Theoretical Study of the [2+3] Cycloaddition of Nitrones to Nitriles—Influence of Nitrile Substituent, Solvent and Lewis Acid Coordination

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Abstract: The [2+3] cycloaddition of nitrone PhCH=N(Me)O to nitriles RC≡N (R = Me, Ph, CF_3) was studied using quantum chemical calculations at the HF/6-31G* and B3LYP/6-31G* level of theory. With MeCN and PhCN, the reaction occurs through a concerted mechanism and leads selectively to Δ^4-1,2,4-oxadiazolines rather than Δ^2-1,2,5-oxadiazolines. Electron withdrawing substituents such as CF_3 at the nitrile provoke a non-synchronous bond formation, with the C−O bond being established on an earlier stage than the C−N bond. Additionally, the reaction becomes thermodynamically and kinetically more favourable. In the reaction of adducts of MeCN with BH_3 or BF_3 as model Lewis acids, the mechanism was found to change from fully concerted in the case of free MeCN towards a two-step reaction in the presence of BF_3, in which C−O bond formation occurs first. The BH_3-mediated reaction occupies an intermediate stage where ring formation occurs in one-step but non-simultaneously, similar to the reaction of CF_3CN. Interaction of the Lewis acid with the nitrile in the course of the reaction facilitates the cycloaddition by stabilizing transition states, intermediate and product rather than by activating the nitrile. The solvent influences the organic reaction mainly by lowering the energy of the reagents, thus leading to a higher activation barrier in a more polar solvent. In the Lewis acid mediated reaction, in contrast, the intermediate is strongly stabilised by a polar solvent and with that the synchronicity of the reaction changes in favour of a two-step mechanism.

Keywords: cycloaddition · computer chemistry · heterocycles · Lewis acids · solvent effects

Introduction

[2+3] Cycloadditions represent a highly atom efficient, elegant and versatile method for the synthesis of five-membered ring systems, and depending on the choice of dipolar reagent and dipolarophile, a large variety of heterocycles can be prepared.[1] Nitrones, in particular, have attracted much attention since they are readily available and easy to handle, and their reactions with olefins give convenient access to oxazolines. Moreover, Lewis acid catalysis allows for further fine tuning of the reactivity and control of regio- and stereochemistry of the cycloaddition.[2] Nitriles, in contrast, although promising starting materials in the synthesis of heterocycles, are only rarely used in cycloaddition reactions due to their low reactivity towards most dipolar reagents. Known transformations include reactions with azides to give tetrazoles,[3] addition to nitrile oxides as an alternative route to the well known 1,2,4-oxadiazoles,[4] reaction with C,N-diacylimines to afford amidooxazoles,[5] or the formal cycloaddition of carbonyl stabilized carbenoids to furnish 1,3-oxazoles.[6]

Reaction of nitrones with nitriles, however, is difficult to achieve and actually only takes place when either electron deficient nitriles[7] or extremely reactive nitrones are used.[8] Taking into account that this restricted reaction is the only known pathway that allows for selective synthesis of Δ^4-1,2,4-oxadiazolines, it is not surprising that this relevant class of heterocycles is still lagging behind in its development.

In our previous work, it was shown that platinum-coordinated nitriles undergo cycloaddition with nitrones under surprisingly mild conditions to give stable Δ^4-1,2,4-oxadiazoline complexes from which the newly formed ligand can be released and isolated, and with this, the limited possibilities of organic chemistry for the synthesis of this type of heterocycles were improved considerably.[9] With chiral platinum compounds, a stereoselective reaction can be performed, thus giving for the first time access to enantiomerically enriched Δ^4-1,2,4-oxadiazolines, with *ee* values of up to 70%.[10] As a working hypothesis, which explains the overall effect and also the fact that Pt^{IV} species achieve a higher degree of activation than Pt^{II} centers, it is anticipated that platinum acts as a Lewis acid; this would make the nitrile more electron deficient. Thus a similar result was obtained as if a nitrile with an electron withdrawing substituent was used. As a consequence, the

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Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author: Tables of total energies, zero point energies, selected bond lengths and angles.

activating effect should not be Pt-specific, but any Lewis acid coordinating to the nitrile should be able to promote this reaction.

As to add more evidence to this assumption, a deeper understanding of the reaction mechanism is necessary, to clarify the following questions: i) how does the energetic profile of the purely organic reaction look like, is the reaction concerted or does it occur in two steps, and how can we understand the observed regioselectivity to give Δ^4-1,2,4-oxadiazolines rather than Δ^2-1,2,5-oxadiazolines; ii) what influence on the reaction mechanism and reactivity do the nitrile substituents exhibit, iii) how does coordination of a Lewis acid to the nitrogen atom of the nitrile modify the course of reaction, and iv) what is the influence of the solvent on these reactions?

In order to answer these questions, a theoretical investigation using ab initio calculations was undertaken, and the results of the study are presented in this work.

Computational Methods

Calculations were performed with GAMESS(US)[11] and GAUSSIAN98.[12] Results were visualized with MOLDEN[13] and PLATON.[14] Molecular geometries were fully optimized at ab initio Hartree–Fock and B3LYP level of theory, using the standard basis set 6-31G*[15] for all atoms. The relative energies of all structures include unscaled zero-point energy corrections. Harmonic vibrational frequencies were computed for all stationary points in order to characterize them as local minima (no imaginary frequency found) or transition states (only one imaginary frequency exists). The vibration associated with the imaginary frequency was examined for being consistent with the ring formation. Reaction pathways were traced from the transition states towards both reactant and product direction along the imaginary mode of vibration using the algorithm developed by Gonzáles and Schlegel.[16] For the calculations of solvent effects, the SCRF method was used.[17]

