Diastereoselective Gas-Phase Carbon−Carbon Bond Activation Mediated by “Bare” Co^+ Cations[†]

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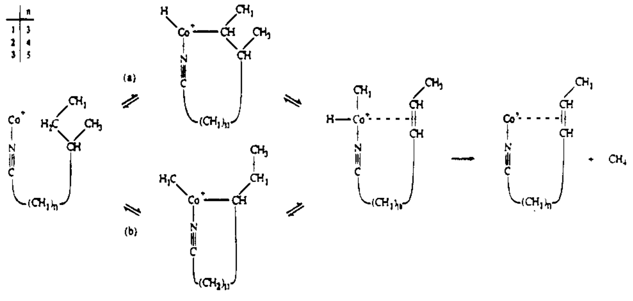
Abstract: The unimolecular decompositions of 5-methylheptanenitrile (**1**), 6-methyloctanenitrile (**2**), and 7-methylnonanenitrile (**3**) complexed to bare Co^+ cations have been investigated by means of tandem mass spectrometry. Extensive regio- and diastereospecific labeling experiments were conducted to gain further insight into the mechanistic details, in particular the stereoselectivity of the Co^+-induced demethanation in the gas phase. The overall reaction follows a 1,2-elimination mode, and, with regard to the regiospecificity, the neutral methane originates exclusively from the (ω-2) and (ω-1) positions of the alkyl chain. For **2** and **3** the examination of diastereospecifically labeled isotopomers reveals that the gas-phase demethanation exhibits a remarkable diastereoselectivity. This unprecedented example for a stereoselective C−C bond activation in gas-phase organometallic chemistry can be accounted for in terms of steric features of the metallacyclic intermediates.

Introduction

Over the past two decades, the gas-phase reactions of “bare” and partially ligated transition-metal ions with a variety of organic substrates have attracted considerable interest.[1] A hallmark of the reactions of, for example, monofunctionalized alkanes with “bare” transition-metal cations is their ability to regioselectively activate C−H and C−C bonds at sites away from the coordinating functional group. This mechanism was first discovered by Schwarz and co-workers[2] and has been termed *remote functionalization* to point out the analogy to Breslow’s seminal studies on biomimetic synthesis.[3]

Nevertheless, detailed investigations of the stereochemical outcome of transition-metal mediated C−H and C−C bond activation are scarce. Hitherto, the topic of *stereoselectivity* in gas-phase organometallic chemistry has been limited either to cyclic systems, in which the metal ion is bound to one side of the π-surface of an aromatic ring,[4] or to acyclic molecules with multidentate ligands that are chelated by the cation.[5] Only recently was the Fe^+-induced dehydrogenation of 3-methylpentan-2-one in the gas phase reported as the first example for *diastereoselective* activation of aliphatic C−H bonds in nonrigid molecules.[6]

Scheme 1



In previous studies,[7] it has been shown that the C−C bond activation of branched aliphatic nitriles by “bare” Co^+ leads preferentially to the loss of neutral alkane fragments, and the regioselectivity of the demethanation can be described in terms of the *remote functionalization* concept (Scheme 1). Here we provide the first evidence that the regiospecific unimolecular loss of neutral methane from the Co^+ complexes of 6-methyloctanenitrile (**2**) and 7-methylnonanenitrile (**3**) complexes constitutes an example for transition-metal mediated *diastereoselective carbon−carbon bond activation* in gas-phase ion chemistry. This conclusion is based on the mass spectrometric investigation of regio- and diastereospecifically deuterated derivatives of the model compounds **1**−**3** (Chart 1).

Experimental Section

The experiments were performed by using a modified VG ZAB/HF/AMD four-sector mass spectrometer of BEBE configuration (B stands for magnetic and E for electric sectors) which has been previously described in detail.[8] Briefly, the metal complexes were generated in a chemical ionization source (CI, repeller voltage ca. 0 V) by 100-eV

[†] Dedicated to Professor Manfred Schulz, Halle, on the occasion of his 65th birthday.

