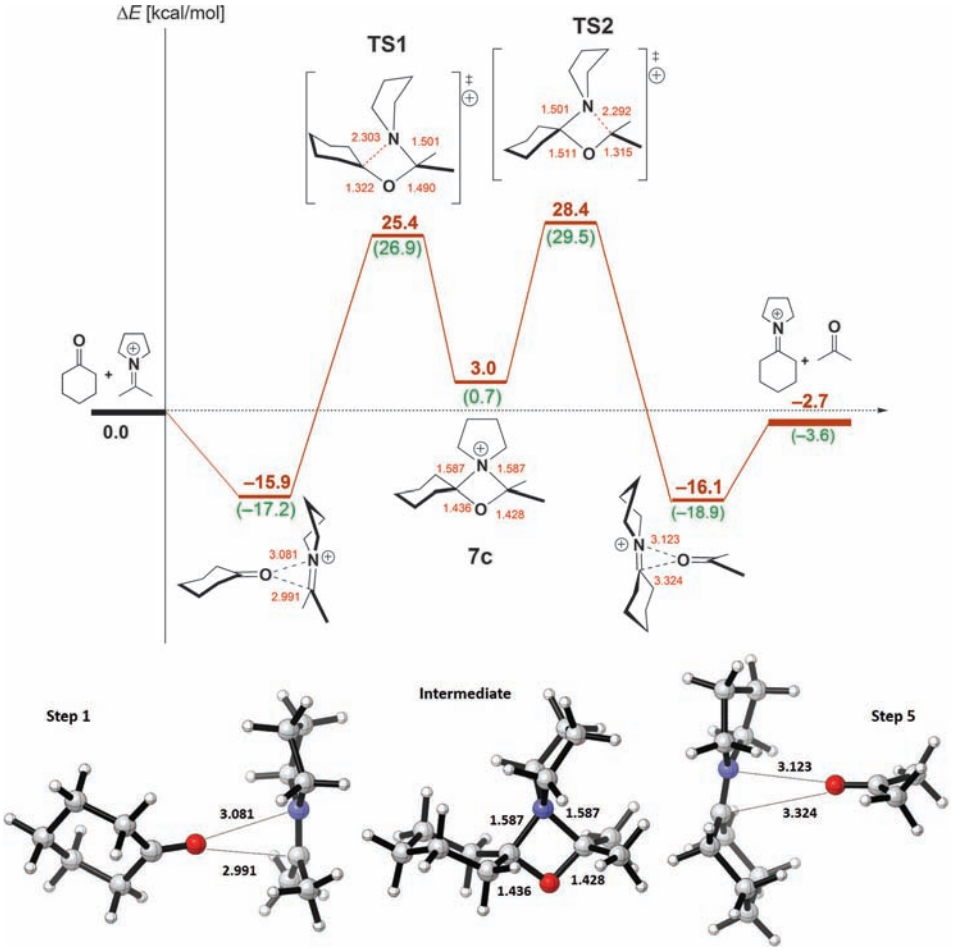


Fig. 10. *Relative energies* [kcal/mol] *of the species and transition states involved in the forward and backward reaction cyclohexanone + isopropylidene-pyrrolidinium ion* vs. *acetone + cyclohexylidene-pyrrolidinium ion, obtained with the M06-2X/6-311 + G(d,p)//B3LYP/6-31 + G(d) method.* The green numbers in parentheses are the results of calculations with the MP2/6-311 + G(d,p)//B3LYP/6-31 + G(d) method. With the latter, the oxazetidinium ion **7c** is predicted to have essentially the same total energy as the starting material(s). The small numbers in red next to bonds and dotted interaction lines are distances in Å.

membered ring derivatives are accessible, but the activation barriers leading to them are too high for a conversion to take place at room temperature (in the gas phase!). The 'primary adducts' have very 'loose' structures, with O–N and O–C distances of 3.0 to 3.1 Å, respectively, while the geometries of the transition states **TS** (*Fig. 9*), **TS1**, and **TS2** (*Fig. 10*) somewhat resemble the amino-oxenium ion conformation proposed in *Schemes 2, c*, and *3, b*, with three of the four interatomic distances N–C–O–C in the bonding range (1.3 – 1.5 Å), and the fourth N–C-distance being much larger (2.3 Å) (see *Figs. 9* and *10*).

