Enantioselective Dehydrogenation of Alkan-2-ols by Gaseous (BINOLate)Ni$^+$

Short Communication

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Dedicated to Professor *Robert G. Bergman* on the occasion of his 60th birthday

Electrospray ionization of methanolic solutions of nickel(II) nitrate, 1,1′-binaphthalene-2,2′-diol (BINOL), and secondary alcohols (ROH) *inter alia* affords monocationic complexes of the type [(BINOLate)Ni(ROH)]$^+$, where BINOLate stands for singly deprotonated BINOL. Upon collision-induced dissociation (CID), the mass-selected ions undergo competing fragmentations involving loss of the alcohol ligand and expulsion of the corresponding carbonyl compound. The latter reaction leads to the hydride complex [(BINOL)Ni(H)]$^+$ and can thus be regarded as the reversal of the reduction of ketones with metal hydrides. The possibility of the occurrence of enantioselective gas-phase reactions is probed for combinations of chiral BINOLate ligands with chiral alkan-2-ols. Whereas aliphatic alkan-2-ols do not show pronounced chiral effects, enantioselective bond activation is observed for 1-phenylethanol, indicating an interaction of the aromatic ring of the alkanol with the positively charged metal center.

Introduction. – While mass spectrometry has elucidated a wealth of mechanistic details about gas-phase reactions of transition-metal ions, even relevant in the context of homogeneous and heterogeneous catalysis [1], only few examples of enantioselective gas-phase reactions have been reported so far. This is indeed a crucial lack of insight, considering the enormous relevance of transition-metal catalysts in asymmetric synthesis, on the one hand, and the often rather limited mechanistic information about these reactions, on the other. In particular, the molecular origin of enantioselectivity in transition-metal-mediated reactions is often unknown, and catalyst optimization thus by and large still based upon mere trial-and-error procedures, instead of relying on more systematic approaches. One major reason for the only few examples of enantioselective reactions in gas-phase chemistry is associated with the use of mass spectrometry, which *a priori* is an achiral method of detection. Moreover, as the desired, usually organic product is released as a neutral molecule after bond-formation has taken place, it escapes detection in conventional mass-spectrometric experiments. The challenge in the discovery of enantioselective gas-phase reactions is thus not only to find appropriate systems which bear chiral effects, but also to identify those systems in which these effects can be measured by monitoring the ionic products of a reaction.

Conceptually, the search for enantioselective reactions in the gas phase, therefore, needs to begin with the investigation of the activation of chiral substrate molecules, S*, by chiral metal-ion complexes, $[ML^*]^{+/-}$, either in an ion/molecule reaction of the mass-selected ion $[ML^*]^{+/-}$ with a chiral neutral reagent S* or by probing diastereoisomeric complexes of the type $[ML^* \cdot S^*]^{+/-}$ by appropriate techniques [2–4].

Experimental. – The experiments were performed with a *VG BIO-Q* mass spectrometer which has been described in [5]. Briefly, the *VG BIO-Q* is a commercial instrument which consists of an ESI source combined with a tandem mass spectrometer of QHQ configuration (Q stands for quadrupole and H for hexapole). In the present experiments, mM solns. of nickel(II) nitrate, 1,1′-binaphthalene-2,2′-diol, and the desired secondary alcohol ROH in pure MeOH were introduced through a fused-silica capillary to the ESI source *via* a syringe pump (*ca.* 5 µl/min). N_2 was used as nebulizing and drying gas at a source temp. of 80°. Maximal yields of the desired $[(BINOLate)Ni(ROH)]^+$ ions were achieved at cone voltages of *ca.* 30 V. The identity of all complexes and of all ion/molecule reactions was confirmed by comparison with the expected isotope patterns[1]) in either the ion-source spectra or in adequate neutral-loss scans. For collision-induced dissociation (CID), the ions of interest were mass-selected using Q1, interacted with Xe as a collision gas in the hexapole H under single-collision conditions (typically $2 \cdot 10^{-4}$ mbar) at variable collision energies ($E_{lab} = 0-20$ eV), while scanning Q2 to monitor the ionic products.

Results and Discussion. – Here, we report an example of a chiral gas-phase reaction for Ni^{II} complexes of secondary alcohols and a BINOLate ligand (BINOLate stands for singly deprotonated 1,1′-binaphthalene-2,2′-diol) [7][8] which are generated *via* electrospray ionization (ESI) [9]. Upon ESI of mM solns. of nickel(II) nitrate, 1,1′-binaphthalene-2,2′-diol, and a secondary alcohol ROH in pure MeOH, *inter alia* monocationic species with the formal composition $[(BINOLate)Ni(ROH)]^+$ are generated. Based on experiment, the alternative alkoxo structure $[(BINOL)Ni(OR)]^+$ cannot be ruled out strictly; for previous studies of transition-metal alkoxide ions, see [10]. However, given that phenols such as BINOL are generally more acidic than alkanols [11], and the experimental observation that collision-induced dissociation (CID) leads to loss of the neutral alcohol ROH concomitant with formation of $(BINOLate)Ni^+$, we further assign the generic structure $[(BINOLate)Ni(ROH)]^+$ to these ions in the following.

