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# Diazo chemistry controlling the selectivity of olefin ketonisation by nitrous oxide<sup>†</sup>

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The thermal reaction of olefins with nitrous oxide was recently put forward as a promising synthetic ketone source. The 1,3-dipolar cycloaddition of N<sub>2</sub>O to the C=C double bond, forming a 4,5-dihydro-[1,2,3]oxadiazole intermediate, was predicted to be the first elementary reaction step. This oxadiazole can subsequently decompose to the desired carbonyl product and  $N_2$  via a hydrogen shift. In this contribution, Potential Energy Surfaces are constructed at the reliable G2M level of theory and used to evaluate thermal rate constants by Transition State Theory. Compelling theoretical and experimental evidence is presented that an oxadiazole intermediate not only can undergo a hydrogen shift, but eventually also a methyl- or even an alkyl-shift. Special emphasis is also given on a hitherto neglected decomposition of the oxadiazole via a concerted C-C and N-O cleavage. For some substrates, such as internal olefins, this diazo route is negligibly slow, compared to the ketone path, leaving no marks on the selectivity. For cyclopentene the diazo cleavage was however found to be nearly as fast as the desired ketone route. However, the diazo compound, viz. 5-diazopentanal, reconstitutes the oxadiazole much faster upon ring-closure than it is converted to side-products. Therefore, a pre-equilibrium between the diazoalkanal and the oxadiazole is established, explaining the high ketone yield. On the other hand, for primary alkenes, such a concerted C-C and N-O cleavage to diazomethane is identified as an important side reaction, producing aldehydes with the loss of one C-atom. For these substrates, the bimolecular back-reaction of the  $C_{n-1}$  aldehyde and diazomethane is too slow to sustain an equilibrium with the oxadiazole; diazomethane rather reacts with the substrate to form cyclopropane derivatives. The overall selectivity is thus determined by a combination of H-, methyl- or alkyl-shift, and the eventual impact of a diazo cleavage in the oxadiazole intermediate.

### Introduction

The exploration of sustainable and economically viable routes to ketones and aldehydes remains an ongoing quest. A promising reaction is the direct ketonization of olefins with nitrous oxide (N<sub>2</sub>O) in the liquid phase. Although discovered quite a time ago,<sup>1</sup> this chemistry was recently reinvestigated<sup>2</sup> and shown to offer large scale potential.<sup>3–4</sup> Interestingly, a severe greenhouse gas<sup>5</sup> is usefully converted to harmless N<sub>2</sub>, and, rather than starting from expensive alcohols, a relatively cheap olefin feedstock is used. Moreover, the thermal stability of nitrous oxide up to 800 °C, and the non-radical character of its oxidation reactions, allows the design of safe and selective processes. Preliminary theoretical calculations predicted that the 1,3-dipolar cycloaddition of N<sub>2</sub>O to the unsaturated bond of the olefin is the first elementary reaction step, forming a 4,5-dihydro-[1,2,3]oxadiazole (OD).<sup>6</sup> Decomposition of the

ro-vibrational data of key structures. See DOI: 10.1039/b704351a

OD intermediate *via* a H-shift yields the desired carbonyl product and N<sub>2</sub> (Scheme 1). The hypothesis that initially formed epoxides would isomerise to the carbonyl products had to be discarded as these compounds are inert under the reaction conditions.<sup>2a</sup> The scarce theoretical studies on the rate-determining cycloaddition of N<sub>2</sub>O report barriers considerably higher than for other dipoles such as fulminic acid and nitrones.<sup>7–9</sup> N<sub>2</sub>O, in contrast to other dipoles, behaves as an electrophile and the dipolarophile as a nucleophile; this type of cycloaddition.<sup>8</sup>



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Entry	Substrate	Rate/mM h <sup>-1</sup>	Selectivity (%)	
1	$\bigcirc$	160 <sup><i>a</i></sup>	0	
2		1 <i>5</i> <sup><i>a</i></sup>	(99) (99)	
3	$\bigcup$	8	(42) + (36) $(5)$	
4	H- H-5	90	(97)	
5	¥75	65	$\begin{array}{c} & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\$	

<sup>*a*</sup> The reactivity difference between cC5 and cC6 olefins results from the highly different ring-strain relaxation upon N<sub>2</sub>O addition: G2M addition barriers of 101.6 *versus* 116.5 kJ mol<sup>-1</sup>, respectively.

