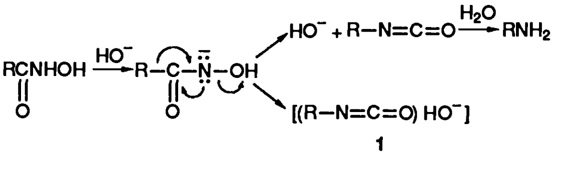
Does the Lossen Rearrangement Occur in the Gas Phase?

Gregory W. Adams,[a] John H. Bowie*,[a] and Roger N. Hayes[b]
[a] *Department of Organic Chemistry, The University of Adelaide, South Australia, 5001 Australia*
[b] *Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0362, USA*

Deprotonated hydroxamic acids and cognate systems undergo a number of rearrangement processes upon collisional activation. It is proposed that ions $RCO\bar{N}OH$ undergo the Lossen rearrangement to form $[(OCNR)HO^-]$, and that this reactive intermediate may decompose to form the ionic products HO^-, $[(R-H)^-NCO]$, NCO^- and RNH^-. Alternatively, hydrogen transfer yields $RCONHO^-$ which may undergo a three-centre reaction to produce RCO_2NH^-; this species may decompose to yield both RCO_2^- and $[(R-H)CO_2]^{\cdot -}$. Fragmentation processes have been investigated by both deuterium labelling and product ion studies.

Deprotonated organic molecules, under conditions of collisional activation, undergo characteristic decomposition in the gas phase. A set of general 'rules' for such fragmentations has been proposed.[1] The charged site is normally involved in fragmentation, and when simple radical or neutral loss is either impossible or energetically unfavourable, skeletal rearrangement of the ion often precedes decomposition. A number of intramolecular rearrangements of even-electron anions have been reported recently; often such reactions have analogies with base catalysed reactions which occur in solution. Some examples include the Wittig,[2] oxy Cope,[3] Claisen,[4] Smiles[5] and Beckmann[6] rearrangements.

The Lossen rearrangement is one of the better known nitrogen anion rearrangements in the condensed phase.[7] Hydroxamic acids (or their acyl derivatives) yield isocyanates when treated with base [eqn. (1)], or sometimes just on heating. If this reaction occurs in the gas phase, then ion–molecule complex **1** [eqn. (2)] should be formed initially. Such a complex should be easily identified by its fragmentation behaviour. This paper therefore reports the fragmentation behaviour of deprotonated hydroxamic acids and cognate systems with a view to determining whether the Lossen rearrangement occurs in the gas phase.



(1)

(2)

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Results and Discussion

The collisional activation mass spectra (CA MS/MS) of a variety of deprotonated hydroxamic acids and cognate systems are listed in Table 1 or illustrated in Figs. 1–3. The tandem mass spectra (MS/MS/MS) of certain product ions from selected spectra are recorded in Table 2. These spectra are mainly charge reversal (positive ion) mass spectra,[8] but some CA MS/MS/MS data are also included.[9-11]

Hydroxamic acids should deprotonate preferentially on nitrogen: this can be seen from the following known ΔH^0_{acid} values—$MeCONH_2$(1430 kJ mol^{-1}),[12] $PhCONH_2$(1452.5 kJ mol^{-1}),[12] CH_3CONMe_2(1569.5 kJ mol^{-1})[12] and NH_2OH(1629 kJ mol^{-1}).† In accord with this prediction, $CD_3CONHOH$ is deprotonated by NH_2^- to form only an $(M-H)^-$ species.