For alkan-2-ol ligands, $RCHOHCH_3$, CID of the mass-selected $[(BINOLate)Ni(RCHOHCH_3)]^+$ ions leads to two primary channels, *Reactions 1* and *2*; at elevated collision energies, consecutive fragmentations of the BINOL residue are observed (*e.g.*, decarbonylation) which are not pursued any further here [8][12].

$$[(BINOLate)Ni(RCHOHCH_3)]^+ \longrightarrow \begin{cases} (BINOLate)Ni^+ + RCHOHCH_3 & (1) \\ [(BINOL)Ni(H)]^+ + RCOCH_3 & (2) \end{cases}$$

Reaction 1 corresponds to a simple loss of the coordinated alkanol, whereas *Reaction 2* indicates the occurrence of C–H bond activation. Formation of the ketone as a product of *Reaction 2*, rather than the conceivable activation of remote C–H

[1]) Calculated using the Chemputer made by *M. Winter*, University of Sheffield (see [6]).

bonds in the alcohol [13][14], is confirmed by isotope labeling at the 2-position, *i.e.*, exclusive losses of $CH_3CD(OH)CH_3$ and CH_3COCH_3 for the complex with 2-deuteropropan-2-ol. From a mechanistic perspective, this redox reaction in which an alkanol is converted to the corresponding carbonyl compound corresponds to the reversal of the reduction of an aldehyde or ketone by a transition-metal hydride [15][16]. Moreover, the combination of a BINOLate ligand with a secondary alcohol, both coordinated to the same metal center, offers the option to probe, whether this gas-phase reaction is subject to enantioselective effects. To this end, the corresponding $[((R)\text{-BINOLate})Ni(RCHOHCH_3)]^+$ complexes were generated by ESI of methanolic solutions of $Ni(NO_3)_2$, (*R*)-BINOL, and the respective alcohol $RCHOHCH_3$, mass-selected, and their CID spectra were recorded. In this communication, we restrict ourselves to the data obtained at the lowest collision energy at which a significant amount of fragmentation was achieved (*i.e.*, 3 eV in the laboratory frame), because this can be considered as being most sensitive with regard to enantioselective effects in CID [7].

Inspection of the data in *Table 1* reveals the following effects. At first, *Reactions 1* and *2* compete effectively with each other, implying that the energy demand of the transition structure associated with the bond activation in *Reaction 2* is of similar magnitude as the bond energies of the alkan-2-ols for the systems under study. The contribution of the bond-activation channel rises significantly from isopropanol to butan-2-ol and then somewhat decreases with increasing size of the substituent; however, this effect is only minor in that both channels have a similar magnitude for the systems summarized in *Table 1*. With regard to enantioselectivity, the following conclusions can be drawn. *i*) For relatively small substituents such as $R = C_2H_5$, no

Table 1. *Branching Ratios of* Reaction 1, *Loss of the Alcohol Ligand, and* Reaction 2, *Loss of the Corresponding Ketone, upon CID of Mass-Selected* $[((R)\text{-BINOLate})Ni(RCHOHCH_3)]^+$ *Ions with Several Secondary Alcohols with Different Substituents R and Sense of Chirality, and the Stereochemical Effects* (*SE*) *Derived Thereof*[a])[b])

R	Sense of chirality	Alcohol	Ketone	*SE*[c])
CH_3		65	35	
C_2H_5	(*R*)	49	51	0.97 ± 0.05
	(*S*)	49	51	
n-C_3H_7	(*R*)	50	50	1.03 ± 0.07
	(*S*)	49	51	
n-C_4H_9	(*R*)	49	51	1.04 ± 0.05
	(*S*)	48	52	
n-C_5H_{11}	(*R*)	51	49	0.97 ± 0.05
	(*S*)	52	48	
n-C_6H_{13}	(*R*)	53	47	0.92 ± 0.05
	(*S*)	55	45	
Ph	(*R*)	63	37	1.39 ± 0.07
	(*S*)	55	45	

[a]) Branching ratios of *Reactions 1* and *2* derived from repeated experiments and normalized to $\Sigma = 100$. [b]) Collision energy of 3 eV in the laboratory frame; collision gas: Xe. [c]) Stereochemical effects defined as $SE = [BR(1)_R/BR(2)_R]/[BR(1)_S/BR(2)_S]$ with the error derived from repeated experiments.

