5-Benzyl-3-methylimidazolidin-4-one-Derived Reactive Intermediates of Organocatalysis – A Comforting Resemblance of X-Ray, NMR, and DFT Solid-Phase, Liquid-Phase, and Gas-Phase Structures

by **Uroš Grošelj**[1]), **W. Bernd Schweizer**, **Marc-Olivier Ebert**, and **Dieter Seebach***

Laboratorium für Organische Chemie, Departement für Chemie und Angewandte Biowissenschaften, ETH-Zürich, Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich
(phone: +41-44-632-2990; fax: +41-44-632-1144; e-mail: seebach@org.chem.ethz.ch)

The X-ray crystal structures of three (*E*)-1-cinnamoylidene iminium PF_6 salts of 5-benzyl-3-methylimidazolidin-4-ones (2,2-dimethyl-, *cis*-2-(*tert*-butyl)-, and *cis*-2-styryl-substituted; **2–4**, resp.) are reported (*Figs. 3–5*). In the 2,2-dimethyl and in the *cis*-2-styryl derivative, **2** and **4**, respectively, a C−H bond of the *cis*-substituent in 2-position points to the center of the benzene ring of the benzyl group above the five-membered ring (*Fig. 6,a* and *b*). NMR Measurements (*Fig. 8*) provide evidence that the same structure is present in solution, and that a fourth derivative of this type, **5** (*Scheme*), has (*Z*)-instead of (*E*)-configuration around the C=N bond. In the *cis*-2-(*tert*-butyl) derivative **3**, the benzyl group is located over the iminium π-system (*Figs. 4* and *6,c*). Overlays with DFT-calculated crotonylidene analogs, **A** and **B**, show that the theoretical and experimental structures are almost superimposable (*Fig. 9* and *Table*). The structures are discussed in view of their role as reactive intermediates in organocatalysis and in view of the help synthetic organic chemists may experience from theory.

In previous publications, we have described the isolation and structural characterization of enamines and iminium salts derived from proline, diphenyl-prolinol, and imidazolidinones, which are reactive intermediates[2]) of organocatalysis [1][2]. In the meantime, the number of species, of which we were able to obtain single crystals for X-ray structure determinations, has increased (*Fig. 1*). This is mainly due to the switch from BF_4 to PF_6 salts, which have much higher melting points and are easier to recrystallize.

At this stage, we would like to briefly discuss only the structures of 5-benzylimidazolidinone derivatives **1–5**. The cinnamoyliden-imidazolidinium salts **2** and **3** were prepared (*Scheme*) by mixing the parent PF_6-ammonium salts[3]) **1a** or **1b**

---

2) We do not use common terms 'enamine catalysis' and 'iminium catalysis', because neither the enamine nor the iminium ion is a catalyst. The catalyst is the chiral *sec*-amine (*cf.* proline, diaryl-prolinol, an imidazolidinone).