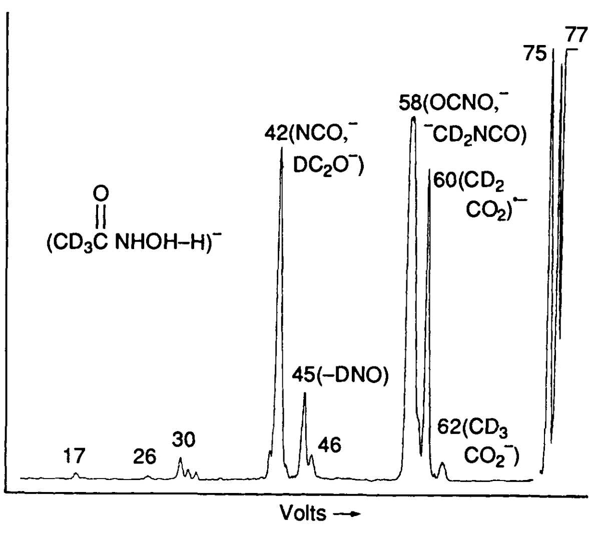

Fig. 1 Collisional activation mass spectrum of deprotonated $CD_3CONHOH$. For experimental conditions see Experimental section. The major components of *m/z* 42 and 58 are NCO^- and $OCNO^-$ respectively [*cf.* the spectrum of $MeCO\bar{N}OH$ (Table 1)].

The fragmentations of deprotonated hydroxamic acids are complex: let us consider the spectra of $MeCO\bar{N}OH$ (Table 1) and $CD_3CO\bar{N}OH$ (Fig. 1) as prototypical examples. The major fragmentations are explicable in terms of reactions directed by the nitrogen anion site. Loss of a hydrogen atom occurs by the two processes shown in eqns. (3) and (4) (Scheme 1): both form a stabilised radical anion. The only reactions which appear to occur following proton transfer from the methyl group to the nitrogen site are those forming HC_2O^-[eqn. (5)] and $MeCO^-$ [eqn. (6)]. The structures of these product ions are confirmed by the data in Table 2. These are interesting reactions, because even though ^-NHOH is a powerful base (ΔH^0_{acid} CH_2CO and NH_2OH = 1526[14] and 1670[13] kJ mol^{-1}, respectively), the electron affinity of $^{\cdot}NHOH$ is calculated to be −17 kJ mol^{-1},[13] indicating that ^-NHOH should be unstable with respect to its radical.‡

The key question, however, is whether a gas phase Lossen rearrangement is operative, *i.e.* whether an incipient methyl

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† *ab initio* calculation at the MP4 (SDTQ)-FC/6-311++G**//-HF/6.311++G** level.[13] Clearly ΔH^0_{acid} $RCONHOH$ should be somewhat lower than this value. ΔH^0_{acid} (HA) is the energy necessary to effect the conversion $HA \rightarrow H^+ + A^-$.

‡ A similar situation occurs for $^-CH_2OH$ which cannot be detected directly, but which may react when stabilised in an ion–molecule complex.[15]

Table 1 Collisional activation mass spectra of deprotonated R^1CONHR^2(R^2 = OH, OMe, NH_2 and NMe_2) species

Neutral precursor	Loss													Formation				
(R^1CONHR_2)	$H^•$	H_2	NH	$NH_2^•$	NH_3	$Me^•$	$R^{2•}$	R^1H	R^2H	$Et^•$	$CHO^•$	HNO	NH_2OH	R^{1-}	R^{2-}	NCO^-	H_2CN^-	CN^-
MeCONHOH	100		12	61[a]				61[a]	5			12	14		1	26	1	1
$CD_3CONHOH$	See Fig. 1																	
EtCONHOH	74		5	39	55			15	15						1	100	2	1
PrCONHOH	100		6	40	12			18	8						1	28		1
$Pr^iCONHOH$	100	4	6	11	12			33	28						2	78		
PhCONHOH	See Fig. 2																	
MeCONHOMe	30					100	20		34						10	31	2	
$MeCONHNH_2$	36						100[a]	100[a]								25		
$CD_3CONHNH_2$	See Fig. 3																	
$EtCONHNH_2$	40						100	32								28		
$PrCONHNH_2$	100						42	43		22						50		
$PhCONHNH_2$		40					32	100			47			12		18		
$PhCH_2CONHNH_2$	95	22					43	53						100		4		
$MeCONHNMe_2$	28					100	33	18								9		

[a] $NH_2^•$ and CH_4 are both 16 amu.