Despite the theoretical investigations, it remains unclear why substantial C–C cleavage, or even skeletal rearrangements occur with some substrates, whereas others can be ketonized in a very high selectivity (Table 1 and ref. 2). The aim of this work is to elucidate a generic molecular mechanism, rationalizing the experimental observations. A sound, comprehensive scheme should benefit the rational development of this novel chemistry.

#### Experimental and theoretical methods

Potential Energy Surfaces (PESs) of relevant reaction steps were constructed at the DFT level,<sup>10</sup> using the Becke three-parameter hybrid exchange functional, combined with the Lee–Yang–Parr non-local correlation functional: B3LYP-DFT.<sup>11</sup> The 6-311++G(d,p) basis set was used to account for long-range interactions. Single-point energies were refined using a variant of the G2M scheme, based on UCCSD(T)/6-31G(d) single-point calculations and MP2/6-311++G(3df,3pd) basis set extrapolations.<sup>12</sup> Zero-Point Energy (ZPE) corrections were made at the B3LYP/6-311++G(d,p) level of theory. For a smaller model system, the G2M results were compared with several benchmark levels such as CBS-QB3<sup>13</sup> and G2M(large),<sup>12</sup> demonstrating its reliability. All calculations were performed

with the Gaussian 03 software.<sup>14</sup> Interesting to note is that all unrestricted calculations automatically defaulted to restricted calculations, indicating that no open-shell singlet states are involved. Thermal reaction rates, at 453 K, were evaluated by Transition State Theory (TST),<sup>15</sup> based on the ro-vibrational PES data obtained at the G2M level of theory. Additionally, these first-principles rate constants were used to estimate branching fractions when different pathways were identified for a given intermediate.

The reactions were studied in 50 mL stainless steel reactors, magnetically stirred and equipped with a thermocouple. Before it was pressurized to 2.5 MPa N<sub>2</sub>O, a filled reactor was flushed several times with medical grade N<sub>2</sub>O to remove O<sub>2</sub> in order to exclude possible radical-chain autoxidation reactions. Reaction products were analysed with GC-FID (CP Sil-5 GC column or a BPX 70 (SGE) column); peak areas were corrected according to the sensitivity coefficients using the internal standard technique.

#### **Results and discussion**

#### 1. Potential energy surfaces

In this work, the mechanistic problem one is faced with is addressed by high level quantum-chemical calculations, validated for the reaction type discussed. In TS<sup>add</sup> (Scheme 1), the  $N_2O \cdots C$  and  $ONN \cdots C$  bonds are still very weak (distances  $\geq$  2 Å), and a similar problem arises with TS<sup>H-shift</sup>. As DFT fails to describe long-range interactions accurately, results obtained with the popular B3LYP-DFT method should be handled with care. At least, crucial diffuse and polarized basisset functions to describe the bond formation process under consideration should be included. Unfortunately, the appropriate ab initio levels of theory, in combination with large basis sets are beyond current computational resources for large systems. Therefore, feasible levels of theory have to be compared with benchmark theories such as CBS-QB313 and G2M(large)<sup>12</sup> for small analogous systems, such as the ethylene plus N<sub>2</sub>O reaction (Table 2). Apparently, the DFT results deviate significantly from the average of the reference methods, even if a very large basis-set is used, i.e. 6-311++G(3df,3pd). On the other hand, the single-point G2M method clearly provides a sound description of the PES. Intrinsic Reaction Coordinate (IRC) analysis of the cycloaddition step demonstrates that it proceeds via a very weak, pre-reactive complex between N<sub>2</sub>O and the olefin. This complex results from weak electrostatic interactions between the dipole and the olefin, and should be considered as the first step in the cycloaddition reaction. However, it will not appear in the rate expression as it is in fast thermal pre-equilibrium with the reactants, strongly shifted towards the latter because of entropic reasons: the ketonization rate is only determined by the relative position of TS<sup>add</sup> and the reactants level. However, the pre-reactive complex can induce regioselective addition of N<sub>2</sub>O to unsymmetrical C=C sites as discussed below.