To understand to which extent the substituents in the systems presented in *Figs. 9* and *10* affect the relative energies, we have also calculated the unsubstituted parent system $H_2C{=}O + H_2C{=}NH_2^+$. The results are compiled in *Fig. 11*. We note that the encounter complex of the two reactants is exothermic by *ca.* −15 kcal/mol. The scatter of the different electronic-structure methods is with −1.4 kcal/mol negligible (note, however, that this will be different for derivatives with large substituents, as dispersion interactions then play a more important role). We might consider this excellent agreement to be due to the mostly electrostatic interactions in the encounter complex, which are well described by all methods employed. This situation changes when we investigate the four-membered ring. While all methods still predict this product to be exothermic, we note remarkable differences. First of all, the B3LYP result indicates a basically thermoneutral reaction, while all other approaches assign a reaction energy of at least −4.6 kcal/mol. We may consider the −6.3 kcal/mol result of CCSD(T) as a reference and note that MP2 slightly overstabilizes the product with −8.3 kcal/mol, while DFT underestimates this value.

It is interesting to note that the primary adduct complex shown in *Fig. 11* has an arrangement very close to what is proposed in *Scheme 3* for the approach trajectory in terms of the rules of stereoelectronic effects and the *Bürgi–Dunitz* trajectory for nucleophilic additions to carbonyl and other electrophilic C=X groups [30]. The difference is that 1 in *Scheme 3* is a point on the reaction trajectory (*i.e.*, not an energy minimum), while the 'gas-phase' complex shown in the middle of *Fig. 11* is an energy

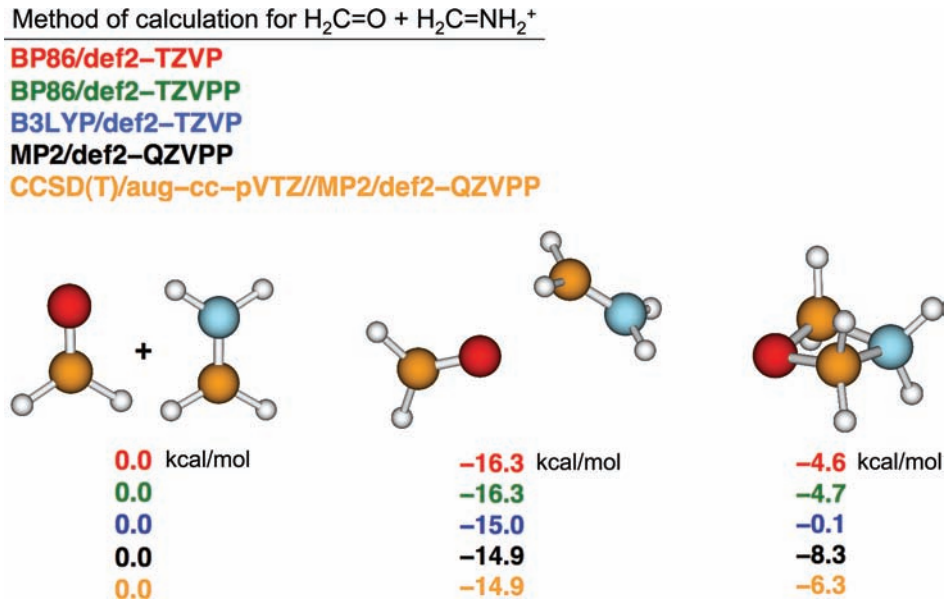


Fig. 11. *Results of quantum chemical calculations of the reaction of the smallest possible partners.* Formaldehyde and formaldehyde-iminium ion were combined to give a 'complex' and the unsubstituted oxazetidinium ion, using five different methods (including the 'gold standard' CCSD(T)) in the 'gas phase'. Apart from the CCSD(T) single-point calculation, all structures were optimized with the respective methods.

minimum. The corresponding primary-adduct complexes with substituents on the reactants (*Fig. 9* and *10*) have structures with *ca.* 3 Å O–N and O–C distances, like trajectories on the way to oxaziridine rings. These energy minima are obviously not classical chemical structures. In fact, not every minimum on the *Born–Oppenheimer* surface (which is what we optimized) represents a classical chemical structure. The neutral molecule (carbonyl component) and the cation (iminium ion) form an encounter complex[31]), which is likely to be the result of electrostatic multipole attractions in the gas phase.