3) These, in turn, are prepared in Et_2O at 0° by adding a solution of the parent amine to a solution of HPF_6, which leads to precipitation of the salts **1**.
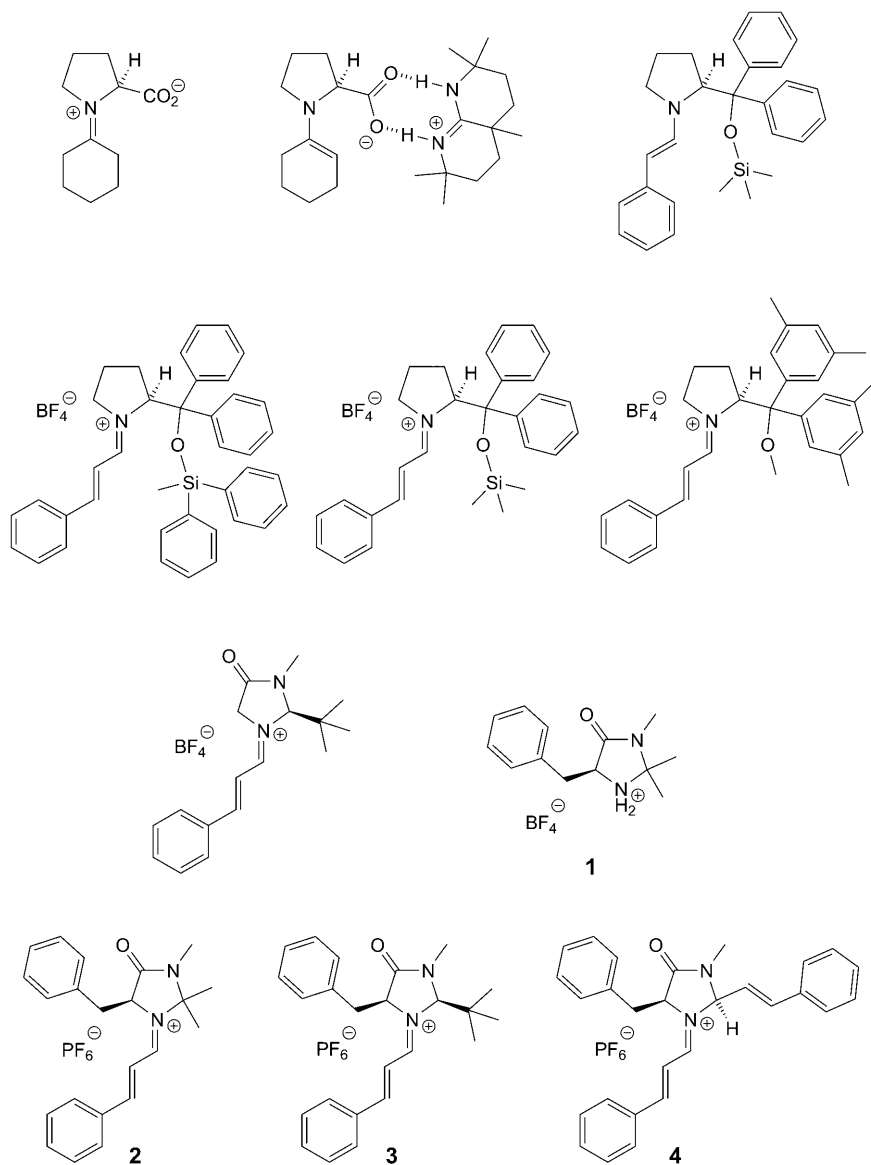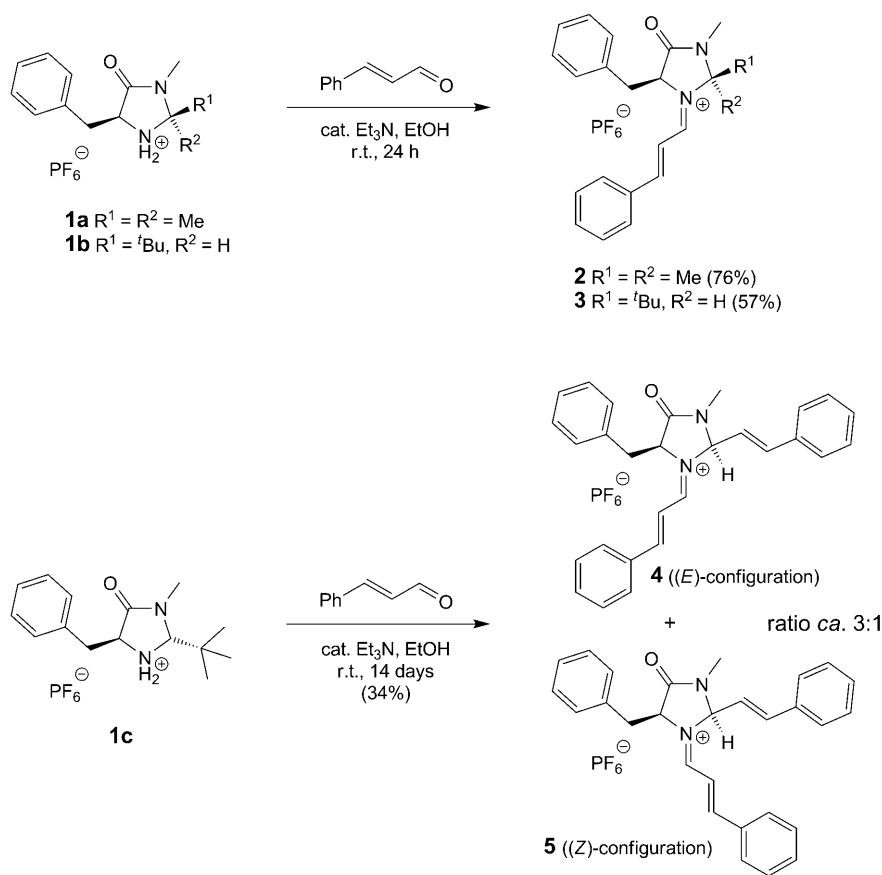
Fig. 1. *Molecular formulae of reactive intermediates in organocatalysis with proline, diaryl-prolinol ethers, and imidazolidinones, of which we have obtained structural data* (NMR and/or X-Ray). Compounds **1** – **4** are discussed herein.

with cinnamaldehyde (1 : 1) in EtOH in the presence of *ca.* 3.5 mol-% Et₃N and stirring at room temperature, until a filterable solid is formed. The (*E*)- and (*Z*)-isomers **4** and **5**, respectively, of the *cis*-5-benzyl-2-styryl-imidazolidinium salt were obtained, when

Scheme. *Preparation of the Iminium Salts* **2**–**5** *from Cinnamaldehyde and the Ammonium Salts* **1**. The (*E*)- and (*Z*)-isomers, **4** and **5**, respectively, were not separated, but recrystallized together.

1a $R^1 = R^2 = Me$
1b $R^1 = {}^tBu$, $R^2 = H$

2 $R^1 = R^2 = Me$ (76%)
3 $R^1 = {}^tBu$, $R^2 = H$ (57%)

1c

cat. Et₃N, EtOH
r.t., 14 days
(34%)

4 ((*E*)-configuration)

+   ratio *ca.* 3:1

5 ((*Z*)-configuration)

the *trans*-5-benzyl-2-(*tert*-butyl)-3-methyl-imidazolidinium salt[4]) **1c** was treated with cinnamaldehyde in the same way, for a prolonged period of time. Interestingly, under the same conditions in CD₃OD, the *cis*-isomer of **1c** led to traces only of this aminal derivative[5][6]). Crystals of **2**–**4** suitable for X-ray structure determination were

---

4) For a preparation of the hydrochloride, see [3].

5) This is in agreement with the fact that *cis*-imidazolidinone derivatives of this type are more stable than the *trans*-isomers; see the discussion in [2][4].

6) This surprising finding may suggest that, during organocatalytic use of imidazolidinones, especially those of *trans*-configuration [5], 'new catalysts' might be formed *in situ*. In the absence of the two Me groups or of the *t*-Bu group in the 2-position of the imidazolidinone ring (*cf.* **2** and **3**), the iminium ions of (*E*)- and (*Z*)-configuration may have comparable stability. This could lead to erosion of stereoselectivity in the attack of nucleophiles from the diastereotopic faces of the enoyl-iminium π-system (*cf.* **4** and **5**). With the *t*-Bu group in the 2-position, (*E*)-configuration of the iminium double bond is assured (the small substituent, *i.e.*, H, on the iminium C-atom is *syn* to the *t*-Bu group; *cf.* **3** and the BMI derivative [2] in *Fig. 1* and *Table*). Likewise, in 1-acyl-2-*tert*-butylimidazolidinones, the (smaller) C=O O-atom is *syn* to the *t*-Bu group in essentially all known structures (see discussion in [2] and [4]).

prepared by recrystallization (diffusion technique using Et$_2$O or petroleum ether (b.p. 30 – 50°) evaporating and condensing into CH$_2$Cl$_2$/heptane solutions of the iminium salts). From the mixture of crystals of the (*E*)- and (*Z*)-isomers **4** and **5**, respectively, we happened to pick a crystal of **4** for the X-ray analysis.