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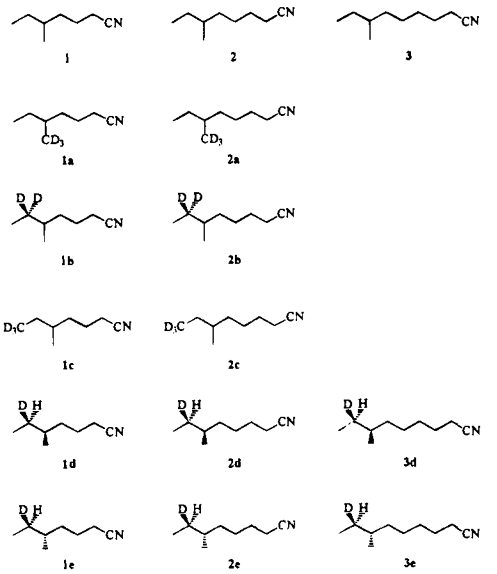
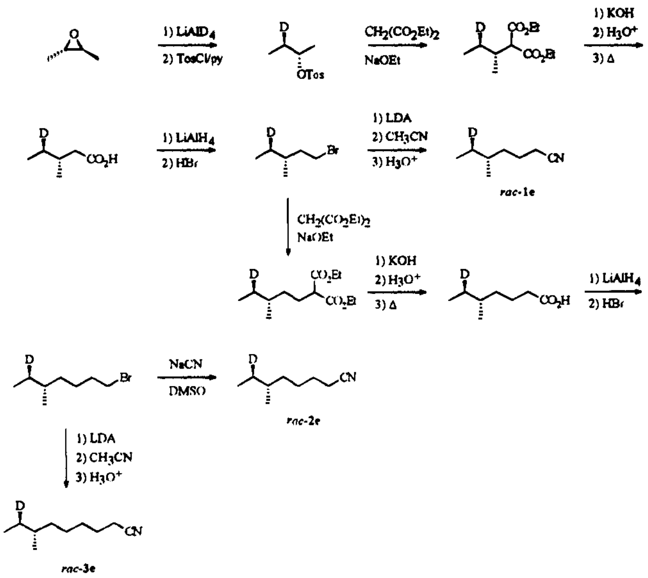
Chart 1



Scheme 2



electron bombardment of an approximately 2:1 mixture of $Co(CO)_3(NO)$ and the organic substrates of interest. The ions were accelerated to 8 keV kinetic energy and mass-selected by means of B(1)/E(1) at a resolution of $m/\Delta m = 2000-3000$ to provide separation of isobaric ions. Unimolecular fragmentations of metastable ions (MI) occurring in the field-free region preceding B(2) were recorded by scanning this sector. All spectra were accumulated and on-line processed with the AMD-Intectra data system; 10 to 20 scans were averaged to improve the signal-to-noise ratio. The data for the racemic pairs of diastereoisomers are the average of at least three independent measurements. The error of the averaged relative intensities in the MS/MS experiments is estimated to be ±10%.[9] Due to the relatively high pressure that prevails in the CI source, efficient collisional cooling of the ions takes place, such that excited states of M^+ ions are not likely to participate in the reactions observed.[10]

The nitriles **1**−**3** and their isotopologues **1a**−**c** and **2a**−**c** were synthesized (as racemic pairs) by standard laboratory procedures, purified either by distillation or by preparative gas chromatography, and fully characterized by spectroscopic means.[7c] The diastereospecifically labeled nitriles **1e**, **2e**, and **3e** were prepared in racemic forms according to the routes depicted in Scheme 2,[11] starting from *trans*-2,3-buteneoxide (Aldrich Chemicals, 96%). The synthesis was achieved by (a) reduction of the epoxide by $LiAlD_4$ (Aldrich Chemicals, >98 % D),[12] (b) tosylation of the corresponding *rac*-[3-D_1]-2-butanols,[13] (c) subsequent nucleophilic displacement with diethyl malonate, (d) saponification of the resulting diester with potassium hydroxide, (e) thermal decarboxylation of the diacid,[14] and (f) reduction of the carboxylic acid by $LiAlH_4$, and bromination of the resulting alcohol with HBr (48%)[15] to yield as central intermediate *rac*-[4-D_1]-3-methyl-1-bromopentane; this compound has been converted to the desired nitriles **1e**, **2e**, and **3e** by standard laboratory procedures.[7c]