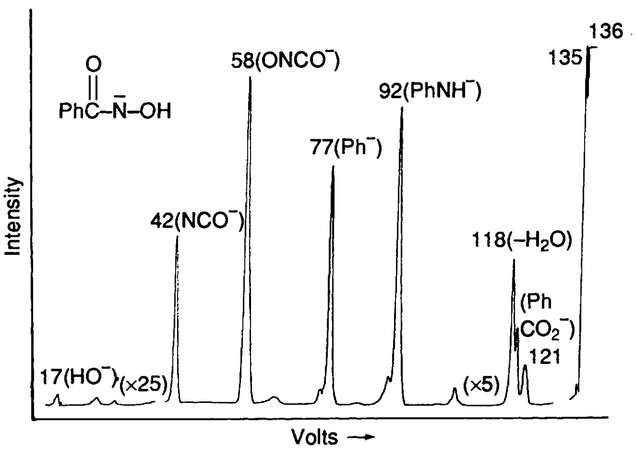
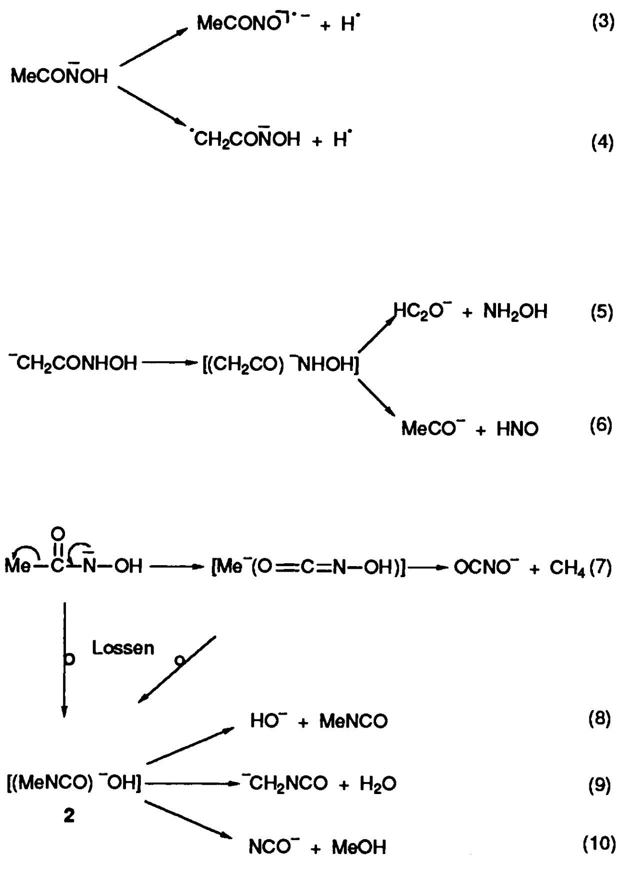
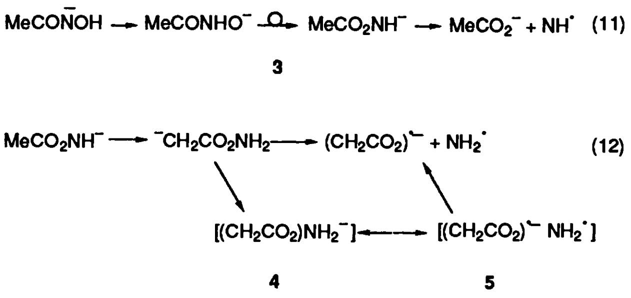


Fig. 2 Collisional activation mass spectrum of deprotonated PhCONHOH



Scheme 1



Scheme 2

anion rearranges to the nitrogen site. It seems that a transient methyl anion system is formed, since a major fragmentation is loss of methane with formation of $OCNO^-$ [eqn. (7)]. The structure of the product ion is confirmed by the data recorded in Table 2.

There a number of fragmentations which require more deep seated rearrangement of the system. These fall into two major categories; (*i*) the formation of HO^- and NCO^- and the loss of H_2O, and (*ii*) the losses of NH and $NH_2^•$. We suggest that the former set of reactions is best rationalised in terms of fragmentation through Lossen intermediate **2**. Whether that intermediate is formed directly from $MeCO\bar{N}OH$ or indirectly from [Me^-(OCNOH)] is not known. We suggest that **2** may decompose directly to form HO^- [eqn. (8)], effect internal deprotonation [eqn. (9)] and undergo an internal S_N2 reaction [eqn. (10)]. The formation of NCO^- is a major process; the structure of this ion is confirmed by the data presented in Table 2.