Results and Discussion

[2+3] Cycloadditions received much attention in theoretical studies already in early days. An extensive computational work explaining the reactivity and selectivities in 1,3-dipolar cycloadditions using semiempirical or extended Hückel methods covers a large number of dipolar reagents and their behaviour in the reaction with olefins.[18] The addition of the parent all-H nitrone to C=C bonds was later on studied on different levels of theory,[19, 20] and recently, Tanaka et al.[21] reported on ab initio studies of the influence of Lewis acids such as BF_3 or BH_3 on the reaction of this nitrone to the C=C bond of acrolein. In all these cases, olefins were used as dipolarophiles, and surprisingly little is known about the mechanism of the cycloaddition of nitrones with hetero-dipolarophiles, the reaction with C=S bonds seemingly the only case examined theoretically.[20]

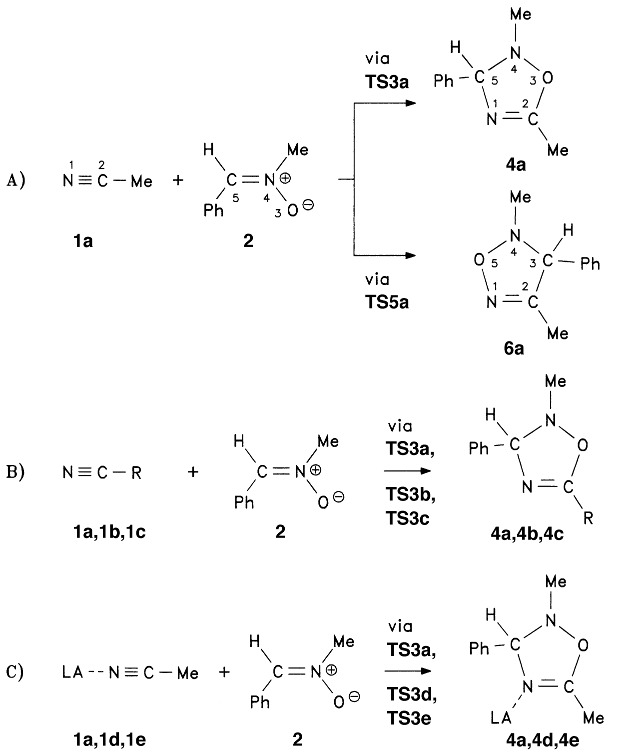
For the present computational study, the reactions of MeCN (**1a**), PhCN (**1b**), CF_3CN (**1c**) and the Lewis acid adducts of MeCN with BH_3 (**1d**) and BF_3 (**1e**) with the nitrone PhCH=N(Me)O (**2**) were chosen (see Scheme 1). With this choice, we tried to keep as close as possible to reactions for which experimental data are available, and which cover a broad range of reactivity.[9, 10, 22] The model Lewis acids BH_3 and BF_3 were selected mainly on the basis of the following arguments: i) the calculations should be feasible on a reasonable time-scale and computational effort, ii) only elements should be included for which 6-31G* parameters are available, to assure a balanced basis set, and iii) the system chosen should enable to study the impact of the “pure” Lewis acid, excluding specific transition metal effects.

Geometry optimisation was performed for nitriles **1a–c**, and the BH_3 and BF_3 adducts of MeCN (**1d** and **1e**). All bond lengths and angles were found in good agreement with corresponding values from X-ray structure determination for similar compounds;[23, 24] this indicates that the calculations at both HF/6-31G* and B3LYP/6-31G* levels reproduce the structures well. A similar consistency between calculated and experimental structural parameters was found for the Δ^4-1,2,4-oxadiazolines **4a–e**[9, 10, 25] and Δ^2-1,2,5-oxadiazoline **6a**.[26] The equilibrium geometry of *N*-methyl-*C*-phenylnitrone (**2**), which showed largest deviations of up to 0.03 Å from the corresponding bond lengths found by X-ray diffraction for similar compounds,[27] was also calculated on 6-31G*/MP2 level of theory. The CN bond thereby becomes longer (1.336 Å) and the NO distance is found slightly shorter (1.267 Å). However, since X-ray structural data are in between the calculated values found by either HF and DFT or MP2 computations, we presumed that HF and DFT calculations might give sufficient accuracy for the qualitative purpose of this study. Earlier calculations of the parent all-H-nitrone were done with B3LYP/6-31G*,[19a] MP2/6-31G*,[21] or STO-3G[17b] and show even larger variation in bond lengths, a previous report on the calculation of *N*-Me-*C*-Ph-nitrone **2** using semiempirical methods (AM1 and PM3) does not quote any geometric parameters for comparision.[21]

Although the HF/6-31G* calculations closely reproduce the structures, it is well documented that activation energies tend to be overestimated at this level of theory. The Hartree Fock energy values presented in this study give the same qualitative trends as the DFT calculations, however, the energies obtained with DFT methods are expected to be closer to experimental data.

Reaction of MeCN with nitrone 2: In order to gain insight into the mechanism of the purely organic reaction, the system nitrile **1a**, nitrone **2** and oxadiazoline **4a** was studied and the transition state **TS3a** leading to the product was located. The possibility for a formation of the other regioisomer **6a** via transition state **TS5a** was also taken into account (see Scheme 1A). Relative energies are given in Table 1, selected bond lengths, angles and bond orders for all structures are given in the Supporting Information.