The barrier of the concerted epoxidation,  $via \text{ TS}^{epox}$  was found to be much higher than that of the cycloaddition channel, in line with previous studies.<sup>6b</sup> Contrary to a

Table 2 ZPE-corrected relative energies  $(kJ mol^{-1})$  of the stationary points on the PES of the ethylene plus N<sub>2</sub>O reaction at various levels of theory

Structure	B3LYP/6-31G(d)	B3LYP/6-311++G(3df,3pd)	$G2M^a$	$G2M(full)^b$	CBS-QB3
$N_2O$ + ethylene	0.0	0.0	0.0	0.0	0.0
Pre-reactive complex	-2.5	-0.2	-4.2	-5.4	-5.8
TS <sup>add</sup>	105.0	125.0	119.2	116.3	117.1
OD	-28.9	2.8	-19.7	-25.9	-18.2
TS <sup>H-shift</sup>	76.6	84.6	64.6	64.0	72.6
TS <sup>diazo</sup>	68.6	78.5	71.1	68.6	75.5
Acetaldehyde $+ N_2$	-282.4	-279.7	-302.9	-305.4	-297.9
$CH_2O + CH_2N_2$	10.5	9.6	16.9	15.9	20.9
$N_2 O$ + ethene	0.0	0.0	0.0	0.0	0.0
TS <sup>epox</sup>	198.7	203.3	205.8	203.8	207.9
Epoxide	-162.3	-158.5	-188.7	-191.6	-184.5

suggestion in the literature,<sup>6b</sup> this reaction mode cannot compete at all with the 1,3-dipolar addition, even at high temperatures (*e.g.* at 1000 K, the formation of the OD is still favoured by a factor  $\approx 10^4$ ). Therefore, this direct epoxidation channel is not discussed in this paper.

#### 2. Decomposition of the oxadiazole

The core objective of this work is the fate of the OD intermediate and its influence on the selectivity. Inspired by earlier work,<sup>16</sup> we examined the concerted NN–O and C–C cleavage in the OD, forming a diazo compound ("diazo-route"), as a possible competitor for the conventional H-shift channel, which results in the desired ketonization (Scheme 2). The decomposition of the OD to the corresponding epoxide faces a much higher barrier<sup>16b</sup> as a result of increasing ring-strain and is therefore not considered in this paper.

**2.1** Cyclopentene and cyclohexene. Competition between the H-shift and the diazo cleavage was firstly investigated for two cyclic model substrates, cyclopentene and cyclohexene, in Fig. 1 and Table 3. It must be noted that for these cyclic olefins, the "diazo-route" results in a *single* product molecule, *i.e.* a 1-diazoalkanal. Whereas for cyclohexene the TST-evaluated rates show the diazo-route to be negligible (ratio of rates H-shift/diazo channel = 9000), the rate constant of the hitherto overlooked diazo channel for cyclopentene is found to be as large as for the desired H-shift. It is the higher ring strain in the bicyclic OD of cyclopentene, compared to that of cyclohexene, that induces this vast difference.



Scheme 2 Possible decomposition channels for the oxadiazole intermediate in the ketonization of cyclic olefins with  $N_2O$ .

It might appear puzzling that, despite the low barrier for C–C cleavage (81.7 kJ mol<sup>-1</sup>, *i.e.* barely higher than the 81.2 kJ mol<sup>-1</sup> for the H-shift, Table 3), the selectivity remains high for cyclopentene (entry 1, Table 1). Indeed, the resulting 4-diazopentanal can eliminate  $N_2$ ,<sup>17</sup> forming a primary carbene which is able to isomerise to 4-pentenal. Interestingly,



Fig. 1 Potential energy surface of the reaction of  $N_2O$  with cyclopentene (upper) and cyclohexene (lower), constructed at the G2M level (see Table 3).