The losses of NH and $NH_2^•$ form $MeCO_2^-$ and $(CH_2CO_2)^{•-}$, respectively. We suggest that these are formed following proton transfer/three-centre rearrangement as shown in eqns. (11) and (12).* The two possible reaction sequences shown in eqn. (12)

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* A reviewer has suggested that $MeCONHO^-$ [eqn. (11)] may also be formed directly by deprotonation of the neutral. This possibility cannot be excluded on available evidence, even though the O–*H* is the least acidic position in the neutral.

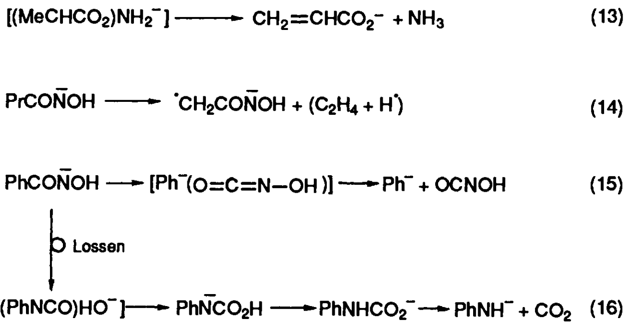
Table 2 Mass spectra (MS/MS/MS) of product ions in particular spectra[a]

Precursor ion (m/z)	Product ion (m/z)	Spectrum type	Spectrum m/z (loss) relative abundance
$(MeCONHOH\text{-}H)^-$ [74]	HC_2O^- (41)	CR	40($H^\bullet$)100, 28(CH)80, 25(O)70, 13(CO)60.
	NCO^- (42)	CR[b]	30(C)25, 28(N)80, 26(O)100, 16(CN)5, 14(CO)10.
	$MeCO^-$ (43)	CR[c]	43(100), 42($H^\bullet$)95, 29(CH_2)70, 28($Me^\bullet$)30, 26($HO^\bullet$)20, 15(CO)70, 14($CHO^\bullet$)30.
$(CD_3CONHOH\text{-}H)^-$ [77]	$OCNO^-$ (58)	CR[d]	44(N)15, 42(O)100, 30(CO)30, 28(NO)35.
	$(CD_2CO_2)^{\bullet-}$ (60)	CR[e]	44(CD_2,O)100, 42(OD)35, 30($CDO^\bullet$)30, 28(CD_2O)20, 16(CO_2)10.
$(PrCONHOH\text{-}H)^-$ [102]	${}^\bullet CH_2CO\bar{N}OH$ (73)	CR	43(NO)35, 42(NOH)100, 30($MeCO^\bullet$)40.
$PhCONHOH\text{-}H)^-$ [136]	$PhCO_2^-$ (121)	CA	77(CO_2)100.
		CR	77(CO_2)100, 51(CO_2 + C_2H_2)40, 50(CO_2 + $C_2H_3^\bullet$)20.
	$PhNH^-$ (92)	CA[f]	91($H^\bullet$)100, 90(H_2)20, 65(HCN)1.
		CR[f]	92(parent)100, 91($H^\bullet$)60, 77(NH)24, 65(HCN)89, 64(28)43, 63(29)32, 52(40)20, 51(41)24, 50(42)20, 39(53)27, 38(54)19, 37(55)10, 26(66)5.
$(CD_3CONHNH_2\text{-}H)^-$ [76]	OCNNH- (57)	CR[g]	56($H^\bullet$)20, 43(N)10, 42(NH)70, 29(CO,N_2)60, 28($N_2H^\bullet$, $CHO^\bullet$)100.
	$CD_3NCO\urcorner^{\bullet-}$ (60)	CA	42($CD_3^\bullet$)100.
		CR	58($D^\bullet$)15, 46(N)45, 44(O)60, 42($CD_3^\bullet$)100, 30(C_2D_3)60, 28(CD_2N)20, 18(NCO)25, 16(CD_3NC)8, 14($CD_3CO^\bullet$)5.
$(PrCONHNH_2\text{-}H)^-$ [101]	${}^\bullet CH_2CO\bar{N}NH_2$ (72)	CR	55(NH_3)20, 43($N_2H^\bullet$)50, 42(N_2H_2)100, 29($MeCO^\bullet$)80, 28(CH_4N_2, C_2H_4O)95.