significant stereochemical effect is observed. This finding is consistent with the reasoning that chiral discrimination in alkan-2-ols is associated with the differentiation between the alkyl substituent R and the terminal CH_3 group, and this difference may be marginal for small substituents. *ii*) Perfectly consistent with this line of reasoning, a minor, but yet significant *SE* occurs for the larger substituent in octan-2-ol with R = *n*-C_6H_{13}. The numerical value of $SE = 0.92 \pm 0.05$ for this couple implies that either bond activation is more facile in the homochiral system, or that the expulsion of the alcohol ligand is favored for the heterochiral complex. *iii*) A more pronounced *SE* is observed for the complex with 1-phenylethanol, which might be attributed to the larger size of the Ph substituent located in close vicinity of the stereogenic center of the alkanol. Interestingly, however, not only the *SE* itself is more pronounced, but also the direction is inverted in that $SE = 1.39 \pm 0.07$ indicates a disfavored bond activation in the homochiral couple, or a more strongly bound alkanol ligand in the case of the heterochiral complex. Before further addressing the origin of this effect, let us deconvolute the chiral effects operative in ligand loss and the C–H bond activation channel, respectively. To this end, it deems indicated to provide some fundamental background of the gas-phase approach used here.

Mass-spectrometric experiments such as those described in this work are *a priori* invariant with regard to the symmetry of the system, and hence no discrimination between enantiomers can be made. Specifically, the experimental observables such as ion mass and kinetic energy do not depend on the chirality of the compounds under study. Moreover, the neutral products of an ion reaction usually escape experimental detection by mass-spectrometric means[2]). For these reasons, the approach applied here for the investigation of the chiral induction by BINOLate complexes of Ni^{II} employs another chiral substrate, the alkan-2-ols, as a probe for monitoring the enantioselective discrimination in the resulting diastereoisomeric complexes of the ligand ((*R*)- or (*S*)-BINOLate) and the substrates ((*R*)- or (*S*)-alkan-2-ols). Provided that a significant energy difference exists for the diastereoisomeric transition structures associated with bond activation, the enantiomeric discrimination can hence be probed by the yields of the corresponding products. Note that, due to the symmetric nature of the mass spectrometric experiments, only the pair of the homochiral complexes ((*RR*) and (*SS*)) *vs.* the pair of the heterochiral complexes ((*SR*) and (*RS*)) can be distinguished from each other, whereas, within the enantiomeric pairs, identical results are to be obtained. The data summarized in *Table 2* for the complexes of (BINOLate)Ni^+ with 1-phenylethanol may serve as a demonstration of these considerations: Comparison of the homochiral complexes ((*RR*) and (*SS*)) with the heterochiral ones ((*RS*) and (*SR*)) reveals a significant stereochemical effect of 1.46 ± 0.10, whereas no *SE* is found within the enantiomers of the homo- and heterochiral pairs (0.99 ± 0.05).

The data given in *Table 2* demonstrate both the applicability and the validity of this mass-spectrometric approach for the investigation of stereochemical reactions in the gas phase. Part of this achievement is associated with the fact that ligand loss is used as a sensitive internal reference channel. An inherent problem associated with this approach is, however, that also the reference channel may be subject to a stereo-

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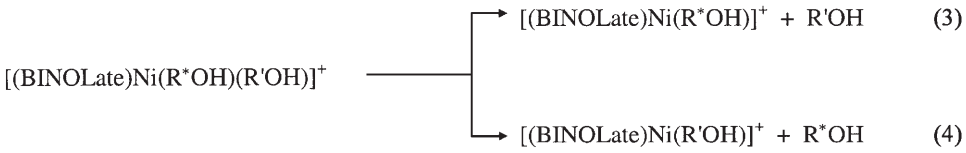
[2]) Neutralization – reionization mass spectrometry [17] has been successfully applied for the characterization of organic products formed in metal-mediated reactions in the gas phase (see [18]).

Table 2. *Branching Ratio of* Reactions 1 *and* 2 *upon CID of Mass-Selected [(BINOLate)-Ni($C_6H_5CHOHCH_3$)]$^+$ Ions with Different Sense of Chirality of the Precursors Used in ESI*[a])[b])

BINOL	1-Phenylethanol	Alcohol	Ketone	*SE*[c])
(*R*)	(*R*)	61	39	1.44 ± 0.07
	(*S*)	52	48	
(*S*)	(*R*)	52	48	1.48 ± 0.07
	(*S*)	62	38	

[a]) Branching ratios of *Reactions 1* and *2* derived from repeated experiments and normalized to Σ = 100. [b]) For larger sensitivity to stereochemical effects [7], these CID experiments were performed at a collision energy of 2 eV in the laboratory frame; collision gas: Xe. [c]) See *Footnote c* of *Table 1*.