Table 3ZPE-corrected relative energies of the stationary points on the PES of the cyclopentene and cyclohexene plus  $N_2O$  reaction at the G2Mlevel

Cyclopentene system	$G2M/kJ \ mol^{-1}$	Cyclohexene system	$G2M/kJ \ mol^{-1}$
$N_2O$ + cyclopentene	0.0	$N_2O$ + cyclohexene	0.0
TS <sup>add</sup>	101.7	TS <sup>add</sup>	116.5
OD	-47.3	OD	-32.2
TS <sup>H-shift</sup>	33.9	TS <sup>H-shift</sup>	33.0
TS <sup>diazo</sup>	34.4	TS <sup>diazo</sup>	68.2
Cyclopentanone + $N_2$	-314.6	Cyclohexanone + $N_2$	-310.4
5-Diazopentanal	-19.5	5-Diazohexanal	-2.2

traces of this compound have been detected by GC-MS. The high ketone selectivity is due to the *unimolecular* re-cyclisation of the 4-diazopentanal to the OD, being much faster than the elimination of N<sub>2</sub> (at 453 K,  $\approx 10 \text{ s}^{-1}$  for N<sub>2</sub> elimination *versus*  $\approx 10^4 \text{ s}^{-1}$  for re-cyclisation).<sup>18</sup> Therefore, a fast (pre-)equilibrium between the OD and the 4-diazopentanal intermediate is established, in a computed 1 : 1 ratio. The H-shift constitutes a very fast and irreversible sink of the OD ( $1.3 \times 10^4 \text{ s}^{-1}$ ), significantly reducing its lifetime (less than  $10^{-4} \text{ s}$ ). This short lifetime also readily explains why the OD could not yet be observed experimentally. As the N<sub>2</sub>-elimination from 4-diazopentanal<sup>17</sup> is rather slow ( $\approx 10 \text{ s}^{-1}$ ), only a very small fraction is converted to ring-opened by-products.

Next, a number of relevant cases are addressed where the diazo-route puts its mark on the olefin plus  $N_2O$  product distribution.

2.2 1-Methyl-1-cyclohexene. Apparently, the substitution of a methyl group for an H-atom at the unsaturated C=C bond in cyclohexene results in a significant drop in selectivity (entry 3, Table 1). The rationalisation behind this enigmatic behaviour starts with the unsymmetrical reaction site in the 1-methyl-1-cyclohexene substrate. Indeed, N<sub>2</sub>O can add in two regioselective ways. We predict theoretically that addition with the O-atom of N<sub>2</sub>O to the substituted C-atom is slightly faster than addition to the unsubstituted site  $(E[TS^{add}] = 114.2$ versus 114.6 kJ mol<sup>-1</sup>, respectively; TST calculated ratio of rate constants  $\approx$  1.8 at 453 K, taking into account entropic effects). Therefore, it can be estimated that the OD depicted in Scheme 3 will be produced in about 65% selectivity.<sup>19</sup> As this OD lacks an  $\alpha$ H-atom at the substituted site, a H-shift as in the case of cyclohexene is impossible for this OD. However, three other reaction paths can be identified (Scheme 3). The first one is the diazo route by concerted C-C and N-O



Scheme 3 Reaction paths of the major oxadiazole (OD) formed after  $N_2O$  addition to the substituted site of 1-methyl-1-cyclohexene: (a) the diazo cleavage, (b) the methyl-shift, and (c) the backbone rearrangement. G2M calculated barrier heights are indicated.