The crystal structures of the salts **1 – 4** are shown in *Figs. 2 – 5*. The 'parent' BF$_4$-ammonium salt of **1a** has a very similar structure as the corresponding chloride [6], with the Ph ring of the benzyl group pointing away from the heterocyclic ring (*Fig. 2*). This is in contrast to the position of the Ph rings in the iminium salts **2** and **4**, where the conformation around the exocyclic, benzylic ethane bond is such that the Ph ring resides over the five-membered ring, facing the *cis*-Me group and the vinylic H-atom of the *cis*-styryl group, respectively. As can be seen from the presentations in *Fig. 6,a* and *b*, in both structures the CH H-atoms point to the center of the Ph ring with distances to the C-atoms of the Ph groups, which are close to the sum of *Van-der-Waals* radii. Not surprisingly, in the 2-(*tert*-butyl) derivative **3**, the benzyl group has swung away and around to sit above the plane of the (*Z*)-enoyl-iminium π-system. The angle between the two π-planes is *ca.* 42°, and the close nonbonding C⋯C distance is 3.25 Å (*Fig. 6,c*). A nice demonstration is given in the overlays of *Fig. 7*, of how the benzyl group moves when we go from the imidazolidinone precursor **1a** to the benzyl-dimethyl-iminium salt **2** (from the front to the back and upwards, with flattening of the ring), and from there to the benzyl-(*tert*-butyl)-iminium salt **3** (back to the front, with essentially no change of the ring conformation).

Selected chemical shifts from the ¹H-NMR spectra of salts **1 – 5** are shown in *Fig. 8*. As noted previously for the BF$_4$ salts [2], the two diastereotopic Me groups in the precursor **1a** have almost the same chemical shift (*ca.* 1.6 ppm), while one of the Me groups in the corresponding iminium salt **2** gives rise to a signal at 0.75 ppm, compatible with a shielding by a benzene ring[7]). On the other hand, the vinylic H-atom, H²′, in the
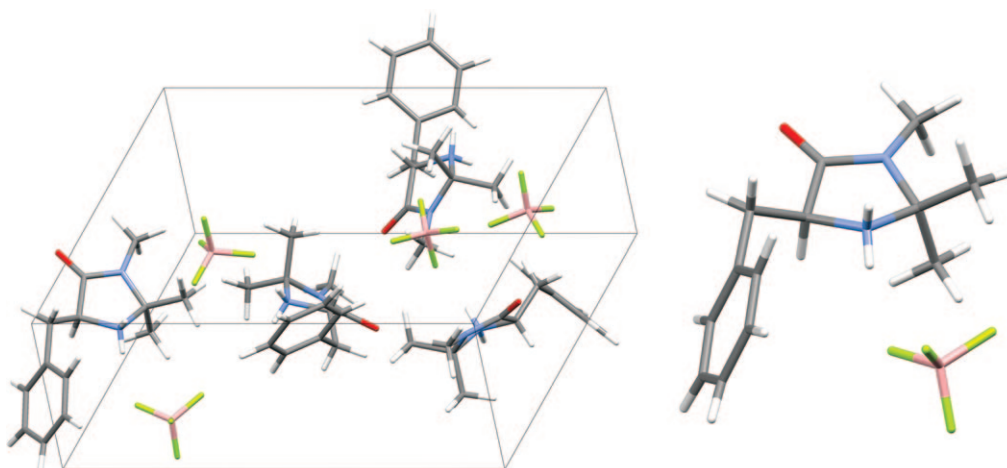

Fig. 2. *Unit cell of the crystal structure of ammonium salt* **1** *and selected view of the molecule*

---

[7]) In the salt **2** (BF$_4$ instead of PF$_6$), we have seen weak NOEs between the high-field Me H-atoms and the *ortho*-H-atoms of the benzylic Ph group [2].
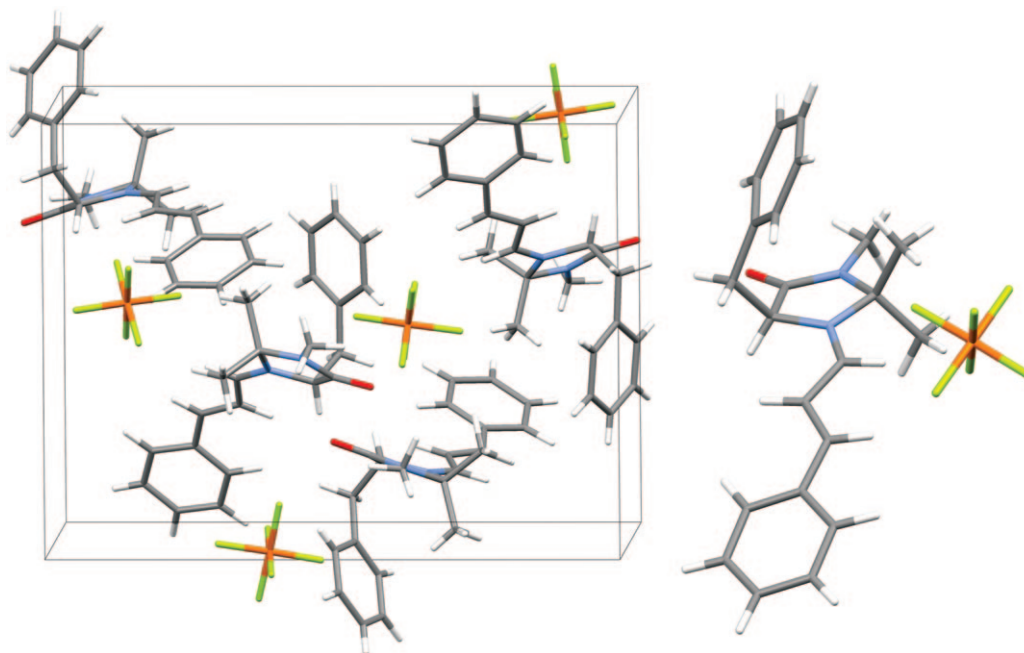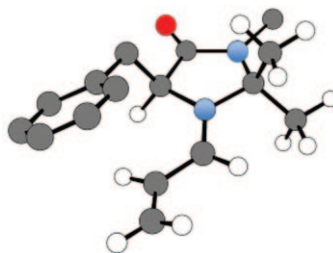
Fig. 3. *Unit cell of the crystal structure of iminium salt **2** and view of the iminium π-system of the molecule*