Results and Discussion

The metastable ions (MI) of the Co^+ complexes of the aliphatic nitriles **1**, **2**, and **3** undergo four major unimolecular decomposition processes (Table 1): (i) dehydrogenation (Δm = 2 amu), (ii) demethanation (Δm = 16), (iii) loss of ethane (Δm = 30), and (iv) loss of C_4H_8 (Δm = 56). As a minor reaction the formation of ethylene (Δm = 28) takes place. In view of the fact that the mechanistic features leading to the generations of molecular hydrogen, ethane, and butene have already been discussed in great detail in a number of previous publications,[1,2,16] we will not comment upon them here, except for only reporting the complete set of data for all isotopologues in Table 2, since, the scope of this paper is to discuss exclusively the demethanation reaction with an emphasis on its unique stereochemistry.

Table 1. Mass Differences (in amu) Observed in the Unimolecular Fragmentations of the Metastable Ion (MI) Complexes **1**/Co^+, **2**/Co^+, and **3**/$Co^{+a,b}$

	Δm				
precursor	−2	−16	−28	−30	−56
1	14	39	1	33	12
2	11	53	1	25	11
3	10	54	4	25	7

[a] Intensities are normalized to $\Sigma_{\text{reactions}}$ = 100%. [b] Reactions with intensities <1% are omitted.

As already mentioned, the metastable ion mass spectra of the Co^+ complexes of 5-methylheptanenitrile (**1**), 6-methyloctanenitrile (**2**), and 7-methylnonanenitrile (**3**) are dominated by the loss of methane, which amounts to 39%, 53%, and 54%, respectively, of all products formed. The regioselectivity of this reaction is clearly revealed by the data given in Table 2. For example, the Co^+ complexes of **1a** and **2a** eliminate CD_3H (Δm = 19), those of **1b** and **2b** exclusively lose CH_3D (Δm = 17), and of **1c** and **2c** only CH_4 (Δm = 16). Thus, in line with the previously described concept of *remote functionalization*[2] the loss of neutral methane occurs via a regiospecific 1,2-elimination involving the internal methyl group at the (ω-2) position together with a hydrogen atom originating from the (ω-1) position, as depicted in Scheme 1. Based on previous studies we assume that for the Co^+ complexes of **3** the same regioselectivity is operative.

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[9] This estimate is based on the maximum deviation from the average of three independent measurements of the racemic pairs of isotopologues.

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Table 2. Mass Differences (in amu) Observed in the Unimolecular Fragmentations of Isotopologous Co^+ Complexes of **1**, **2**, and **3**[a,b]

	Δ*m*														
precursor[c]	−2	−3	−16	−17	−19	−28	−29	−30	−31	−32	−33	−56	−57	−58	−59
1a	7	5			32	2			34					3	15
1b	7	5		42				1		32			9	4	
1c	13	5	44								25				13
1d	13	2	17	22			1		31			4	10		
1e	14	3	19	23			1		27			4	9		
2a	8	5			54	3		3	18					2	9
2b	7	4		53				1		25			8	3	
2c	6	4	51					1			24				16
2d	10	2	20	26			2		25			4	11		
2e	9	2	37	15			1		25			4	7		
3d	9	2	24	31			2		22			2	7		
3e	10	2	38	18			2		18			4	7		