cleavage (Scheme 3, route a), yielding a diazoalkanone. A second path is the shift of the methyl group (route b), yielding 2-methylcyclohexanone.<sup>20</sup> In order to explain the formation of cyclopentyl methyl ketone (entry 3, Table 1) one also has to consider a backbone rearrangement (route c).<sup>21</sup> Important for the chemistry is that these methyl and alkyl shifts face a higher barrier (83.3 and 79.0 kJ mol<sup>-1</sup>, respectively) than the H-shift in the OD of cyclohexene (i.e. 65.2 kJ mol<sup>-1</sup>, see Table 3), making the diazo route (barrier of 94.0 kJ mol<sup>-1</sup>) competitive for this OD. Analogous to the cyclopentene case, the OD can thus establish a (pre-)equilibrium with the diazo-compound. However, in this case, the diazo/OD equilibrium ratio at 453 K is calculated to be as high as 260, i.e. much higher than for cyclopentene. Therefore, subsequent reactions of the diazo compound become significantly more important here. The ratio of irreversible decomposition rates of the diazo-compound and the OD can be estimated as  $k^{\text{diazo}}/k^{\text{OD}} \times [\text{Diazo}]_{\text{eq}}/k^{\text{OD}}$  $[OD]_{eq} \approx \{10/(3.5 \times 10^4)\} \times 260 \approx 0.07$ , with  $k^{OD}$  the sum of the rate constants of the methyl- and alkyl-shift. Thus, on taking into account that this OD isomer is only formed in about 65% selectivity, the isomerisation product of the carbene, hept-6-en-2-one, is predicted to be produced for about 5%, in quantitative agreement with experimental observation (entry 3, Table 1). A smaller fraction (about 35%, vide supra) of the N2O molecules will add with the O-atom to the unsubstituted site, yielding, after a fast H-shift, some additional 2-methylcyclohexanone.

**2.3 Linear olefins.** Linear internal olefins are selectively converted to two equimolar ketone isomers (entry 4, Table 1). This is, again, consistent with the TST calculated ratio of the ketonisation and diazo channel rates of about 80 at 453 K  $(E[TS^{add}] = 73.3 \text{ kJ mol}^{-1} \text{ and } E[TS^{diazo}] = 90.4 \text{ kJ mol}^{-1}$ , respectively). As for cyclohexene, the diazo channel is thus also negligible for the linear internal olefins, explaining the excellent selectivity. Inspired by the high ketonisation efficiency of such simple model substrates, we recently proposed this new N<sub>2</sub>O chemistry to ketonise unsaturated renewables, ranging from purified methyl esters, over commercial biodiesel, to triacylglycerides.<sup>22</sup>

In the ketonisation of 1-alkenes, the formation of aldehydes with the loss of one C-atom is observed in high yields (entry 5, Table 1). Up to now, it was not yet clear whether this was caused by the formation of :CH<sub>2</sub> or CH<sub>2</sub>N<sub>2</sub> species.<sup>2d</sup> Calculations on 1-hexene as a model substrate (Scheme 4) reveal that the addition of the terminal N-atom of N<sub>2</sub>O to the primary C-atom is slightly faster than addition with the O-atom ( $E[TS^{add}] = 112.5 \text{ versus } 117.7 \text{ kJ mol}^{-1}$ ; TST calculated ratio



Scheme 4 Ketonization of 1-hexene with  $N_2O$ . The reported branching fractions are based on the TST evaluated rate constants (based on G2M-PES data).

of rate constants  $\approx$  2.9, taking into account the entropic effects), again induced by a small difference in the charges on the two unsaturated C-atoms. Therefore it is estimated that the first attack will account for about 75%. Diazo cleavage in this dominant OD A is responsible for the production of substantial amounts of diazomethane (see Scheme 4; E[TS<sup>H-</sup> <sup>shift</sup>] = 83.7 kJ mol<sup>-1</sup> versus  $E[TS^{diazo}]$  = 89.1 kJ mol<sup>-1</sup>). Diazomethane, as well as its decomposition product :CH<sub>2</sub>, is known to react very fast with C=C bonds,<sup>23</sup> forming the observed cyclopropane derivatives (Table 1, entry 5). Note that the yield of  $C_{n-1}$ -aldehyde indeed matches that of the cyclopropane derivative. Also, the fast CH<sub>2</sub>N<sub>2</sub> reaction with the substrate will far outrun its reaction with the  $C_{n-1}$ aldehyde to regenerate the OD (here in an unfavourable bimolecular process instead of an intramolecular reaction for cyclic olefins, vide supra). Consequently, no equilibrium can be established between the OD and CH<sub>2</sub>N<sub>2</sub>. Therefore, the ratio of rate constants of the H-shift channel and the diazo-cleavage represents the flux ratios (*i.e.* ratio  $\approx 2.4$  estimated by TST). In this case, the diazo cleavage is thus very effective in generating by-products. The less favourable OD B will decompose almost exclusively via a H-shift to hexanal ( $E[TS^{H-shift}]$ = 76.1 kJ mol<sup>-1</sup> versus  $E[TS^{diazo}] = 90.8$  kJ mol<sup>-1</sup>). The theoretically predicted product distribution (Scheme 4) is not only in line with our experimental results on 1-octene (entry 5. Table 1), but also with those reported in the literature for other primary olefins.<sup>2d</sup>