[a] The majority of product ions were not formed in high enough abundance to allow the detection of collision induced negative ion decompositions: all of the charge reversal (positive ion) spectra are weak and 'noisy' abundances are correct to within ± 5%; [b] for the spectrum of NCO^- see [9]; [c] this is the spectrum of $MeCO^-$ *not* the isomer $^-(CH_2CHO)$, see [10]; [d] for the spectrum of $OCNO^-$ see [11]; peaks m/z 15–12 are lost in baseline noise; [e] the CR MS/MS data for authentic $(CD_2CO_2)^{\bullet-}$ [formed from [D_6] acetic anhydride/DO^-, VG ZAB 2HF instrument] are: 44(CD_2,O)100, 42($DO^\bullet$)30, 40(D_2O)5, 30($CDO^\bullet$)25, 28(CD_2O)28, and 16(CO_2)5; [f] in this case the MS/MS/MS plots are too weak to be meaningful; the recorded spectra are for m/z 92 formed *in the source* of the ZAB 2HF. The corresponding spectra of deprotonated aniline are as follows: CA MS/MS: 91($H^\bullet$)100, 90(H_2)21 and 65(HCN)1; CR/MS/MS: 92(parent)100, 91($H^\bullet$)62, 77(NH)22, 65(HCN)83, 64(28)34, 63(29)28, 52(40)18, 51(41)23, 50(42)17, 39(53)26, 38(54)20, 37(55)10 and 26(66)4; [g] for the spectrum of $OCNNH^-$ see [11].

are particularly interesting. The data in Table 2 confirm the structure of the product radical anion but whether the decomposition of $^-CH_2CO_2NH_2$ is concerted [eqn. (12)], or stepwise (*i.e.* proceeding through 4⟷5) is open to debate.†

In general terms, other deprotonated hydroxamic acids fragment similarly. Several features require specific mention however; (*i*) when the alkyl substituent is ≥ Et, the intermediate analogous to 4(5) (Scheme 2) may also eliminate ammonia [see eqn. (13), Scheme 3], (*ii*) the standard reaction shown in eqn. (14) occurs when a propyl substituent is present (it has been shown previously that such reactions are two-step: loss of a terminal hydrogen atom is followed by elimination of ethene[22]), and (*iii*) for a phenyl derivative, both Ph^-[eqn. (15), E_A ($Ph^\bullet$) = 87 kJ mol^{-1} [23]] and $OCNO^-$ [*cf.* eqn. (6)] are formed, as are $PhCO_2^-$[*cf.* eqn. (11) and Table 2] and $PhNH^-$ (see Fig. 2, also Table 2). The structure of $PhNH^-$ is confirmed by comparison of its spectra (Table 2) with those of deprotonated aniline. The formation of $PhNH^-$ involves loss of CO_2: this reaction is likely to proceed *via* the intermediacy of a Lossen complex [see eqn. (16), and *cf.* eqns. (8)–(10)]. The deprotonated hydroxamic acid *O*-methyl ether shows reactions analogous to those described in eqns. (3) and (8)–(10) (Scheme 1).



$$[(MeCHCO_2)NH_2^-] \longrightarrow CH_2{=}CHCO_2^- + NH_3 \quad (13)$$

$$PrCO\bar{N}OH \longrightarrow {}^{\bullet}CH_2CO\bar{N}OH + (C_2H_4 + H^{\bullet}) \quad (14)$$

$$PhCO\bar{N}OH \longrightarrow [Ph^-(O{=}C{=}N{-}OH)] \longrightarrow Ph^- + OCNOH \quad (15)$$

$$[(PhNCO)HO^-] \longrightarrow Ph\bar{N}CO_2H \longrightarrow PhNHCO_2^- \longrightarrow PhNH^- + CO_2 \quad (16)$$