benzyl-(*tert*-butyl)-substituted iminium salt **3** experiences a shielding effect (1.1 – 1.4 ppm), as compared to H$^{2'}$ in the other three iminium salts. Finally, the vinylic H-atoms, H$^{1''}$, in the styryl-substituted iminium salts **4** and **5** give rise to signals at high field (*ca.* 4.3 ppm), which must, again, be caused by shielding from the Ph ring of the benzyl group. The conclusion from these NMR data is that the conformations observed in the crystal structures (*cf.* especially *Fig. 6*) must also be present or at least partially populated in solution.

We are now in a position to compare two closely related pairs of DFT-calculated[8]) and X-ray-determined structures of imidazolidinone-derived iminium ions (*Fig. 9* and *Table*). *Houk* and co-workers have calculated the structures of the iminium ions **A** and

---

⁸)   MM3 Calculations do not 'find' the conformation with the benzylic Ph ring in close proximity to the *cis*-Me group in iminium ions derived from 5-benzyl-2,2,3-trimethylimidazolidinone; rather, the Ph group winds up above the iminium π-system at this level of theory [8] (picture adopted from [8b]).
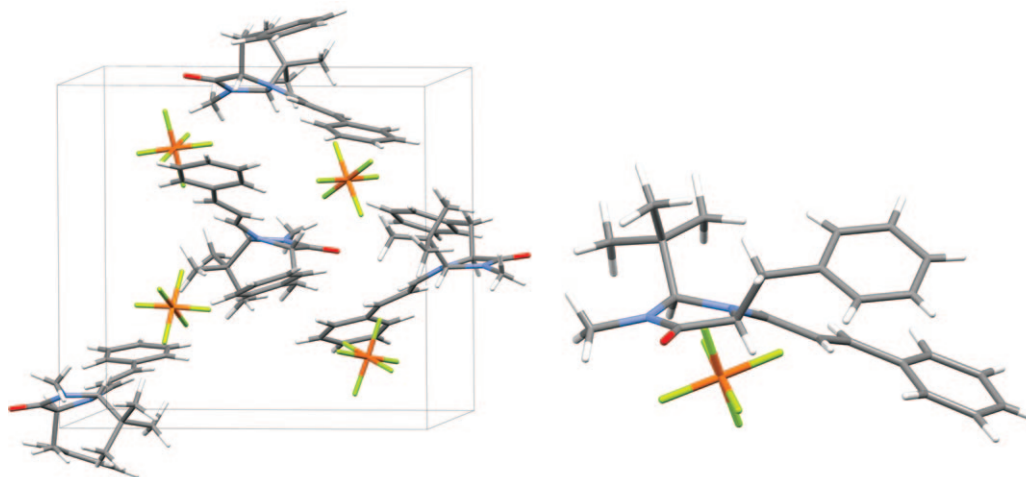
Fig. 4. *Unit cell of the crystal structure of iminium salt* **3** *and view along the plane of the iminium π-system with the benzyl group on top.* The *t*-Bu group is disordered over two positions in the crystal. For clarity, only the 70% populated position is shown.
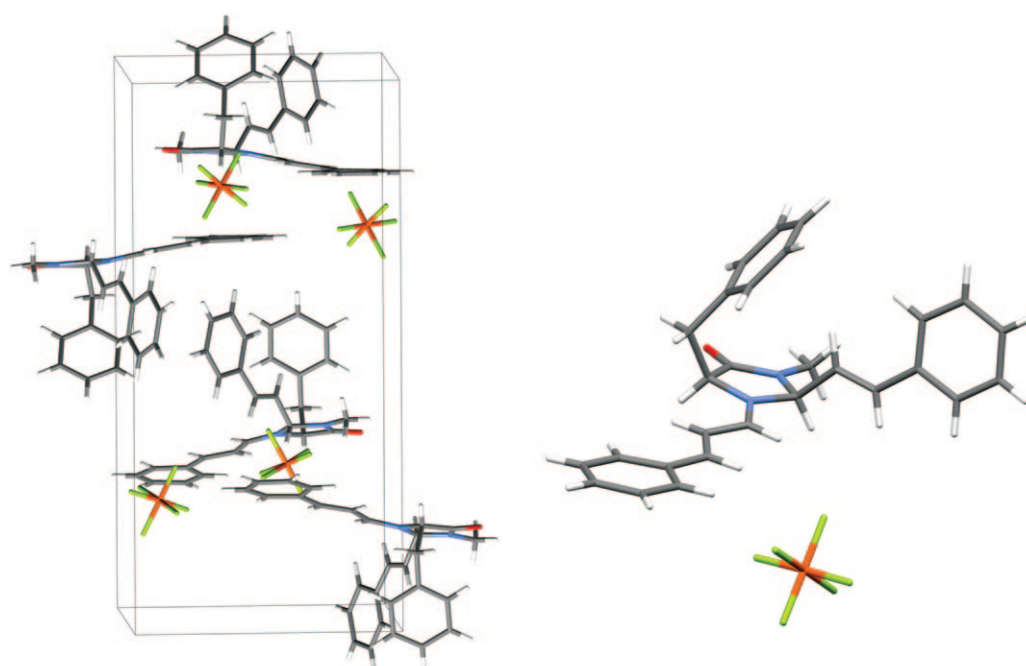