Comparison of the relative energy of starting materials (**1a**+**2**) and product **4a** show that the overall reaction is in fact thermodynamically favoured, although only to a moderate extent. Product **4a** is more stable than the starting materials, and a reaction should therefore be possible. The activation barrier of 35.3 $kcal\,mol^{-1}$ in HF or 21.7 $kcal\,mol^{-1}$ in the DFT calculations, however, is comparatively high, and with that, it becomes comprehensible that the reaction was never ob-



Scheme 1. Reactions studied: A) regiochemistry, B) influence of the nitrile substituent (**a**: R = Me, **b**: R = Ph, **c**: R = CF_3), C) influence of Lewis acid coordination (**a**: without LA, **d**: LA = BH_3, **e**: LA = BF_3).

served experimentally[22] but could only be achieved by metal mediation.[9, 10]

The structure of the transition state **3a** is shown in Figure 1. The nitrone carbon and oxygen approach the C≡N triple bond simultaneously, leading to a five-membered cycle in an envelope conformation, with the nitrone's nitrogen atom at the flap. The bond orders reflect that the C2–O3 and C5–N1 bonds are formed to equal extents of about 40% of their final value, and therefore, the reaction can be considered concerted. The transition state geometry still resembles more the starting materials than the product, it is hence an early transition state on the reaction coordinate. The nitrile N1-C2-Me starts to bend out of linearity, and the CN bond becomes slightly longer. In the nitrone part, an elongation of the O3–N4 and N4–C5 bonds and a bending of the O3 atom out of the Ph-C5-N4 plane are observed.

Calculation of the intrinsic reaction coordinate (see Figure 2) confirms this interpretation, since both pathways from the transition state lead steadily down to the starting materials and the oxadiazoline, without any evidence for a potential intermediate. In the course of the reaction, the nitrone approaches the nitrile with the bond forming O3 and C5 atoms simultaneously ($s = -10$ to -2). During this approximation, both nitrile C≡N triple bond (N1–C2) and nitrone C=N (N4–C5) do not change, and only when the system is already close to the transition state, a restructuring of these bonds takes place ($s = -2$ to 3). In the same region of the reaction path the ring closure occurs, with formation of the O3–C2 bond being only slightly more advanced to the formation of the C5–N1 bond. The overall reaction can therefore be considered to occur with a high degree of concertedness.

Comparision of HOMO/LUMO energies gives evidence that the reaction is controlled by the interaction of HOMO of nitrone (−8.08 eV) and LUMO of nitrile (+5.76 eV) rather than by LUMO(nitrone)–HOMO(nitrile) interaction (+2.50 eV and −12.63 eV), if frontier orbital considerations were to apply.

Since the nitrone might also have some contribution towards a resonance structure with neutral oxygen and negative charge at carbon, the possibility of the formation of the other regioisomer was also studied by calculating the corresponding product **6a** and the transition state **5a** leading to it. As a result of these calculations, production of this regioisomer was found even less probable, since the transition state is considerably higher in energy than the reactants, thus causing an activation barrier of 64.4 kcal mol^{-1} in HF or 36.2 kcal mol^{-1} in DFT which is unlikely to be overcome thermally. Additionally, the product Δ^2-1,2,5-oxadiazoline is significantly higher in energy than the starting materials, showing that the reaction is also thermodynamically disfavoured. For further studies, this reaction pathway can be

Table 1. Relative energies [kcal mol^{-1}] and dipole moments (Debye) for the reactions of nitriles **1a-1e** with nitrone **2** via intermediate **I** and transition states **TS3a**–**TS3e** and **TS5a** to give Δ^4-1,2,4-oxadiazolines **4a**–**e** and Δ^2-1,2,5-oxadiazoline **6a**. Relative energy of nitrile+nitrone = 0 kcal mol^{-1}.

Gas phase	HF/6-31G*				B3LYP/6-31G*			
reaction	transition state		oxadiazoline		transition state		oxadiazoline	
	E	μ	E	μ	E	μ	E	μ
1a+**2**→**4a**	+35.3	1.4	−16.6	1.4	+21.7	1.1	−11.1	1.3
1a+**2**→**6a**	+64.4	6.2	+19.8	4.0	+36.2	5.8	+17.5	3.4
1b+**2**→**4b**	+34.9	1.3	−18.2	1.3	+20.4	1.0	−12.8	1.1
1c+**2**→**4c**	+23.8	6.0	−24.4	3.2	+12.8	4.3	−17.9	3.4
1d+**2**→**4d**	+20.1	9.6	−27.2	4.7	+14.3	6.5	−18.8	4.4
1e+**2**→**I**	+13.4	11.1	+13.0	13.6	+6.7	8.6	(–)	(–)
I→**4e**	+14.2	10.8	−29.6	5.7	(–)	(–)	−26.5	5.4

SCRF, [ε] = 8.9	HF/6-31G*				B3LYP/6-31G*			
reaction	transition state		oxadiazoline		transition state		oxadiazoline	
	E	μ	E	μ	E	μ	E	μ
1a+**2**→**4a**	+47.1	1.6	−5.3	1.5	+31.6	1.3	−1.3	1.4
1e+**2**→**I**	+13.8	14.7	+6.9	22.1	+8.1	16.2	+6.4	22.3
I→**4e**	+15.7	12.4	−23.4	6.7	+11.5	11.8	−18.8	6.4

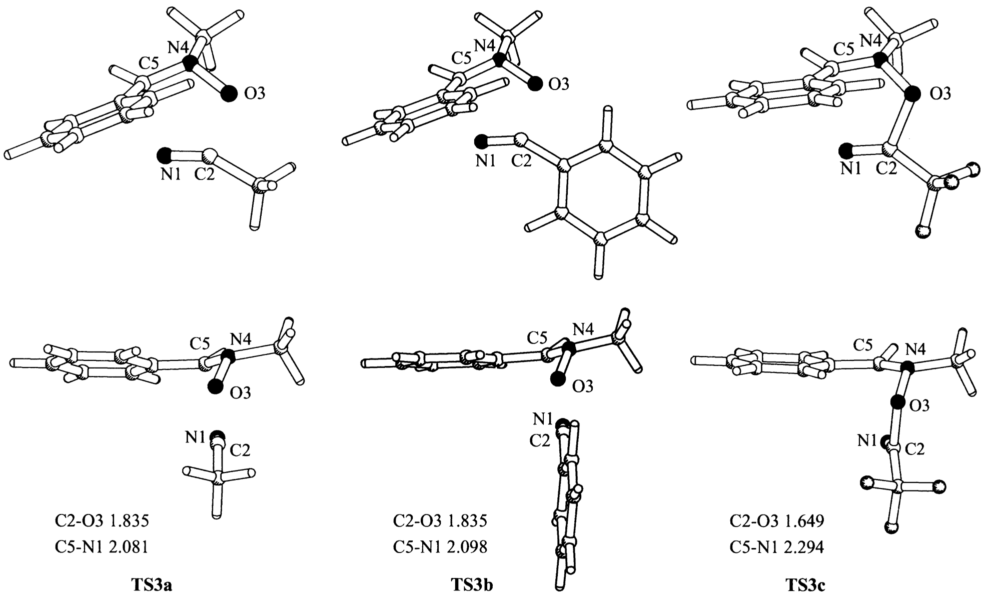


Figure 1. Transition states and intermediate in the reaction of nitriles with nitrone **2**.