6. Conclusions and Outlook. – Experiments have shown that, under the best conditions of moisture exclusion that we were able to achieve, there was interconversion between *in situ* formed or stoichiometrically employed iminium ions and carbonyl compounds. An organic-chemists' analysis provides mechanistic models for such an interconversion in the *absence* of H_2O or other possible catalysts such as traces of amines or acids (formed by hydrolysis of the iminium ions). A four-membered-ring intermediate (1,3-oxazetidinium ion of type **7**) and, alternatively, a (1,3)-sigmatropic shift through a four-membered ring transition state (**TS** in *Scheme 3*) have been proposed for such 'un-disturbed' interconversions. A literature search revealed that oxazetidines themselves are quite stable compounds and have been described many times[22]), so that a metathesis process involving an oxazetidinium ion as intermediate appeared reasonable. The speculative analysis on the basis of fundamental reactivities, of stereoelectronic effects, and of simple orbital-symmetry considerations of organic chemistry [12][30] was probed by quantum-chemical calculations on generic reactants as small as $H_2C{=}NH_2^+$ and $H_2C{=}O$. The conclusions of this theoretical investigation are *i*) that the oxazetidinium ions are stable species, comparable in energy with the separated educts, *ii*) that, in the gas phase, carbonyl compounds and iminium ions collapse without activation energy to form primary adducts of surprising structures, *iii*) that in the transition states between primary adduct complexes and four-membered rings the C,O bonds are more or less formed (< 1.5 Å), while the C,N bonds are not (*ca.* 2.5 Å), and *iv*) that the transition states leading to the oxazetidinium ions are prohibitively high in energy to be accessible at room temperature. In the calculations no amino-oxenium ion minima of type **6** were identified (*cf. Schemes 2* and *3*), and consequently no transition state for a 1,3-sigmatropic shift (as proposed in *Scheme 3*) was found.

There are four proposals for future experiments, which come to our minds: *a*) Our experiments may not have been carried out under *good-enough anhydrous* conditions and should be repeated by physical organic chemists, using perfect conditions of Ar- and vacuum-line techniques. *b*) Irradiation of an *anhydrous* solution containing a mixture of a carbonyl compound and an iminium salt could lead to an oxazetidinium ion in a formally 'allowed' photo $[2+2]$ cycloaddition. *c*) Gas-phase experiments, in which a jet of iminium ions is crossed by a jet of aldehyde or ketone molecules, with mass-spectrometric detection, might be the 'ultimate' investigation to detect an oxazetidinium ion that is formed in a 'thermal' process. *d*) Due to electrostatic multipole interactions, calculations involving free ions in the gas phase – without

[31]) Visit: http://goldbook.iupac.org/E02087.html

counterions and without solvation! – may be inherently problematic or misleading, and should be reconsidered with a shell of explicit solvent molecules and an appropriate counterion in first-principles molecular dynamics simulations, which was beyond the scope of this work.

We gratefully acknowledge discussions with *A. Eschenmoser*, full of insight into the chemists' analysis of the interconversions described herein.

Experimental Part

General. All reactions were performed under Ar in dried glassware using anh. solvents except when using aq. reagents. All chemicals were of reagent grade and used as supplied, unless stated otherwise. Extracts were dried over technical grade $MgSO_4$. Alumina from *Woelm* was used for drying NMR solvents. M.p.: *Büchi 510* melting point apparatus; uncorrected. Optical rotations: *Jasco P-2000 Polarimeter*. IR Spectra: as neat solid/oil on a *PerkinElmer Precisely Universal ATR Sampling Accessory*; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AVANCE* (at 300 and 75 MHz, resp.), *Bruker AVANCE III* (^{13}C at 150 MHz), *DRX* (at 400 and 101 MHz, resp.), and *AV* (at 400 and 101 MHz, resp.) or on a *Varian Gemini-300* (at 300 and 75 MHz, resp.) spectrometer chemical shifts (δ) in ppm relative to Me_4Si (0.00 ppm). High-resolution (HR) MS: performed by the MS service at the Laboratory for Organic Chemistry, ETH Zürich on a *IonSpecUltima 4.7-T-FT Ion Cyclotron Resonance* (ICR; HRMS-MALDI, in 2,5-dihydroxybenzoic acid matrix) spectrometer.