Fig. 5. *Unit cell of the crystal structure of iminium salt* **4** *and selected view of the molecule*

B derived from crotonaldehyde [9]. In both the gas phase and the aqueous solution, the most stable theoretical structure of the ions with 5-benzyl-2,2-dimethyl substitution has
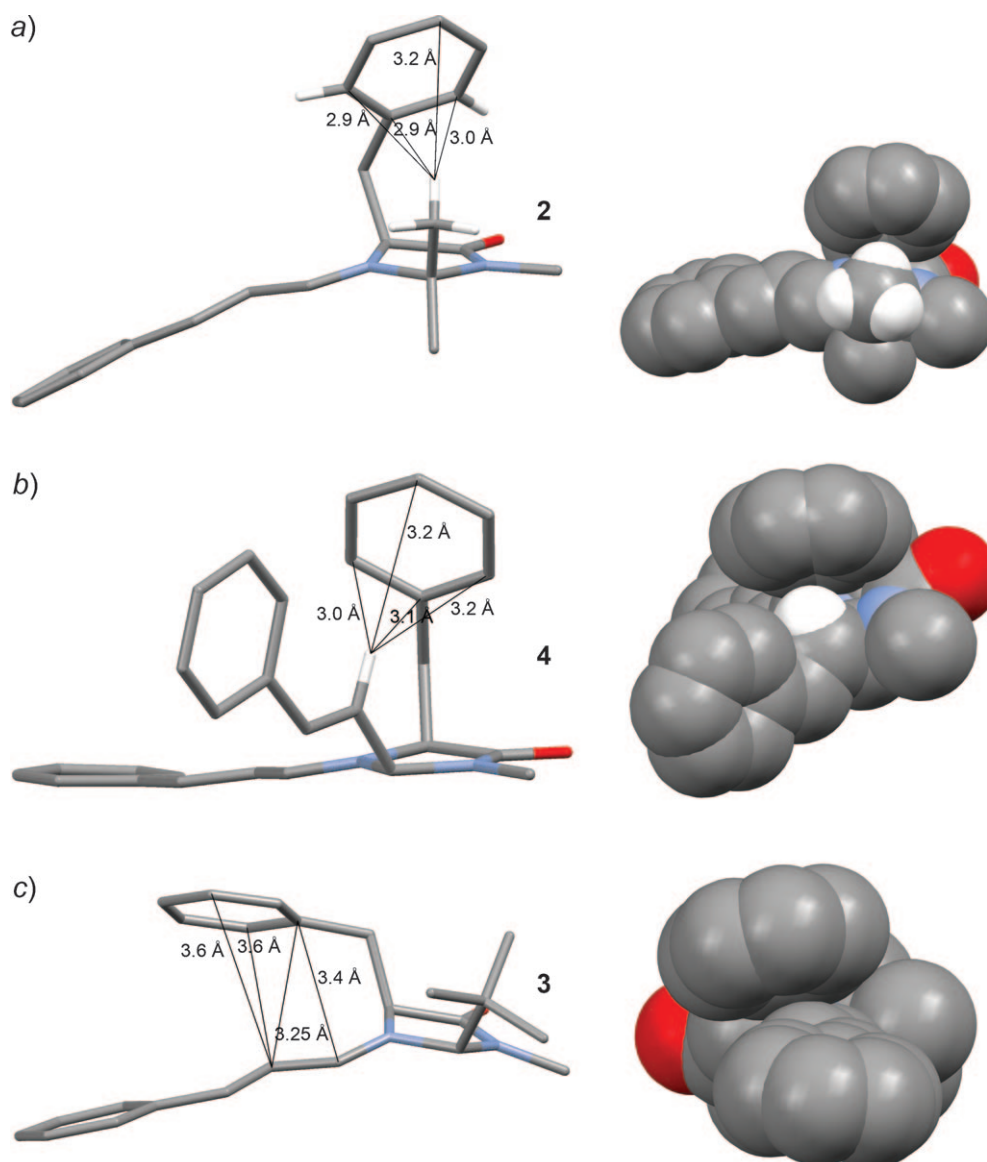
Fig. 6. *Stick and spacefill models of the iminium ions* **2 – 4** *in the crystalline state.* Closest distances between nonbonding C- and H-atoms are indicated. Note that the *Van-der-Waals* radius of H-atom is *ca.* 1.2 Å, and the 'half-thickness' of a benzene ring and of a π-system in general is *ca.* 1.7 Å.