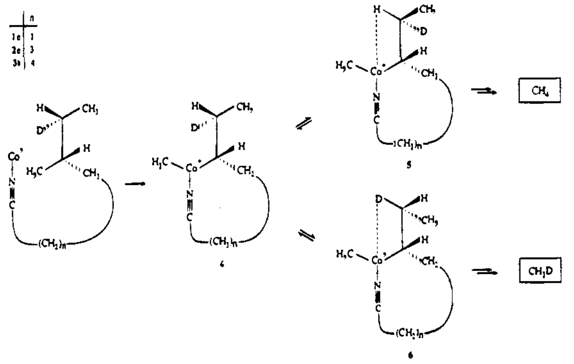
[a] Intensities are normalized to $\Sigma_{\text{reactions}} = 100\%$. [b] Reactions with intensities <1% are omitted. [c] All stereoisomers of **1**, **2**, and **3** have been measured as racemic pairs.

Table 3. Normalized Data for the Unimolecular Demethanation of the Co^+ Complexes of **1d,e**, **2d,e**, and **3d,e**[a]

	Δ*m*		
precursor[b]	$-CH_4$	$-CH_3D$	CH_4/CH_3D
1d	44 ± 4	56 ± 4	0.8 ± 0.1
1e	45 ± 2	55 ± 2	0.8 ± 0.1
2d	44 ± 1	56 ± 1	0.8 ± 0.1
2e	70 ± 2	30 ± 2	2.4 ± 0.2
3d	44 ± 1	56 ± 1	0.8 ± 0.1
3e	68 ± 2	32 ± 2	2.1 ± 0.2

[a] Intensities are normalized to the sum of methane loss = 100%. [b] The diastereoisomers **1d,e**, **2d,e**, and **3d,e** have been measured as racemic pairs.

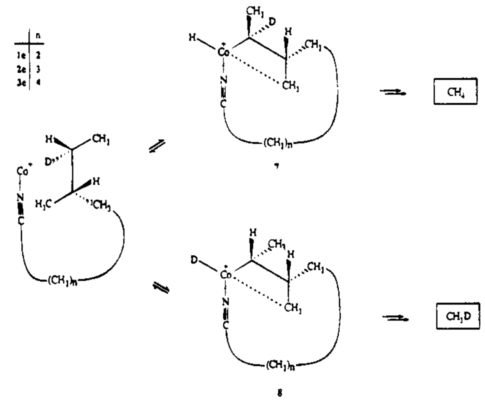
Scheme 3



The most remarkable feature of the data presented in this paper concerns, however, the unparalleled *diastereochemistry* associated with the demethanation (Tables 2 and 3) of **2d**/Co^+ and **3d**/Co^+ versus their diastereomeric complexes **2e**/Co^+ and **3e**/Co^+, respectively. As evidenced by the data in Table 3, for the complexes of **2e**/Co^+ and **3e**/Co^+ the ratio of CH_4/CH_3D loss is significantly larger than that of the diastereomeric complexes of **2d**/Co^+ and **3d**/Co^+, thus clearly pointing to the operation of a diastereoselective discrimination. For the shorter homologue **1**/Co^+, the MI data for the losses of CH_4/CH_3D from the diastereoisomers **1d**/Co^+ and **1e**/Co^+ are identical within the experimental error.