Preparation of ^{18}O-Labelled Cyclohexanone. To a soln. of TFA (2.02 ml, 26.4 mmol) in $H_2{}^{18}O$ (5.0 ml, 270 mmol, 97 atom-% ^{18}O) was added 1-(cyclohex-1-enyl)pyrrolidine (4.00 g, 26.4 mmol) in Et_2O (5 ml) at 0°, and the mixture was stirred for 30 min. The aq. layer was extracted with benzene, and the combined org. layers were dried ($MgSO_4$). The solvent was removed *in vacuo* and the obtained crude product was subjected to bulb-to-bulb distillation (45 mm Hg, 70–75°). Cyclohexanone (421 mg, 16%) was obtained as colorless liquid. The ratio of the ^{18}O incorporation was estimated by HR-MS (84% ^{18}O-labelled); in a second run the ^{18}O labeling was 70%. ^1H-NMR (400 MHz, $CDCl_3$): 1.70–1.76 (*m*, CH_2); 1.84–1.90 (*m*, 2 CH_2); 2.34 (*t*, $J = 6.7$, 2 CH_2CO). ^{13}C-NMR (100 MHz, $CDCl_3$): 25.0, 27.0, 42.0, 212.08 (C=^{18}O); 212.13 (C=^{16}O). HR-MS (EI): 100.0772 (100, $[M]^+$, $C_6H_{10}{}^{18}O^+$; calc. 100.0774); 98.0729 (19.5, $[M]^+$, $C_6H_{10}{}^{16}O^+$; calc. 98.0732).

Exchange Reaction between ^{t}Bu-Substituted Oxazolidinone **1** *and (^{18}O)-Cyclohexanone with Formation of the Cyclohexanone-Derived Oxazolidinone* **3** *and Pivalaldehyde* (see *Figs. 1* and *4*). Solns. of **1** [4][6][7d] (18.3 mg, 0.10 mmol) and (^{18}O)cyclohexanone (0.21 ml, 2.0 mmol) in deuterated solvents (0.75 ml (D_6)DMSO or (D_6)benzene (C_6D_6), dried with activated 4-Å mol. sieves) were prepared in oven-dried (150°) NMR tubes. This procedure was carried out outside or inside a glove box (Ar atmosphere ≤ 6 ppm H_2O). Alternatively, some H_2O-saturated (D_6)benzene (3.44×10^{-2} mmol/ml) was added. NMR Spectra were recorded after certain time intervals as shown in *Fig. 4* for a C_6D_6 solution.

Preparation of (S)-N-(Trimethylsilyl)proline Trimethylsilyl Ester. As described in [7], a vigorously stirred suspension of (*S*)-proline (3.50 g, 30.0 mmol) in diethyl(trimethylsilyl)amine (Et_2NSiMe_3; 13.3 ml, 70.0 mmol) was heated to 110° in a distillation apparatus (dried by heat gun at 1.2 mbar) for 2 h under N_2. As the reaction progressed, Et_2NH was distilled off from the mixture, which became homogeneous. After 2 h, the resulting soln. was allowed to cool to r.t. and the disilylated proline derivative was obtained by distillation (52–54°/0.15 mbar) as a colorless liquid (5.08 g, 65%). ^1H-NMR (300 MHz, $CDCl_3$): 0.04 (*s*, Me_3SiN); 0.25 (*s*, Me_3SiO); 1.62–2.06 (*m*, 2 CH_2); 2.98–3.11 (*m*, CH_2N); 3.82 (*dd*, $J = 8.4$, 3.2, $CHCO_2$). ^{13}C-NMR (75 MHz, $CDCl_3$): −0.87, −0.32, 25.8, 31.7, 47.0, 61.6, 177.5.