a H-atom of the *cis*-Me group pointing to the center of the Ph ring. In the calculated structure of the *cis*-5-benzyl-2-(*tert*-butyl)-substituted ion, the Ph group is above the enoyl-imino system. The overlays in *Fig. 9*, and the values for pyramidality and torsion angles around the C=N bonds in the *Table* reveal a striking resemblance between X-
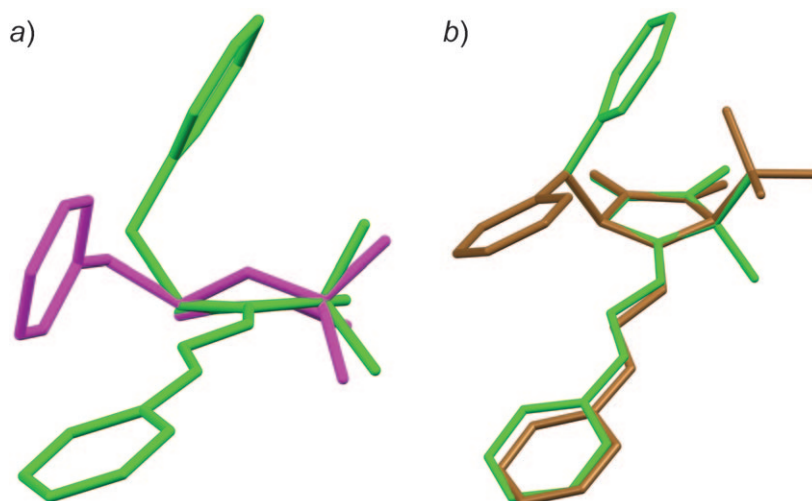
Fig. 7. *Overlays showing the conformational changes of the exocyclic, benzylic ethane bond and of the imidazolidinone ring upon iminium-ion formation* (*a*) *and upon replacement of the geminal Me groups by* t-*Bu/H* (*b*). Color code: **1a**, magenta; **2**, green; **3**, brown. *a*) The upward movement of the substituents in 2- and 5-position, out of the ring plane and with pyramidalization on N(1), upon iminium formation (*i.e.*, **1a → 2**) is analogous to the same change observed upon *N*-acylation of imidazolidinones (a consequence of 1,5-repulsion) [2][4]. *b*) The only larger change occurring upon introduction of the *cis-t*-Bu group and replacement of *trans*-Me by H (*i.e.*, **2 → 3**) is a 120° rotation around the exocyclic ethane bond, which places the benzylic Ph group over the iminium π-system.

ray-determined and DFT-calculated structures, with which our NMR measurements are also compatible.

In conclusion, two imidazolidinone-derived cinnamoylidene iminium salts, **2** and **4**, with 5-benzyl-2,2-dimethyl and *cis*-5-benzyl-2-styryl substitution have a conformation around the exocyclic, benzylic ethane bond such that a H-atom on the group in 2-position points to the center of the Ph ring. This conformation is present in the crystalline state (X-ray) and in solution (NMR), and it is found to be the most stable structure in the gas phase of the crotonylidene analog **A** (high-level DFT calculation [9]). Thus, it is not caused by crystal-packing forces or by counterion effects. To the practicing organic chemist, dealing, for instance, with organocatalysis, this conformation **C** is counter-intuitive. Rather, we would tend to expect a conformation **D**, with the benzylic phenyl group over the conjugated iminium π-system[7]). This latter conformation is present in the crystal structure (and it is the most stable one by the DFT theoretical calculation for the crotonylidene analog **B**) of the *cis*-5-benzyl-2-(*tert*-butyl)-substituted iminium ion **D′**[9]). A third possible staggered conformation **E**, we

---

[9])   Generally and not surprisingly, the organocatalysis with **D′** as the reactive intermediate ('second-generation imidazolidinone catalysis') gives rise to higher stereoselectivities than with the benzyl-dimethyl-substituted analogue ('first-generation imidazolidinone catalysis') [10]. In other cases, *cf.* the α-halogenation of aldehydes through imidazolidinone-derived enamines as reactive intermediates, it may be the other way around [11].
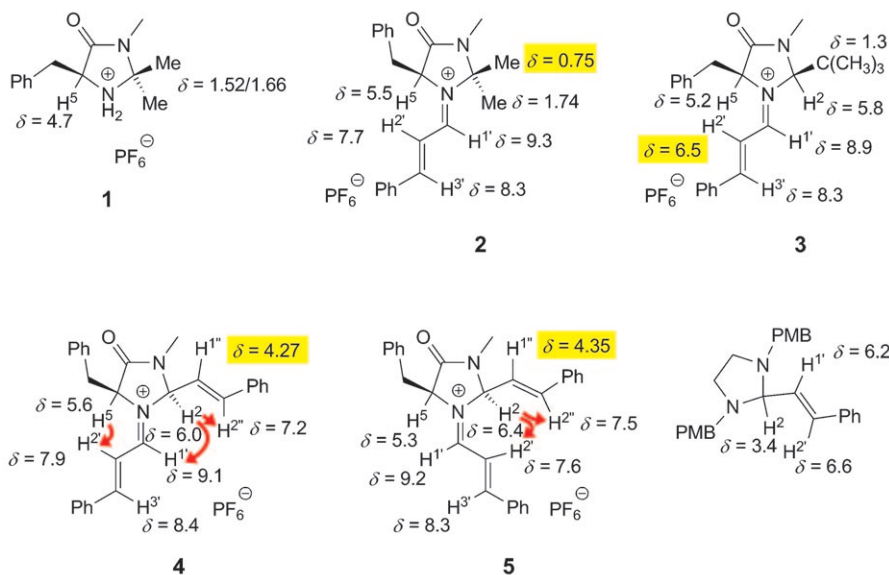
Fig. 8. *Characteristic NMR data of the PF$_6$ salts* **1a** *and* **2**–**5**, *and of a cinnamaldehyde aminal* [7] (for comparison). The chemical shifts δ are given in [ppm]. PMB = *para*-methoxybenzyl. The chemical shifts of the BF$_4$ salts (see [2]) differ from those shown here by 0.1–0.2 ppm. The NMR spectra of compounds **1a** and **2** were recorded in (D$_6$)DMSO, of compounds **3**–**5** in (D$_6$)acetone, and of the animal in CDCl$_3$. The chemical-shift values marked by a yellow background indicate shielding (upfield shift) by the benzene ring of the benzyl group. The spectra of the (*E*)- and (*Z*)-isomers **4** and **5**, respectively, as a mixture, are very similar. The configurational assignment is derived from steady-state NOE difference experiments; **4**: NOE enhancement at H$^{2''}$ and H$^{1'}$ upon saturation of H^2, as well as NOE enhancement at H$^{2'}$ upon saturation of H^5; **5**: NOE enhancement at H$^{2''}$ and H^2 upon saturation of H^2 (see the red arrows in the formulae of **4** and **5**).