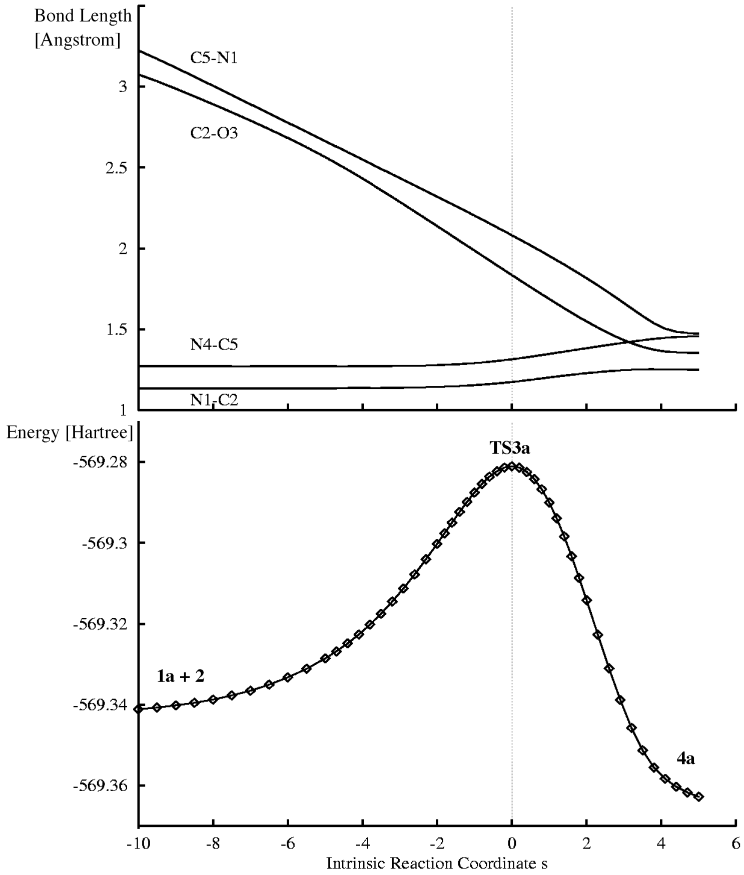


Figure 2. Intrinsic reaction coordinate (amu$^{1/2}$ bohr) for the reaction **1a**+**2**→**4a**.

excluded. Experimentally, this result is clearly confirmed since in all cases of a reaction of a nitrile with a nitrone, the formation of the Δ^4-1,2,4-oxadiazoline was observed exclusively, no Δ^2-1,2,5-oxadiazoline was produced.

Influence of the nitrile substituent: In order to understand the effect of the nitrile substituent on the course of the reaction, nitriles MeCN **1a**, PhCN **1b** and CF_3CN **1c** were compared and their tendency to react with nitrone **2** to give the corresponding products **4a–c** via transition states **TS3a–c** was studied (Scheme 1B). Relative energies are summarized in Table 1, selected bond lengths, angles and bond orders are given in the Supporting Information.

The reaction of PhCN with nitrone **2** shows practically the same energetic profile as the corresponding reaction of MeCN, although the latter one was never observed experimentally whereas the first one can at least be achieved in moderate yields when forcing conditions are applied.[22] The activation energy is slightly lower, and the reaction energy is somewhat higher, but both effects are too subtle for a detailed interpretation on the level of theory used.

The transition state **TS3b** (see Figure 1) resembles geometrically the one found for the reaction of MeCN; the bond order analysis shows that the C2–O3 bond is formed to only a moderately higher extent (approx. 41% of the final value) than the C5–N1 bond (approx. 36% of the final value), the reaction therefore can be considered concerted.

Analysis of the frontier orbital energies might suggest that reaction of PhCN is more feasible because the two π orbitals with CN contribution are energetically not equivalent (in contrast to MeCN). The one which is orthogonal to the plane of the aromatic ring mixes with the aromatic π system, thus leading to a LUMO at lower energy (+2.44 eV, as compared to +5.76 eV for MeCN). In contrast, the orbital with CN π contribution in the aromatic plane (+5.99 eV) is not affected by the π system of the aromatic ring and is comparable in energy with the corresponding orbitals in MeCN, but energetically higher than the LUMO of PhCN. However, the transition state geometry reveals that the nitrone obviously interacts with the energetically less favourable orbital *in plane* with the aromatic system, leading to a structure in which the phenyl substituent of the nitrile still keeps in conjugation to the unaffected π system of the C–N bond. If the energetically more favourable π orbital were involved in the reaction with the nitrone, a bending of the NCPh unit would result in a loss of conjugation, and this might explain why PhCN and MeCN are similar in reactivity, although the frontier molecular orbitals suggest a much higher reactivity of PhCN. All attempts to localize a transition state in which the phenyl group is perpendicular to the remaining CN π bond failed.