Preparation of the Oxazolidinone **4** *Derived from 4,4-Dimethylcyclohexanone* (see *Eqn. 9*). (*S*)-1-(trimethylsilyl)proline trimethylsilyl ester (2.59 g, 10.0 mmol) was dissolved in CH_2Cl_2 (20 ml) and the soln. was cooled to −20°. 4,4-Dimethylcyclohexanone (1.26 g, 10.0 mmol) was added to the soln., and the mixture was stirred for 18 h. Volatile materials were removed *in vacuo*, and the residue was dissolved in benzene. Insoluble materials were removed by filtration, and the solvent was evaporated under reduced pressure. Drying under h.v. yielded **4** (1.52 g), together with 4,4-dimethylcyclohexanone

(0.5 equiv.), as a pale-yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.64 (*s*, Me); 0.70 (*s*, Me); 1.01 – 1.83 (*m*, 12 H); 1.99 – 2.08 (*m*, 1 H, CH_2N); 2.30 – 2.35 (*m*, 1 H, CH_2N); 3.55 (*dd*, $J = 9.7$, 4.6, CHN).

Exchange Reaction between the Dimethylcyclohexanone-Derived Oxazolidinone **4** *and* (*^{18}O*)*Cyclohexanone* (see *Fig. 3*). In an oven-dried (150°) NMR tube, a soln. of **4** (7 mg; prepared as described above) and (^{18}O)cyclohexanone (5 mg) was prepared in C_6D_6 (0.75 ml; dried over activated 4-Å mol. sieves). The NMR spectrum of the resulting mixture was recorded after 24 h.

Preparation of Pyrrolidinium Perchlorate. As described in [8], to a soln. of pyrrolidine (8.16 ml, 0.100 mol) in Et_2O (50 ml) was added $HClO_4$ (70%, 15 ml) in EtOH (15 ml) at 0° over 10 min. After 20 min, the precipitated colorless solid was filtered and washed with Et_2O. Recrystallization (^{i}PrOH/Et_2O) gave the title compound (7.31 g, 43%). Colorless needles M.p. 240 – 243° (^{i}PrOH/Et_2O) ([8b]: M.p. 240 – 242°). IR: 3233*m*, 3151*m*, 1590*m*, 1461*m*, 1375*m*, 1043*s*, 911*m*, 874*m*, 823*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.07 – 2.12 (*m*, 2 CH_2); 3.47 (*t*, $J = 7.0$, 2 CH_2N).

Preparation of 1-Isopropylidenepyrrolidinium Perchlorate. As described in [8b], acetone (1.47 ml) and pyrrolidinium perchlorate (1.72 g, 10.0 mmol) were mixed in an *Erlenmeyer* flask. A drop of Et_3N was added to the resulting soln., whereupon crystals formed immediately, with evolution of heat. The crystals were washed with Et_2O and dried under h.v. 1-Isopropylidene pyrrolidinium perchlorate (1.96 g, 93%) was thus obtained. Colorless solid. Recrystallization gave needles of m.p. 231 – 233° (^{i}PrOH/Et_2O) ([8b]: M.p. 232 – 233°). IR: 2993*w*, 2964*w*, 1686*m*, 1441*m*, 1369*m*, 1066*s*, 922*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.22 – 2.27 (*m*, 2 CH_2); 2.54 – 2.55 (*m*, 2 Me); 3.96 – 4.03 (*m*, 2 CH_2N). Anal. calc. for $C_7H_{14}ClNO_4$ (211.64): C 39.73, H 6.67, N 6.62; found: C 39.44; H 6.38, N 6.63.

Preparation of 1-Cyclohexylidenepyrrolidinium Perchlorate (*cf. Fig. 6*). As described in [8b], cyclohexanone (1.93 ml, 18.7 mmol) was added to pyrrolidinium perchlorate (1.60 g, 9.33 mmol) in an *Erlenmeyer* flask. Dissolution was achieved by addition of EtOH (3 ml), and then a drop of Et_3N was added. Crystals were formed immediately with evolution of heat; they were washed with Et_2O and dried under h.v. 1-Cyclohexylidenepyrrolidinium perchlorate (2.21 g, 94%) was obtained. Colorless solid. Recrystallization gave needles of m.p. 238 – 240° (^{i}PrOH/Et_2O) ([8b]: M.p. 239 – 240°). IR: 2951*w*, 2871*w*, 1664*m*, 1438*w*, 1077*s*, 1067*s*, 854*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.66 – 1.74 (*m*, 2 CH_2); 1.90 – 1.98 (*m*, 2 CH_2); 2.19 – 2.24 (*m*, 2 CH_2); 2.80 (*t*, $J = 6.6$, 2 CH_2); 3.97 – 4.01 (*m*, 2 CH_2N); Anal. calc. for $C_{10}H_{18}ClNO_4$ (251.71): C 47.72, H 7.21, N 5.56; found: C 47.55, H 6.97, N 5.59.