would expect to be destabilized by 1,5-repulsion [2][12] (*i.e.*, $A^{1,3}$ strain [13]) between the Ph group and the C=O O-atom. In comparing conformations **C** and **D**, it is tempting to invoke the so-called 'CH/π interaction' in **C** *vs.* the so-called 'π–π stacking interaction' in **D**. Since these interactions are still controversial among physical and theoretical chemists[10]), we refrain from using those terms; the net force is the sum of all *intra*molecular forces: *Coulomb* attractions and repulsions, polarizations, *Van-der-*

---

[10]) As is evident from the titles of some leading references: '*Attractions and Repulsions in Molecular Crystals: What Can Be Learned from the Crystal Structures of Condensed Ring Aromatic Hydrocarbons?*' [14]; '*Hydrogen-Bond-Like Nature of the CH/π Interaction as Evidenced by Crystallographic Database Analyses and Ab Initio Molecular Orbital Calculations*' [15]; '*High-Accuracy Quantum Mechanical Studies of π–π Interactions in Benzene Dimers*' [16]; '*Magnitude and Physical Origin of Intermolecular Interactions of Aromatic Molecules: Recent Progress of Computational Studies*' [17]; '*Quantum Mechanical Calculations for Benzene Dimer Energies: Present Problems and Future Challenges*' [18]; '*Do Special Noncovalent π–π Stacking Interactions Really Exist?*' [19]; '*CH/π interactions in methane clusters with polycyclic aromatic hydrocarbons*' [20].
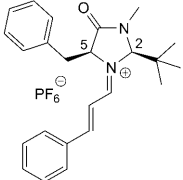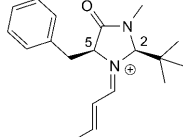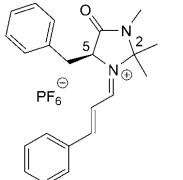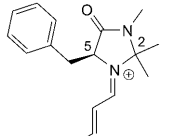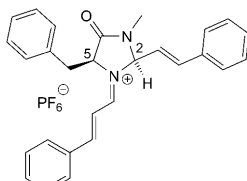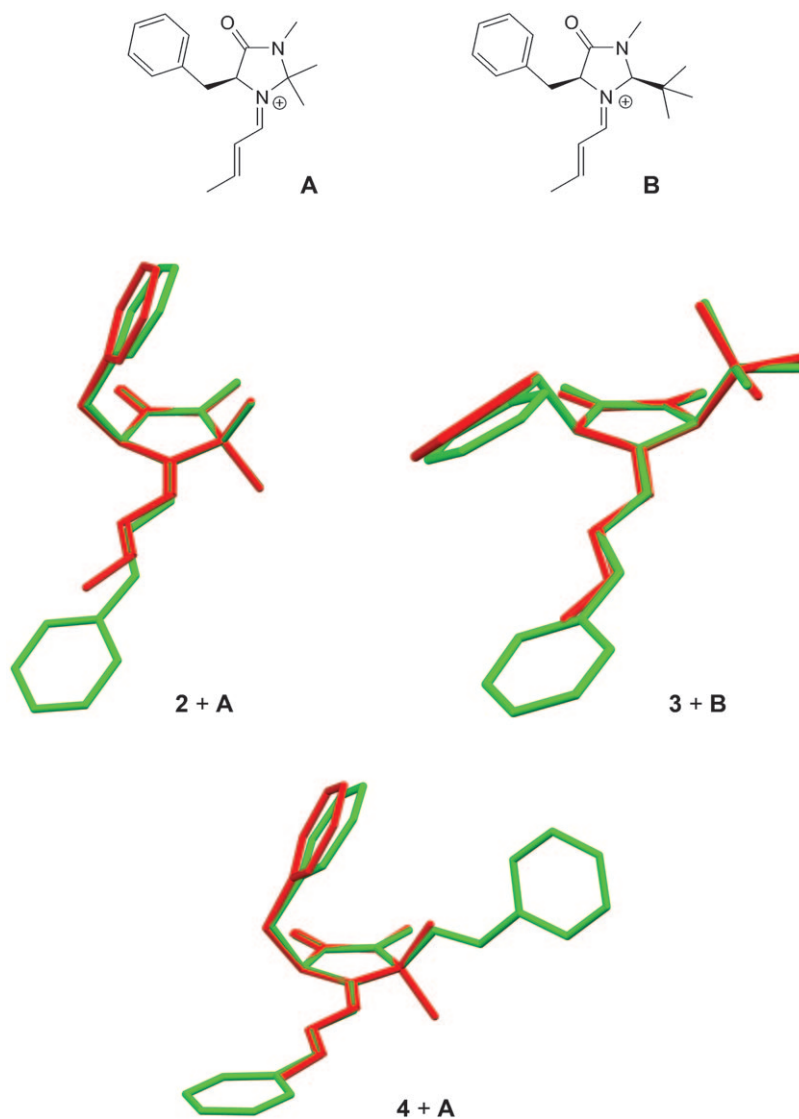
Fig. 9. *Overlays of measured solid-phase* (PF$_6$ *salts* **2** – **4**) *and DFT-calculated* [9] *gas-phase structures,* **A** *and* **B** [9], *of imidazolidinone-derived iminium ions.* The calculated structures are shown in red, the measured ones in green.

Waals repulsions, and dispersion forces. Factorizing or decomposing may lead to biased conclusions.