As an example of an electron deficient nitrile, CF_3CN was studied. Experimental data showed that CCl_3CN reacts about 10000 times faster than PhCN,[22] and this trend should be even more pronounced for the more electron deficient CF_3CN. The calculations point out that product **4c** is considerably stabilized, as compared to the starting materials, and therefore, the thermodynamic driving force for this reaction is much stronger. Additionally, the transition state is lower in energy, and with that, the activation energy of the reaction is considerably reduced. Moreover, the structure of the transition state **TS3c** is somehow different, as shown in Figure 1. It resembles more a five-membered cycle in twist conformation, with the nitrone N4 and C5 atoms at left and right hand side of the plane formed by the nitrile N1, C2 and nitrone O3 atoms. The C2–O3 bond is formed already to more than 50% of its final value whereas the C5–N1 bond exists to about 29% only; this suggests that this reaction still occurs through a one-step mechanism but with a non-simultaneous bond formation. Due to the electron withdrawing effect of the substituent, the carbon atom of the CN bond is more prone towards nucleophilic attack by the nitrone oxygen.

Frontier orbital considerations show that the LUMO in CF_3CN (+4.26 eV) is lowered with respect to MeCN (but higher in energy than the corresponding LUMO of PhCN), and this gives evidence that both FMO energies and the gradual change in reaction mechanism have a strong influence on the reactivity.

Influence of nitrile coordination to a Lewis acid: For the investigation of the influence of a Lewis acid on the reactivity and the mechanism of the reaction, BH_3 and BF_3 were chosen as model Lewis acids. Free MeCN **1a**, BH_3-coordinated MeCN **1d** and BF_3-coordinated MeCN **1e** were structurally optimized, as well as the resulting products **4a**, **d**, **e** formed via transition states **TS3a**, **d**, **e** (Scheme 1 C). Relative energies are given in Table 1, relevant bond lengths, angles and bond orders are listed in the Supporting Information.

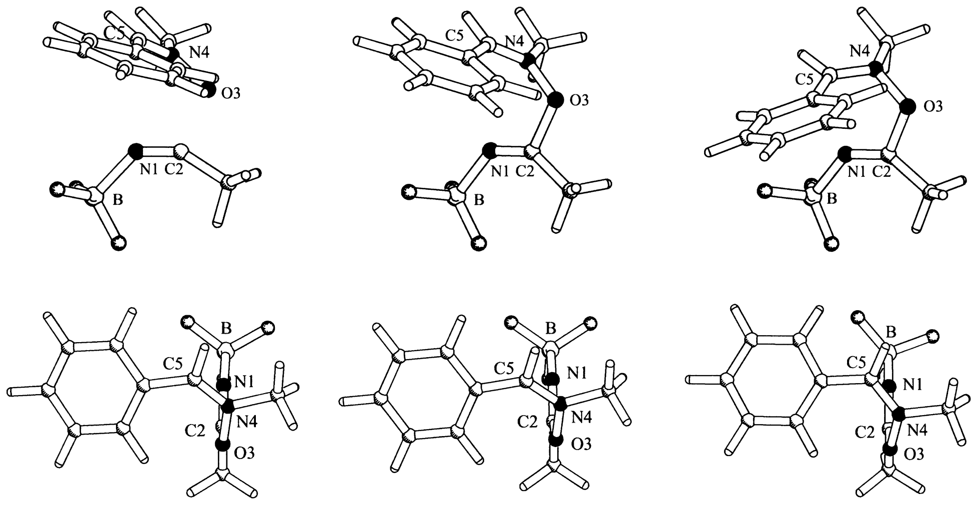
Analysis of the geometry of the BH_3 and BF_3 adducts of MeCN reveals that coordination of the model Lewis acids to MeCN is weak. In fact, BH_3 forms a complex, as seen in the N–B bond length and the average N-B-H bond angle. BF_3, however, practically does not interact with MeCN at all, for the B-N distance is too long for being considered a bond, and the boron atom is surrounded by the fluorine atoms in a triangular coordination plane rather than in the expected tetrahedral environment. Likewise, the geometry of the nitrile is practically unchanged in the presence of BF_3. As a further consequence, the Lewis acid scarcely influences the energetic position of the frontier orbitals, and therefore, one might expect the reactivity of the nitrile to be not much modified by the Lewis acid.

On the other hand, both BH_3 and BF_3 form Lewis acid complexes with the oxadiazoline, and N–B bond orders in a range 0.4 to 0.5 are observed. The structure of the heterocycle barely changes upon coordination, a weakening of the N1=C2 and C5–N1 bonds being the only effect, reflected in the bond orders but not to a significant extent in the bond lengths. This observation is in accord with X-ray structural data of free and coordinated oxadiazolines[9, 10, 25] which equally show insignificant geometric changes of the heterocycle upon complexation. However, coordination to a Lewis acid leads to a stabilization of the product with respect to the starting materials, thus enhancing the thermodynamic driving force of the reaction. BF_3 as the stronger Lewis acid provokes a more pronounced effect than BH_3.

In the reaction with BH_3, a transition state was localized which resembles much the transition state found for the reaction with CF_3CN. The C2–O3 bond is formed to 60% already whereas the C5–N1 bond is still weak (17%) but present, and with that, the tendency towards a non-simultaneous formation of the two ring forming bonds is more distinct than in the case of CF_3CN. These results show that electron-withdrawing groups exhibit the same qualitative effect, independent of their location at the carbon or the nitrogen side of the C≡N triple bond.

In the Hartree–Fock calculations, the BF_3 adduct with MeCN **1e** was found to react with nitrone **2** through a two-step mechanism. The starting materials convert via a first transition state **TS3e-1** into an intermediate **I** in which the C2–O3 bond is already present but the C5–N1 bond is not yet formed. The intermediate then passes a second transition state **TS3e-2** to generate the product. These results parallel to quite some extent the work of Tanaka[21] who showed that the reaction of all-H nitrone with BF_3-coordinated acrolein equally proceeds stepwise, leading to a Michael adduct complex intermediate which then cyclizes to the final product of the formal [2+3] cycloaddition.