Scheme 3

The reaction of hydrazides ($RCONHNH_2$) with nitrous acid in solution yields RNCO *via* a Curtius rearrangement.[24] Interestingly, the reaction between $RCONHNH_2$ systems and strong base in solution does not lead to a Lossen rearrangement; instead, hydrolysis is noted.[24] What is the situation in the gas phase? The mass spectra of $RCO\bar{N}NH_2$ and cognate systems are listed in Table 1, and a specific example is illustrated in Fig. 3. The spectrum of $CD_3CO\bar{N}NH_2$ (Fig. 3) has fewer peaks than that of $CD_3CO\bar{N}OH$ (Fig. 1). Fig. 3 shows losses of $H^\bullet$, CD_3H and CD_3NH_2 [*cf.* eqns. (3), (7) and (10)], but there are no losses of $D^\bullet$, $NH^\bullet$, NH_3, N_2H_2 or NH_2NH_2, and no formation of NH_2^- [*cf.* eqns. (4), (11), (9), (6), (5) and (8)]. The

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† It is generally accepted that negative ion decompositions often proceed in a stepwise manner.[1,16,17] If that is so in this case, there is then the question as to whether the reaction proceeds through ion/neutral complex 4 or radical/radical anion complex 5. This dilemma has been discussed before (*e.g.* for alkoxide decompositions[18] and the Wittig rearrangement),[19] but in our past reports we generally use the concept of an ion/neutral complex for convenience.[1] In simplistic terms for a system [A (neutral)]$^-$, if the electron affinity of $A^\bullet$ is more positive than that of the neutral, the reactive intermediate should look like [A^-(neutral)]. If the situation is reversed, [$A^\bullet$(neutral)$^{\bullet-}$] must be considered, even though there are examples of reactions occurring through [A^-(neutral)] in these circumstances.[15] The argument, is, of course somewhat pedantic since in many cases the true structure will be intermediate between the two extremes. Very few reactions have been reported in which the intermediacy of a radical/radical anion complex has been proposed.[18,19] In the particular case of 5, the electron affinity of $NH_2^\bullet$ is 74 kJ mol^{-1},[20] and even though the electron affinity of CH_2CO_2 is not known, the radical anion is known to be stable.[21] Thus fragmentation through 5 must be considered to be plausible.

dimethylamino derivative (Table 1) exhibits similar behaviour. Two other pertinent observations are: (*i*) loss of $NH_2^{\cdot}$ from $CD_3CO\bar{N}NH_2$ yields $(CD_3NCO)^{\cdot -}$ (Table 2) *not* $(CD_2CO_2)^{\cdot -}$ [*cf.* eqn. (12)], and (*ii*) the spectrum of $PhCO\bar{N}NH_2$ lacks the pronounced peak due to $PhNH^-$ which, if present, would support the operation of the Lossen rearrangement [*cf.* Fig. 2, also eqn. (16)]. We conclude that (*i*) three-centre rearrangements of the type shown in Scheme 2 do not occur in these systems, and (*ii*) with the possible exception of NCO^-, there are no detectable product ions resulting from a Lossen anion/neutral complex [*cf.* **2**, also eqns. (8)–(10) and (16)].

The major fragmentations noted for $MeCO\bar{N}NH_2$ are summarised in Scheme 4. The processes resulting in losses of $H^{\cdot}$ and CH_4 are shown in eqns. (17) and (18), respectively; the structure of the product ion of eqn. (18) is confirmed by the data listed in Table 2. We suggest that $MeNCO]^{\cdot -}$ and NCO^- (see data in Table 2) may be formed *via* Lossen radical/radical anion complex **6** [eqns. (19) and (20)].*