A straightforward analysis of these experimental results is complicated by the fact that methane loss may proceed via two different mechanisms which cannot be distinguished by isotopic labeling studies. (i) The mechanism depicted in Scheme 3,[17] involves an initial insertion of the metal ion into the $C-CH_3$ bond at the (*ω*-2) position to generate **4**; this is followed by an exocyclic *β*-hydrogen (or *β*-deuterium) transfer via a planar four-centered intermediate from the (*ω*-1) position to the metal center, and the reaction is terminated by reductive elimination of CH_4 or CH_3D, respectively. We propose that in this sequence the diastereoselective discrimination is due to the preferential formation of the sterically less congested eclipsed conformer **5**; for the diminished loss of CH_3D from the diastereoisomers **2e** and **3e** the sterically more demanding eclipsed conformer **6** would serve as an intermediate en route to demethanation. In addition, the reaction **4** → **5** may profit due to a primary kinetic isotope effect as compared with **4** → **6**. Consequently, CH_4 loss is favored over the elimination of CH_3D. For the analogous intermediates **5′** and **6′** derived from the diastereoisomers **2d** and **3d**, the stereochemistry of the hydrogen and deuterium atoms at the (*ω*-1) positions is interchanged. The fact that from these precursors CH_3D loss is favored as compared to CH_4 elimination (by a factor of 1.25) clearly underlines that the possible operation of primary kinetic isotope effect in the hydrogen (deuterium) transfer steps alone cannot explain the data for the **2e** and **3e** complexes. Rather, a conformational aspect as indicated by the different steric demands of **5** and **6** (and, analogously, of **5′** and **6′**) has to be taken into account. (ii) The second mechanism, depicted in Scheme 4, commences with an insertion of the metal ion into the C−H (or C−D) bond of the (*ω*-1) position to generate **7** or **8**, followed by an endocyclic *β*-methyl shift via a presumably planar four-centered intermediate. As in Scheme 3, the reaction is terminated by reductive eliminations of CH_4 or CH_3D, respectively. In analogy to the mechanism discussed in Scheme 3 we assume that the system will populate preferentially the conformationally favored intermediate **7** rather than the more sterically demanding metallacycle **8**.

Scheme 4



These first principle considerations show that for either

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(17) For the sake of clarity, in Schemes 3 and 4 only the reactions of one diastereoisomer of the racemic pairs of **1e**, **2e**, and **3e** are presented.

reaction sequence the elimination of CH_4 is favored over CH_3D for the complexes **2e**/Co^+ and **3e**/Co^+ both in terms of conformation and of a primary kinetic isotope effect. On the other hand, the more pronounced loss of CH_3D for the complexes **2d**/Co^+ and **3d**/Co^+, despite a possibly retarding kinetic isotope effect associated with the migration of a deuterium atom, clearly calls for the existence of an overriding factor; this we assign to the different energy demand associated with the formation of diastereomeric metallacyclic intermediates.

Although the experimental data do not allow us to unequivocally settle the question of initial C−C insertion/β-H transfer versus C−H insertion/β-CH_3 migration, some aspects of related work are worth mentioning. First, thermochemical considerations imply that Co^+ should preferentially undergo C−C rather than C−H bond insertion with alkanes.[18] In addition, for the demethanation of the branched nitriles examined in this study, the tertiary C−CH_3 bond is weaker than the secondary C−H bonds of the (ω-1) position. As far as remote functionalization is concerned, earlier deuterium-labeling and MS/MS experiments for the reactions of linear nitriles complexed to transition-metal ions suggest that, for $M^+ = Co^+$, small alkane fragments are eliminated by initial C−C bond activation followed by β-hydrogen shift and reductive elimination.[19] Further evidence for the direct oxidative addition of remote C−C bonds, followed by β-hydrogen transfer and reductive elimination, was provided in the Fe^+-mediated demethanation of *tert*-butyl substituted nitriles.[7d] On the other hand, it has been reported that insertion into a directional C−CH_3 bond is less facile on energetic grounds as compared to the insertion into a C−H bond.[20] Moreover, several recent studies of the relative energetics of C−H and C−C bond activation of simple, unsubstituted alkanes in the gas phase have shown that an initial C−H insertion followed by β-C−C cleavage is the energetically favored reaction path for the demethanation of, for example, propane.[21] Furthermore, theoretical studies of the activation of alkane C−H and C−C bonds by different transition metals show that the barrier for C−C bond insertion is in general 14−20 kcal/mol higher than the barrier for C−H bond insertion.[22] Thus, while for Co^+ the insertion product of C−C bond activation is thermodynamically more stable as compared to the C−H inserted species, the associated activation barriers render C−H bond activation the kinetically favored process. In fact, these latter two considerations point toward the operation of an initial C−H insertion followed by β-methyl shift;[23] note, however, that the initial step may also not necessarily be rate-determining.[24,25] Notwithstanding these conflicting arguments, in overview several factors favor initial C−C bond activation in the particular cases studied here: (i) The deuterium distributions in the other reaction products from **1−3**/Co^+ (hydrogen, ethene, ethane, and butene) demonstrate that bond activation occurs in almost all positions of the terminal *sec*-butyl groups, suggesting that initial bond activation is feasible at various positions. (ii) The losses of CH_4 and CH_3D from **1−3**/Co^+ are associated with small and even inverse kinetic isotope effects (see below); hence, neither C−H(C−D) bond activation nor H(D) transfer are rate-determining. (iii) The endocyclic β-methyl migrations from **7** and **8** would be associated with considerable steric constrains, such that initial C−C bond insertion according to Scheme 3 seems to be more likely. However, whatever mechanism is operative, the present results provide, for the first time, experimental evidence of a transition-metal mediated *diastereoselective* carbon−carbon bond activation in the gas phase.