The *lesson* for the organic chemist is twofold: *a*) The sum of weak interactions, which may not even be part of our repertoire of qualitative models, may add up to a surprising structure or structural effect; after all, a difference of only 1.4 kcal/mol leads to an equilibrium ratio of 10 : 1 or to 90% selectivity with two competing transition states at room temperature. *b*) High-level theoretical calculations have now reached a

Table. *Pyramidalities of the Iminium N-Atoms and Torsion Angles around the C=N Bonds in the Crystal and DFT-Calculated Structures of the Iminium Salts **2 – 4** and Ions **A** and **B** [9], respectively.* Pyramidality as distance between the N-atom and the plane of its three C-atom bonding partners. In a totally planar system, pyramidality would be 0.0 Å and the sum of the dihedral angles 180°.

| | | Pyramidality Δ on N(1) [Å] | Torsion angles [°] | |
			C−C−N−C(2)	C−C−N−C(5)
3		X-ray structure	0.099	− 167.0	− 1.9
A		DFT-calculated structure	0.115	− 172.7	− 10.0
2		X-ray structure	0.059	− 166.6	4.5
B		DFT-calculated structure	0.023	− 174.2	2.3
4		X-ray structure	0.040	− 174.1	− 0.2

state of speed and accuracy that enable the organic chemist not only to explain results but also to plan and optimize reactions[11]).

All experimental details of the results mentioned herein will be published in a forthcoming full paper. The coordinates of X-ray crystal structures shown in *Figs. 2 – 5* (compounds **1 – 4**) have been deposited with the *Cambridge Crystallographic Data Centre* (*CCDC*)[12]).

---

[11] See the discussions and citations in the reference list of [2].

[12] The data (CCDC 711493 – 711496) can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam. ac.uk).
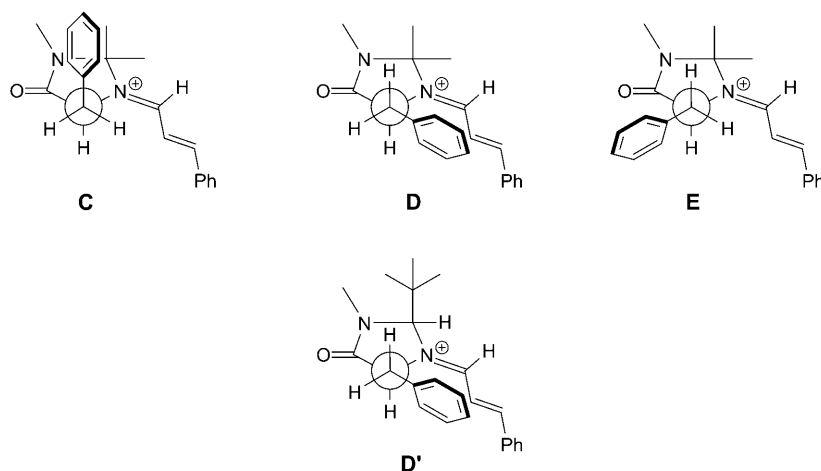
We thank *J. D. Dunitz* for insightful discussions.

Note Added in Proof. The X-ray structure and NMR spectra of compound **2** have been described independently after submission of our manuscript [21].

REFERENCES

[1] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425.

[2] Dieter Seebach, Uroš Grošelj, D. Michael Badine, W. Bernd Schweizer, Albert K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999.

[3] R. Naef, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 135.

[4] D. Seebach, B. Lamatsch, R. Amstutz, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradón, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mouriño, E. Pfammatter, D. A. Plattner, C. Schickli, W. B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravitlles, E. Molins, *Helv. Chim. Acta* **1992**, *75*, 913.

[5] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77.

[6] J. C. Burley, R. Gilmour, T. J. Prior, G. M. Day, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2008**, *64*, o10.

[7] I. A. Perillo, C. de los Santos, A. Salerno, *Heterocycles* **2003**, *60*, 89.

[8] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874.

[9] R. Gordillo, J. Carter, K. N. Houk, *Adv. Synth. Catal.* **2004**, *346*, 1175; R. Gordillo, K. N. Houk, *J. Am. Chem. Soc.* **2006**, *128*, 3543.

[10] G. Lelais, D. W. C. MacMillan, 'History and Perspectives of Chiral Organic Catalysts', in 'New Frontiers in Asymmetric Catalysis', Eds. K. Mikami, M. Lautens, John Wiley & Sons, New Jersey, 2007, pp. 313.

[11] M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108; T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826.

[12] G. Quinkert, E. Egert, C. Griesinger, 'Aspekte der Organischen Chemie: Struktur', Verlag Helvetica Chimica Acta, Basel, 1995; G. Quinkert, E. Egert, C. Griesinger, 'Aspects of Organic Chemistry: Structure', Verlag Helvetica Chimica Acta, Basel, 1996.

[13] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841; R. W. Hoffmann, *Angew. Chem.* **1992**, *104*, 1147; *Angew. Chem., Int. Ed.* **1992**, *31*, 1124; R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134; *Angew. Chem., Int. Ed.* **2000**, *39*, 2055.

[14] J. D. Dunitz, A. Gavezzotti, *Acc. Chem. Res.* **1999**, *32*, 677.

[15] O. Takahashi, Y. Kohno, S. Iwasaki, K. Saito, M. Iwaoka, S. Tomoda, Y. Umezawa, S. Tsuboyama, M. Nishio, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2421.

[16] O. M. Sinnokrot, C. D. Sherrill, *J. Phys. Chem. A* **2006**, *110*, 10656.

[17] S. Tsuzuki, T. Uchimaru, *Curr. Org. Chem.* **2006**, *10*, 745.

[18] W. B. Schweizer, J. D. Dunitz, *J. Chem. Theory Comput.* **2006**, *2*, 288.

[19] S. Grimme, *Angew. Chem.* **2008**, *120*, 3478; *Angew. Chem., Int. Ed.* **2008**, *47*, 3430.

[20] S. Tsuzuki, K. Honda, A. Fujii, T. Uchimaru, M. Mikami, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2860.

[21] J. B. Brazier, G. Evans, T. J. K. Gibbs, S. J. Coles, M. B. Hursthouse, J. A. Platts, N. C. O. Tomkinson, 'Solution Phase, Solid State, and Theoretical Investigations on the MacMillan Imidazolidinone', *Org. Lett.* **2009**, *11*, 133.