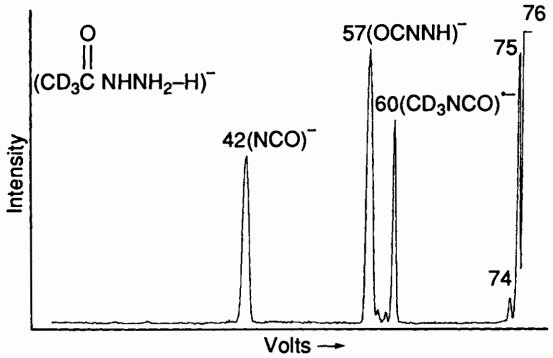
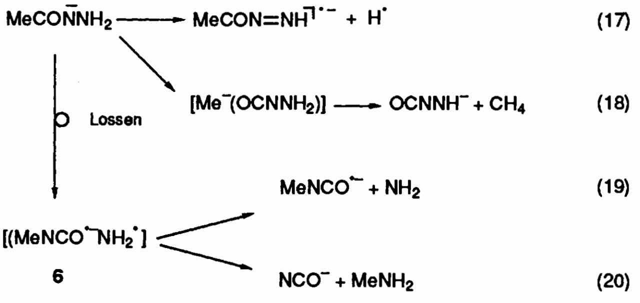


Fig. 3 Collisional activation mass spectrum of deprotonated $CD_3CONHNH_2$



Scheme 4

In conclusion, deprotonated hydroxamic acids undergo several rearrangement reactions under conditions of collisional activation in the gas phase. One of these is suggested to be the classical Lossen rearrangement, and the second involves an unusual 1,2 oxygen rearrangement to the carbonyl site.

Experimental

Collisional activation mass spectra (MS/MS) were recorded using a Vacuum Generators ZAB 2HF mass spectrometer operating in the negative chemical-ionisation mode.[25] All slits were fully open to obtain maximum sensitivity and to minimize energy resolution effects.[26] The chemical ionisation slit was used in the ion source, ionising energy 70 eV (tungsten filament); ion source temperature 180 °C, accelerating voltage 7 kV. Deprotonation of all neutrals was effected by H_2N^- (from NH_3). The initial source pressure of NH_3 was 1×10^{-5} Torr (1 Torr = 133.332 Pa). The substrate pressure (liquids introduced through the septum inlet at 150 °C; solids through the direct probe with no heating) was typically 5×10^{-7} Torr. The estimated total pressure in the ion source is 10^{-1} Torr. The pressure of helium in the second collision cell was 2×10^{-7} Torr measured by an ion gauge situated between the electric sector and the second collision cell. This produced a decrease in the main beam signal of *ca.* 10%, and corresponds to essentially single collision conditions.

Consecutive collision induced dissociation spectra (MS/-MS/MS) and charge reversal[8] MS/MS/MS spectra were measured with a Kratos MS 50 TA instrument previously described.[27] Neutral substrates were deprotonated by MeO^- (from $MeONO$[28]) in a Kratos Mark IV chemical ionisation source; ion source temperature 100 °C, electron energy 280 eV, emission current 500 μA and accelerating voltage 8 kV. Samples were introduced through an all glass heated inlet system at 100 °C. The indicated source pressure of substrate was 2×10^{-5} Torr and of methyl nitrite 1×10^{-6} Torr giving an estimated source pressure of *ca.* 10^{-1} Torr. The indicated pressure of helium in the collision cells was 2×10^{-6} Torr giving a decrease in the main beam signal of 30%.

All of the hydroxamic acid derivatives are known and were prepared by literature procedures, *viz* $R^1CONHOR^2$; R^1 = Me, Et, Pr, Pr^i, R^2 = H;[29] R^1 = Ph, R^2 = H;[30] and $R^1 = R^2$ = Me.[31] All hydrazides are known, *viz.* $R^1CONHN(R^2)^2$; R^1 = Me, Et, Pr, Ph, $PhCH_2$, R^2 = H;[32] and $R^1 = R^2$ = Me.[33] The two deuterium labelled compounds were prepared from CD_3CO_2Et by the standard procedures.[29,32] ($^2H_3$ > 99%).

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* If NCO^- is formed by a radical reaction in this case, then whether process (9) is a radical or S_N2 reaction is open to question.

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