There remain at least three other aspects which should be mentioned briefly: (i) for the Co^+ induced dehydrogenation of **1−3** we cannot probe the stereoselectivity since the process does not fulfill the necessary condition of being regiospecific (Table 2); similarly, the details for the loss of ethane from the terminal part of the alkyl chains of **1−3** remain uncovered, as in this process the chiral information provided by the (ω-1) and (ω-2) positions does not matter. Finally, for the loss of C_4H_8 it is not possible within the experimental error to draw any conclusions regarding the stereochemistry of the reaction. (ii) Surprisingly, the metastable ion (MI) mass spectra of the Co^+ complexes of the *rac*-[6-D_1]-5-methylheptanenitriles **1d**/Co^+ and **1e**/Co^+ do not exhibit any diastereoselectivity with regard to the loss of methane. This may reflect the larger ring strain of the intermediate metallacycles formed as compared to the higher homologues, such that all barriers increase along with the internal energy content of the metastable ions and the subtle differences due to stereochemistry vanish.[26] However, other explanations are conceivable and remain to be explored in the future. (iii) The ratio of CH_4/CH_3D loss (0.8 ± 0.1) for the diastereomeric complexes of **2d** and **3d** points to an inverse isotope effect, although this ratio is more likely to reflect conformational preferences of the various intermediates as discussed above. While inverse kinetic isotope effects have been reported in a number of previous studies,[27] the experimental data available do not permit to unequivocally argue in favor of such an effect. Surely, a hidden hydrogen rearrangement[27a] does not explain the observed effect. Further, while it is theoretically possible to observe inverse kinetic isotope effects in a reaction proceeding through a single rate-determining step,[27b,c] experimental results[28] seem to indicate that inverse kinetic isotope effects appear in reactions involving a rapid pre-equilibration with a transient intermediate which possesses increased zero-point energy relative to its precursor.[29]

Conclusions

Diastereospecifically labeled nitriles such as *rac*-[7-D_1]-6-methyloctanenitrile **2d,e** and *rac*-[8-D_1]-7-methylnonanenitrile **3d,e** represent highly interesting systems for probing subtle

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details of the *stereochemistry* of the Co^+-mediated *remote functionalization of carbon—carbon bonds* in the gas phase. Analysis of the unimolecular fragmentation patterns of these Co^+ complexes demonstrates that the loss of neutral methane follows a regiospecific 1,2-elimination mode. The unprecedented diastereoselective discrimination operative in this reaction can be rationalized in terms of different steric demands (1,2-interaction between the (ω-2) and (ω-1) positions) in the metallacyclic intermediates.

Nevertheless, even the extensive use of isotopic labeling techniques is not powerful enough for a complete quantitative analysis of both isotope and steric effects. Hence, theoretical modeling is highly indicated to unravel the mechanistic details, such as the energetically preferred primary site of insertion of the metal ion (i.e., initial C—H versus C—C bond activation) as well as the influence of rotational barriers. In particular, we propose the drastic chain-length effect[2b,30] on the occurrence of diastereoselectivity (**1** versus **2** and **3**) provides a case in point for the development of reliable theoretical models for the stereo- and regiochemistry of metal-mediated C—H and C—C bond activation in the gas phase.

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