The structures of intermediate **I** and transition states **3e-1** and **3e-2** for the BF_3-mediated reaction are shown in Figure 3. Bond lengths, angles and bond orders reflect that the Lewis acid binds to the transition states and intermediate even more strongly than to the final product of reaction, thus leading to a considerable lowering of the activation barrier of the reaction. The cycloaddition is therefore not accelerated by modifying the reactivity of the starting material, as often considered for



C5-N1 3.026 C2-O3 1.770

TS3e-1

C5-N1 2.967 C2-O3 1.529

I

C5-N1 2.408 C2-O3 1.489

TS3e-2

Figure 3. Transition states and intermediate in the reaction of BF_3-coordinated acetonitrile with nitrone **2**.

other Lewis acid mediated reactions,[2] but rather by stabilizing transition states and intermediates.

The intrinsic reaction coordinate, shown in Figure 4, correctly connects the reactants **1e**+**2** with the product **4e** via transition state **TS3e-1**, intermediate **I** and transition state **TS3e-2**. In the course of the reaction, the C≡N triple bond changes to a C=N bond already on an early stage, when passing the first transition state (s = –2 to 3). At the same time, the nitrone oxygen establishes the bond to the nitrile carbon atom to approximately 60% of its final value. The nitrone C=N bond remains unaffected, and the C5–N1 bond is still far from being formed.

Both **TS3e-1** and **I** can be best described as five-membered cyclic structures in twist conformation, with the nitrone C5=N4 bond crossing over the nitrile N1≡C3 bond. In the further progress of the reaction, rotation of the nitrone unit around the C2–O3 bond then brings the bond forming atoms C5 and N1 closer together, and the twisted conformation converts into an envelope conformation. Simultaneously with the ring closure between C5–N1, the nitrone N4=C5 transforms into a single bond and the C2–O3 bond formation is completed, but these processes essentially occur only after the second transition state **TS3e-2** (s = 13 to 20) at a very late stage of the reaction.

Remarkable is the change of the B–N1 distance in the course of the reaction. Upon approximation of the nitrone, the nitrile starts to bend and to develop a stronger interaction with the Lewis acid. During formation of the C2–O3 bond (when passing the first transition state **TS3e-1**), the B–N1 bond becomes even stronger until it reaches a minimum distance of 1.585 Å and a maximum bond order of 0.6 in the intermediate **I**. The subsequent ring closure can only be performed if the B–N1 bond is loosened to some extent, and this almost causes the Lewis acid to be expelled from the nitrogen atom (s = 13 to 16). The final product, however, gets stabilized by re-establishing the coordination to the Lewis acid, but the B–N1 bond remains weaker than in the intermediate (s = 16 to 22).

In the gas phase DFT calculations, only one transition state was localized. Its structure is similar to the one obtained for the reaction of the BH_3 coordi-

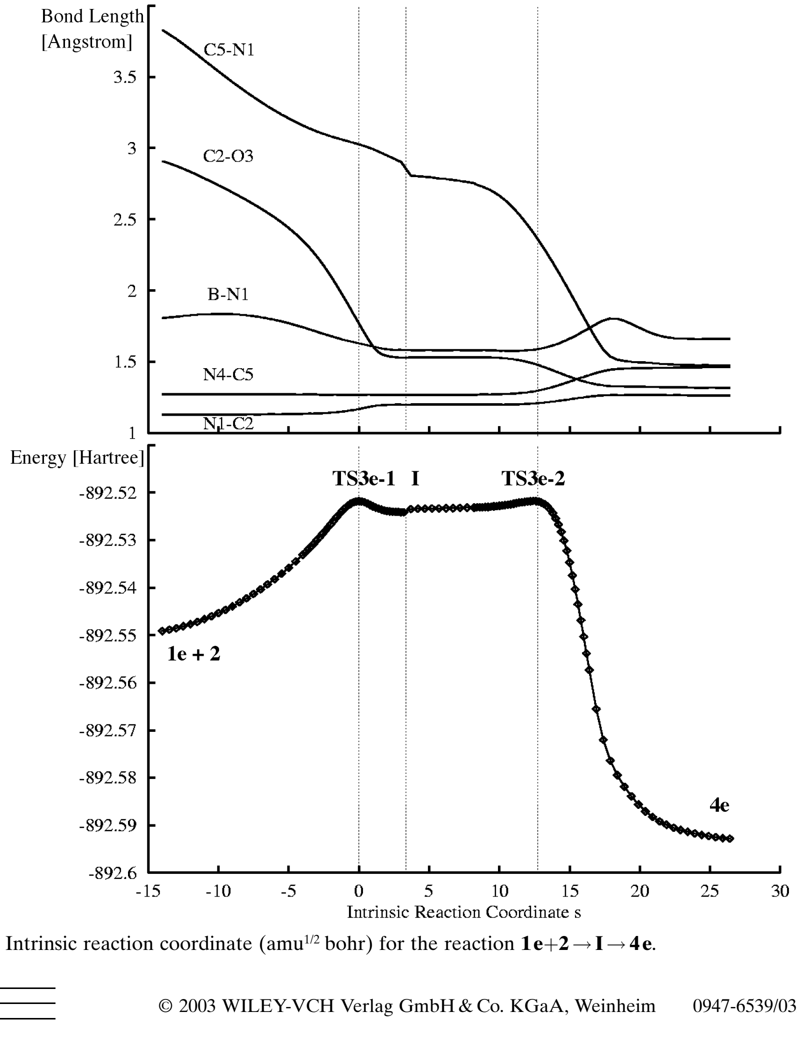


Figure 4. Intrinsic reaction coordinate ($amu^{1/2}$ bohr) for the reaction **1e**+**2** → **I** → **4e**.

nated acetonitrile but the C5–N1 distance is longer; this indicates that the reaction is less synchronous. Tracing the intrinsic reaction coordinate from this transition state leads in fact to the starting materials and the product, however, the slope around the transition state is very flat and the energetic profile in this range resembles more a plateau composed from two transition structures and an intermediate of very similar energy, before it eventually drops down to the energetic minima. More evidence for this hypothesis can be obtained from the development of the bond lengths of the newly forming C–O and C–N bonds along the reaction coordinate, which looks quite similar to the one shown in Figure 4 for the HF calculation of the same reaction, with a clearly stepwise generation of the ring forming bonds. This shows that the BF_3-mediated reaction is just at the borderline to a two-step reaction where the two transition states and the intermediate are too close in energy to be clearly distinguished.