#### Conclusions

Summarizing, this work elucidates the key-parameters which steer the selectivity in the ketonisation of olefins with N<sub>2</sub>O. A first important factor is the regioselective addition of N<sub>2</sub>O to unsymmetrical C=C sites: the addition of the O-atom of N<sub>2</sub>O to the most positively charged C-atom is slightly favoured. Subsequently, all possible decomposition routes of the oxadiazole intermediate should be considered, *i.e.* the known Hshift, methyl- and alkyl-rearrangements, but also the concerted C-C and N-O cleavage. For some substrates, the latter channel faces a higher barrier, making it completely unimportant, while for others the fate of the resulting diazo compound should be detailed. If the diazo compound reconstitutes the OD faster than it eliminates N<sub>2</sub> leading to a reactive carbene, an equilibrium will be established between OD and the diazo intermediate. This is for instance the case for cyclopentene, for which the intramolecular addition, in 4-diazopentanal, of the diazo functionality to the aldehyde group is very fast. For 1-alkenes however, the diazo cleavage gives rise to  $CH_2N_2$  plus a  $C_{n-1}$  aldehyde, and the rather slow bimolecular re-association of both fragments to regenerate the OD cannot compete with the reaction of CH<sub>2</sub>N<sub>2</sub> with the olefin substrate, which results in a significant yield of cyclopropane derivatives. Nevertheless, even in the cases where the OD can equilibrate with the diazo compound, byproducts can arise if the equilibrium is strongly shifted towards the diazo compound. The bottom-line conclusion of this work should therefore be that the subtle role of the hitherto overlooked diazo compound governs the selectivity of this emerging olefin to carbonyl chemistry. The mechanistic insights provided by this work should be highly useful in future assessments of the potential of a certain substrate, prior to experimental testing.

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- 17 TST predicts  $k(453 \text{ K}) \approx 4 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$  for the addition of diazoethane to cyclopentene; given [cyclopentene] = 11.3 M, the pseudo-first order rate constant can be estimated at  $\approx 0.5 \text{ s}^{-1}$ . On the other hand, the unimolecular N<sub>2</sub>-elimination from diazopentanal is endothermal for about 114.6 kJ mol<sup>-1</sup>, but can benefit from a very loose variational TS, putting the estimated rate constant at  $k(453 \text{ K}) \approx 10 \text{ s}^{-1}$ . Clearly, the formation of carbene will be favoured.
- 18 Note that the alternative ring-closure, *i.e.* addition of the C-atom of the -CH-N<sub>2</sub> group to the carbonyl O-atom was reported earlier to face a higher barrier than the addition with the terminal N-atom to the carbonyl O-atom, reconstituting the OD.<sup>16b</sup>.
- 19 This moderate regioselectivity is induced by the charges on  $N_2O$  (N=N-O:  $-0.07/\pm0.64/-0.57,$  respectively) and on the sp<sup>2</sup>-C atoms (substituted C: +0.06, non-substituted C: -0.22); calculated Mulliken charges at the UCCSD(T)/6-31G(d)//B3LYP-DFT/ 6-311++G(d,p)-level.
- 20 A methyl shift was already suggested in the ketonization of 2,3-dimethylbut-2-ene by Buckley,<sup>1b</sup> in order to explain the formation of 3,3-dimethylbutan-2-one.
- 21 Such a rearrangement of the backbone has also been observed by Panov *et al.* during the gas phase ketonization of cyclohexene with N<sub>2</sub>O at higher temperature.<sup>2e</sup> Indeed, for cyclohexene this channel is usually much slower than the competing H-shift; only at elevated temperatures can competition take place.
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