Exchange Reaction between 1-Isopropylidenepyrrolidinium Perchlorate and Cyclohexanone (see *Fig. 5*). A soln. of the acetone-derived iminium salt (5.0 mg, 0.024 mmol) and cyclohexanone (61 µl, 0.591 mmol) in $CDCl_3$ (0.75 ml, treated with basic Al_2O_3, Act. I) was prepared in an oven-dried (150°) NMR tube inside or outside a glove box (Ar atmosphere, ≤ 6 ppm H_2O). Alternatively, some H_2O-saturated $CDCl_3$ (25 µl, containing *ca.* 4.5 equiv. of H_2O) was added. NMR Spectra were recorded after certain time periods as shown in *Fig. 5*.

Reaction between Pyrrolidinium Perchlorate and Cyclohexanone (see *Fig. 6*). $CDCl_3$ (0.75 ml; treated with basic Al_2O_3, Act. I) and cyclohexanone (9.8 mg, 0.10 mmol) were added to the ammonium salt (17.2 mg, 0.10 mmol) in an oven-dried (150°) vial. There was no complete dissolution; the supernatant white suspension was filtered and transferred into an oven-dried (150°) NMR tube. The molar ratio of ammonium salt to cyclohexanone (*ca.* 1 : 4), given as mixing ratio in *Fig. 6*, was determined by the NMR integration. NMR Spectra were then recorded after certain time periods.

Description of the Calculations. The geometries were optimized with Gaussian 09 [31] with B3LYP/6-31G(d) or, for zwitterions, B3LYP/6-31 + G(d,p), in the gas phase. All equilibrium geometries (local minima on the *Born–Oppenheimer* surface) were characterized by real frequencies only and all transition states by one imaginary frequency. The total energies were then computed by single-point calculations with M06-2X and MP2. For uncharged species, the differences of using diffuse functions or not in the search for equilibrium geometries, *i.e.*, the differences between MP2/6-311 + G(d,p)//B3LYP/6-31G(d) and MP2/6-311 + G(d,p)//B3LYP/6-31 + G(d) total energies, were insignificant in practice (of the order of 0.1 – 0.4 kcal/mol); for the charged species, the differences (*ca.* 2 – 3 kcal/mol) became only significant (12 – 20 kcal/mol) when the effect of polar solvents was included. The point is to locate B3LYP equilibrium geometries and transition states as quickly as possible. The effect of solvation (mainly in DMSO, but also in some cases in H_2O) was calculated with the SMD procedure (universal solvation model based on solute electron density) [32].

Structure optimizations with *Ahlrichs*-type TZVP, TZVPP, and QZVPP basis sets [33] were carried out with the *Turbomole* program (version 6.4) [34]. The electronic-structure models applied were DFT (with the B3LYP [35] and BP86 [36] density functionals) and MP2. To speed up the BP86 and MP2 calculations, the resolution of the identity approximation was invoked with the corresponding auxiliary basis sets as implemented in *Turbomole*.

The coupled-cluster single-point calculations with *Dunning* aug-cc-pVTZ basis sets [37] were performed with the MOLPRO program (version 2010.1) [38].

All energy differences refer to electronic energies. Thus, zero-point vibrational energy differences, as well as enthalpic and entropic effects have not been considered. It can be expected that these corrections will not change the overall picture of all reaction steps that feature the same number of reactants on both sides of the reaction arrow. For association or dissociation reactions, however, the entropic effect can be 10 kcal/mol per excess molecule on one side of the reaction arrow due to the translational contribution to the entropy difference that is either annihilated or created in an association or dissociation reaction, respectively (see, *e.g.*, [39]). While this entropy effect is present in gas-phase reactions, we do not need to take it into account here, as our focus is on the condensed phase (although all calculations have been carried out for isolated species).

Thermal and entropic corrections to obtain relative ΔG° values were, thus, not evaluated. According to our experience, the changes are minimal (favoring open forms, of course, but by less than 3 kcal/mol).

For computational details and for additional calculations about alternative mechanisms of the interconversions, see the *Supplementary Material* (http://onlinelibrary.wiley.com/doi/10.1002/hlca.201400221/suppinfo).

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