Solvent effects: The solvent effect on dipolar cycloadditions can not be generalized that easy. For some cycloadditions such as the reaction of nitrile oxides with alkenes or alkynes, the solvent noticeably influences the activation barrier and synchronicity of the reaction[28] and also affects the regioselectivity.[29] In contrast, for the closely related reaction of nitrones with olefins, only a minor dependence on the solvent is found both experimentally[30] and theoretically.[20]

In order to understand the influence of a solvent on the cycloaddition of nitrones to nitriles, the reactions of uncoordinated MeCN **1a** and BF_3-coordinated MeCN **1e** with nitrone **2** were calculated using the SCRF method. This method is based on the Kirkwood–Onsager model of a molecule in a spheric cavity surrounded by a dielectric medium.[31] A dielectric constant of 8.9 was applied in the calculations, corresponding to dichloromethane which is the solvent used experimentally for the Pt-mediated reactions. The corresponding relative energies and dipole moments of the transition states, intermediate and products are given in Table 1.

Both organic and BF_3-mediated reaction do not change qualitatively in a more polar solvent insofar as the organic reaction still occurs via a concerted mechanism whereas the BF_3-mediated reaction takes place in a two-step process. However, for the organic reaction of **1a**+**2**, the activation barrier increases and the reaction energy decreases to almost thermoneutrality. Both factors clearly disfavour the reaction in a more polar solvent, and this indeed matches with the experimental observation that the reaction of PhCN with nitrone **2** takes place in toluene,[22] whereas no conversion is achieved when the more polar PhCN is used as a solvent. Considering the electrostatic moments of the species involved in the reaction, this result can be rationalized. The starting materials **1a** and **2** possess much larger electrostatic moments (4.0 and 3.9 D) than the transition state **TS3a** or the product **4a**. Therefore, one would expect the polar solvent to stabilize the starting materials to a higher extent.

In the BF_3-mediated reaction, the most polar species is the intermediate **I**, followed by the two transition states **3e-1** and **3e-2**. Both starting materials and product **4e** are of lower polarity and quite similar to each other. Therefore, one would expect only small changes in the reaction energy but a considerable decrease in activation energies. As a consequence, the reaction should be more feasible in a polar solvent, in contrast to the non-catalyzed reaction described above. The SCRF calculations reflect these expectations only partially. The reaction energy is found smaller and the activation barriers is higher than in the gas phase calculations. However, the intermediate is clearly stabilised and the entire reaction has a much more pronounced two step character than in the gas phase. Also the structures of the transition state **TS3e-1** and the intermediate **I** change considerably when a electrostatic field representing the solvent is applied. The main feature observed is a much larger C2-O3-N4-C5 torsion angle (104.2 vs 78.7 for **TS3e-1**, 125.4 vs 65.2 for **I**), leading to longer C5–N1 distances (3.65 vs 3.02 for **TS3e-1**, 3.65 vs 2.96 for **I**). In a polar solvent, the intermediate can therefore be described as a 1,5-dipole, and one might ask whether such a species can be trapped by another reagent before the ring closure to the oxadiazoline occurs. This would open up a route to a novel multicomponent chemistry.

Conclusion

Cycloaddition of *N*-methyl-*C*-phenylnitrone to nitriles MeCN and PhCN occurs through a concerted mechanism under synchronous generation of the ring-forming bonds. However, the activation energy of the reaction is high and its thermodynamic motivation is only moderate. For both kinetic and thermodynamic reasons, the formation of Δ^4-1,2,4-oxadiazolines is highly preferred, and the formation of the corresponding Δ^2-1,2,5-oxadiazolines is much unlikely to occur.

Electron withdrawing substituents on the nitrile (e.g. CF_3) change the reaction mechanism from a concerted reaction to a one step reaction with non-simultaneous bond formation. This is clearly noticeable in the geometry of the transition state which shows that the C–O bond is formed to a much higher extent than the C–N bond. Additionally, both product and TS are stabilized, and with that, the activation barrier becomes lower and the reaction enthalpy larger.

Coordination of a Lewis acid results qualitatively in the same but more pronounced effects, further favouring the reaction. With the stronger Lewis acid BF_3, the cycloaddition tends towards a two step mechanism via an intermediate, in which the C–O bond is formed to a high extent already, whereas the C–N is still open. The Lewis acid coordination does not modify the reactivity of the nitrile, but rather stabilizes transition states, intermediates and products. This alternative concept of activation is not used deliberately in organic chemistry but would certainly deserve more attention due to its potential to give new inspiration for a further development in Lewis acid promoted chemistry.

The computational results obtained with BH_3 and BF_3 reproduce the experimental findings of the activation of nitriles by coordination to platinum species surprisingly well. Therefore, one might assume that platinum indeed acts as a nitrile-specific Lewis acid. As a consequence, it should be possible to use the computational strategy applied in this work for the prediction of new metal mediated cycloaddition reactions involving nitriles. Further work in this sense is in progress in our group.

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[1] a) R. Huisgen, *Angew. Chem.* **1963**, *75*, 604; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565; b) R. Huisgen, *Angew. Chem.* **1963**, *75*, 741; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633; c) *1,3 Dipolar Cycloaddition Chemistry, Vol. 1–2* (Ed.: A. Padwa), Wiley, New York, **1984**.

[2] a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449.