chemical effect. As indicated above, an increased amount of the bond-activation channel for one set of epimeric complexes is, therefore, either an indication for an energetically preferred transition structure of this particular channel or the result of a disfavored reference channel, where the latter is correlated with the relative bond energies of the homo- and heterochiral complexes of (BINOLate)Ni^+ with the alkan-2-ols. An unambiguous deconvolution of these effects is extremely demanding, and, hence, a different approach is required in order to probe the reference channel in an independent manner. For this purpose, we generated trisligated complexes of the type [(BINOLate)Ni^+(R*OH)(R′OH)]$^+$, where R*OH stands for the chiral alkan-2-ol ligand and R′OH is another, achiral reference alcohol. With regard to the latter, heptan-4-ol turned out to serve well this purpose. Hence, quarternary mixtures of BINOL, $Ni(NO_3)_2$, heptan-4-ol, and the chiral alkan-2-ols (R = *n*-C_6H_{13} and Ph, resp.) dissolved in MeOH were subjected to ESI, and, under soft ionization conditions, sufficient amounts of the desired trisligated complexes could be generated, which were mass-selected and subjected to CID.



Provided that the alkanols are the most weakly bound ligands, occurrence of *Reactions 3* and *4* can be expected in the dissociation of such complexes, where the branching ratio reflects the relative binding energies of the alkanols to the (BINOLate)Ni^+ fragment. With respect to stereochemistry, *Reaction 3* preserves the diastereoisomeric energetic difference and may hence be insensitive to the chirality of the components. Instead, *Reaction 4* leads to a pair of separated enantiomers as products which are indistinguishable in the mass spectrometer, and differences in abundances should, to a first approximation, reflect energetic differences of the diastereoisomeric precursor pairs. Specifically, dissociation of the trisligated [(BINOLate)Ni^+(R*OH)(R′OH)]$^+$ precursor ions leads to the bisligated

[(BINOLate)Ni^+(R*OH)]$^+$ ions. Hence, *Reaction 3* is directly linked with the *Reactions 1* and *2* described above, and the use of heptan-4-ol provides the required additional independent reference channel which is not subject to an *SE* [7][19]. By this approach, the *SE* values associated with the binding of octan-2-ol and 1-phenylethanol, respectively, to (BINOLate)Ni^+ were determined, which turned out being close to unity for these couples. Thus, the ratio of octan-2-ol and heptan-4-ol losses is 67:33 with a negligible *SE* of 1.01 ± 0.04 for the different combinations of enantiomers. In the case of the trisligated phenylethanol complex, the heptan-4-ol reference ligand is lost with large preference (13:87), whereas the experimentally measured *SE* is again insignificant (1.03 ± 0.05). With this additional information, we can conclude that the stereochemical effects reported in *Table 1* for the complexes of octan-2-ol and 1-phenylethanol are indeed associated with the crucial bond-activation step in the dehydrogenation of the alkan-2-ols to the corresponding ketones. By reference to the concept of microscopic reversibility, the diastereoselective discrimination observed in *Reaction 2* for these two alkanols may thus be regarded as a gas-phase model for the enantioselective reduction of carbonyl compounds by metal-hydride species [20] probed at strictly molecular level.

Last but not least, the direction of the observed effects deserves some attention. Within the series of the alkan-2-ols, variation of the alkyl chain continuously increases the steric demand of the substituents. The observed *SE* values, therefore, reflect the increasing differentiation between the substituents of the stereogenic center. In line with this way of reasoning, the *SE* values are insignificant for the small substituents such as C_2H_5 and only become significant for the largest system studied, *i.e.*, octan-2-ol, for which bond activation is slightly favored in the homochiral complex (*Table 1*). In contrast, dehydrogenation of the heterochiral complexes is preferred upon interaction of (BINOLate)Ni^+ with 1-phenylethanol. This inversion of the directionality of the *SE* implies that the fundamental interaction of the substituents with the stereogenic metal center is different in these two cases. As mere steric repulsion of the substituents may safely be assumed in the case of octan-2-ol, the results for 1-phenylethanol indicate the existence of an attractive interaction between the arene substituent and the positively charged metal center [21]. This line of reasoning finds further (indirect) support in the data of the trisligated complexes in that heptan-4-ol is apparently more strongly bound to (BINOLate)Ni^+ than octan-2-ol, whereas 1-phenylethanol is an even better ligand than heptan-4-ol. Much like in *Cram* and anti-*Cram* models for the addition of nucleophiles to carbonyl groups [22], such a favorable electronic interaction of the largest substituent with the reaction center leads to an inversion of the stereochemical outcome as compared to a mere steric interaction. The stereoselectivity reported here may trigger further investigations about the suggested interaction of the Ni-center with the arene ring, and the present systems may prove small enough in size for future theoretical treatments.

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