[3] a) R. M. Herbst, K. R. Wilson, *J. Org. Chem.* **1957**, *22*, 1142; b) Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2001**, *3*, 4091.

[4] a) G. Leandri, M. Pallotti, *Ann. Chim. (Roma)* **1957**, *47*, 376; b) R. Huisgen, W. Mack, E. Anneser, *Tetrahedron Lett.* **1961**, 587.

[5] B. Fischer, A. Hassner, *J. Org. Chem.* **1990**, *55*, 5225.

[6] a) R. Huisgen, H. J. Sturm, G. Binsch, *Chem. Ber.* **1964**, *97*, 2864; b) R. K. Armstrong, *J. Org. Chem.* **1966**, *31*, 618; c) M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliott, J. W. Hoekstra, M. Oppenhuizen, *J. Org. Chem.* **1980**, *45*, 3657.

[7] a) Ya. D. Samuilov, S. E. Solov'eva, A. I. Konovalov, *Dokl. Akad. Nauk. SSSR Ser. Khim.* **1980**, *255*, 606; b) Ya. D. Samuilov, S. E. Solov'eva, A. I. Konovalov, *Zh. Obshch. Khim.* **1980**, *50*, 138; c) R. Plate, P. H. H. Hermkens, J. M. M. Smits, R. J. F. Nivard, H. C. J. Ottenheijm, *J. Org. Chem.* **1987**, *52*, 1047; d) A. Padwa, D. N. Kline, K. F. Koehler, M. Matzinger, M. K. Venkatramanan, *J. Org. Chem.* **1987**, *52*, 3909; e) L. A. G. M. van den Broek, *Tetrahedron* **1996**, *52*, 4467; f) H. Sang, E. G. Janzen, L. Poyer, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1183; g) A. Diaz-Ortiz, E. Diez-Barra, A. de la Hoz, A. Moreno, M. J. Gomez Escalonilla, A. Loupy, *Heterocycles* **1996**, *43*, 1021.

[8] a) Y. Yu, M. Ohno, S. Eguchi, *J. Chem. Soc. Chem. Commun.* **1994**, 331; b) Y. Yu, N. Watanabe, M. Ohno, S. Eguchi, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1417; c) Y. Yu, H. Fujita, M. Ohno, S. Eguchi, *Synthesis* **1995**, 498.

[9] a) G. Wagner, A. J. L. Pombeiro, V. Yu. Kukushkin, *J. Am. Chem. Soc.* **2000**, *122*, 3106; b) G. Wagner, M. Haukka, J. J. R. Fraústo da Silva, A. J. L. Pombeiro, V. Yu. Kukushkin, *Inorg. Chem.* **2001**, *40*, 264.

[10] G. Wagner, M. Haukka, *J. Chem. Soc. Dalton Trans.* **2001**, 2690.

[11] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comput. Chem.* **1993**, *14*, 1347.

[12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, **2001**.

[13] G. Schaftenaar, J. N. Noordik, *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123.

[14] A. L. Spek, http://www.cryst.chem.uu.nl/platon/

[15] a) P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213; b) M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, *J. Chem. Phys.* **1982**, *77*, 3654.

[16] C. Gonzáles, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523.

[17] M. M. Szafran, M. M. Karelson, A. R. Katritzky, J. Koput, M. C. Zerner, *J. Comput. Chem.* **1993**, *14*, 371.

[18] a) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, J. K. George, *J. Am. Chem. Soc.* **1973**, *95*, 7287; b) K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[19] a) J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 1064; b) G. Leroy, M. T. Nguyen, M. Sana, *Tetrahedron* **1978**, *34*, 2459; c) Y. L. Pascal, J. Chanet-Ray, R. Vessiere, A. Zeroual, *Tetrahedron* **1992**, *48*, 7197; d) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1996**, *61*, 346; e) M. T. Rispens, E. Keller, B. de Lange, R. J. Zijlstra, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 607.

[20] R. Sustmann, W. Sicking, R. Huisgen, *J. Am. Chem. Soc.* **1995**, *117*, 9679.

[21] J. Tanaka, S. Kanemasa, *Tetrahedron* **2001**, *57*, 899.

[22] P. H. H. Hermkens, J. H. van Maarseveen, C. G. Kruse, H. W. Scheeren, *Tetrahedron* **1988**, *44*, 6491.

[23] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1.

[24] B. N. Storhoff, H. C. Lewis, Jr., *Coord. Chem. Rev.* **1977**, *23*, 1 and references therein.

[25] a) J. M. M. Smits, P. T. Beurskens, J. R. M. Smits, R. Plate, H. Ottenheijm, *J. Crystallogr. Spectrosc. Res.* **1988**, *18*, 15; b) L. Eberson, C. M. Hartshorn, M. P. Hartshorn, J. J. McCullough, *Synth. Commun.* **1997**, *27*, 3779; c) L. Eberson, J. J. McCullough, C. M. Hartshorn, M. P. Hartshorn, *J. Chem. Soc. Perkin Trans. 2* **1998**, 41.

[26] D. Moya Argilagos, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 238.

[27] a) K. Folting, W. N. Lipscomb, B. Jersley, *Acta Crystallogr.* **1964**, *17*, 1263; b) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Acta Chem. Scand.* **1997**, *51*, 1234; c) R. M. Coates, S. J. Firsan, *J. Org. Chem.* **1986**, *51*, 5198; d) C. P. Falshow, N. A. Hashi, G. A. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1837.

[28] F. P. Cossío, I. Morao, H. Jiao, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1999**, *121*, 6737.

[29] Y. Hu, K. N. Houk, *Tetrahedron* **2000**, *56*, 8239.

[30] R. Huisgen, H. Seidl, I. Brüning, *Chem. Ber.* **1969**, *102*, 1102.

[31] a) J. G. Kirkwood, *J. Chem. Phys.* **1934**, *2*, 351; b) L. Onsager, *J. Am. Chem. Soc.* **1936**, *58*, 1486.

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