methanol (200 mL) and then dried under vacuum. To cap the unchanged chloride moieties with methoxy groups, the resin was stirred for 15 min in CH_2Cl_2/methanol (1/1, v/v; 15 mL) containing an excess of Et_3N (383 μL, 2.75 mmol). The resin was filtered and washed with CH_2Cl_2 (50 mL), water (150 mL), and methanol (200 mL). To remove any traces of unchanged chiral monomer **6** in the resin, **8b** was then continuously extracted in a Soxhlet device with THF for 24 h and dried under vacuum. Solid-state ^{31}P NMR (85 % H_3PO_4 external reference): $\delta = -11.6$ ppm (br s).

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Noncovalent Chemistry of Nitrous Oxide: Interactions with Secondary *cis* Amides in Solution**

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The environmental impact of nitrous oxide (N_2O) is enormous. As one of the most abundant components of the atmosphere, N_2O plays a critical role in the destruction of the ozone layer and contributes to the greenhouse effect.[1] Emission of N_2O into the atmosphere has already reached 13 million tons and is constantly growing. The widespread use of nitrogen-containing fertilizers and the industrial manufacture of nylon are critical contributors to this amount. The major natural suppliers of N_2O are enzyme-supported nitrification/denitrification processes in soils in which this gas is the key intermediate.[2] N_2O is also involved in a number of biochemical processes, especially related to anesthesia.[3] Together with O_2 and CO, N_2O belongs to the family of blood gases.

The chemistry of N_2O is limited, although it is considered to be a reliable and nontoxic source of oxygen for catalysis.[4] It is commonly known as a noncoordinating gas and as a very poor ligand. Although several metal complexes react with N_2O, $[Ru(NH_3)_5(N_2O)]^{2+}$ is the *only* characterized complex to date.[5]

The rules governing reversible interactions between N_2O and various receptor sites, which usually precede the covalent fixation and are also responsible for the biochemical action, are still poorly understood. We report herein the previously unnoticed noncovalent interactions between secondary amides and N_2O in apolar solutions. N_2O frequently circulates in biological fluids,[2,3] and its rather weak dipole–dipole interactions with hydrophobic fragments of proteins has been noticed.[6] At the same time, the possibility of its involvement in hydrogen bonding with proteins and enzymes has been routinely ignored.

Hydrogen bonding is one of the most important forces in Nature and is responsible for self-assembly and enzyme selectivity.[7] In chemistry, it has been used in the design of effective receptors for polar neutral molecules and anions in the gas phase, in solution, and in the solid state.[8] Molecules of gases are known to form hydrogen bonds in the gas phase. Among the typical examples are the adducts of acidic HF, HCl, HBr, and HCN with N_2, CO, CO_2, and OCS,[9] and weak PhOH···Ar (N_2, CO) molecular clusters.[10] At the same time,

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surprisingly little is known about hydrogen bonding with gases in *solution*. Nature employs hydrogen bonds for the complexation of blood gases by heme proteins.[11] In the crystal structures, the amino acid residues on the distal porphyrin face of hemoglobin and myoglobin are seen in close proximity to the metal-bound O_2, thus indicating their involvement in hydrogen bonding with O_2. Surprisingly, solution spectroscopic studies with hemes and their synthetic models only very recently confirmed such hydrogen bonding.[12,13]

We found that secondary *cis* amides interact with N_2O in apolar solutions, but *trans* amides do not. Whereas the ^{1}H NMR spectra of a number of alkyl and aryl *trans* amides[14] remained unchanged upon saturation with N_2O (in $CDCl_3$), ε-caprolactam **1** (a typical *cis* amide) exhibited modest but reproducible complexation-induced spectral changes. Specifically, upon saturation of a 5×10^{-2} M $CDCl_3$ solution of ε-caprolactam **1** with N_2O,[15] the singlet assigned to NH shifted from $\delta = 6.31$ ppm to $\delta = 6.08$ ppm ($\Delta\delta = 0.23$, 295 ± 2 K) (Figure 1). Similar shifts were obtained upon addition of H_2O, a hydrogen-bonding solvent: the signal for NH shifted from $\delta = 6.31$ ppm to $\delta = 6.05$ ppm ($\Delta\delta = 0.26$, 295 ± 2 K). In [D_6]benzene, the singlet for NH shifted from $\delta = 8.20$ ppm to $\delta = 7.95$ ppm ($\Delta\delta = 0.25$) upon saturation with N_2O. These modest but reproducible shift changes imply N–H···N_2O bonding. Caprolactam (**1**) is a self-complementary molecule and weakly aggregates in $CDCl_3$ solution with a dimerization constant (K_D) of ~3 M^{-1}.[16] Apparently, interaction with N_2O (and H_2O) introduced a new equilibrium into the system and interrupted the self-association.[17]

Secondary *cis* amides are generally not synthetically available, but some exceptions are known. We prepared the hindered amide, *N*-(*n*-octanoyl)-2,4,6-tri-*tert*-butylaniline (**2**),[18] which exists as an equilibrated mixture of two stereoisomers (*E*)-**2** and (*Z*)-**2** (inseparable under standard conditions), with *cis* and *trans* amide group arrangements, respectively.[19] These have two distinct ^{1}H NMR spectra and thus offer a unique opportunity to compare them simultaneously upon interaction with N_2O.

The (*E*)-**2**/(*Z*)-**2** ratio is ~1:8 at 295 ± 2 K in $CDCl_3$ and [D_6]benzene. Two bulky *t*Bu groups in *ortho* positions to the NH–C(O) fragment place the amide group perpendicular to the plane of the benzene ring. The steric hindrances block the C=O oxygen atom and prevents self-aggregation of the (*Z*)-**2** amide group. In contrast to typical secondary amides, the singlet for the NH group of (*Z*)-**2** remains concentration-independent within 2×10^{-1}–1×10^{-3} M range. In the (*E*)-**2** amide group, the carbonyl oxygen atom and the NH group are not shielded; the signal for NH is concentration-sensitive as a result of self-aggregation.[20]

A solution of amide (*Z*)-**2** produced no visible changes in the ^{1}H NMR spectrum upon saturation with N_2O, but amide (*E*)-**2** appeared to interact with N_2O (Scheme 1, Figure 2). Upon saturation of the 3×10^{-2} M solution of (*E*)-**2** with the gas, the NH singlet shifted from $\delta = 7.04$ ppm to $\delta =$ 6.81 ppm ($\Delta\delta = 0.23$, 295 ± 2 K). Upon saturation of the same solution with H_2O, the singlet for NH shifted to $\delta = 6.76$ ppm ($\Delta\delta = 0.28$, 295 ± 2 K).

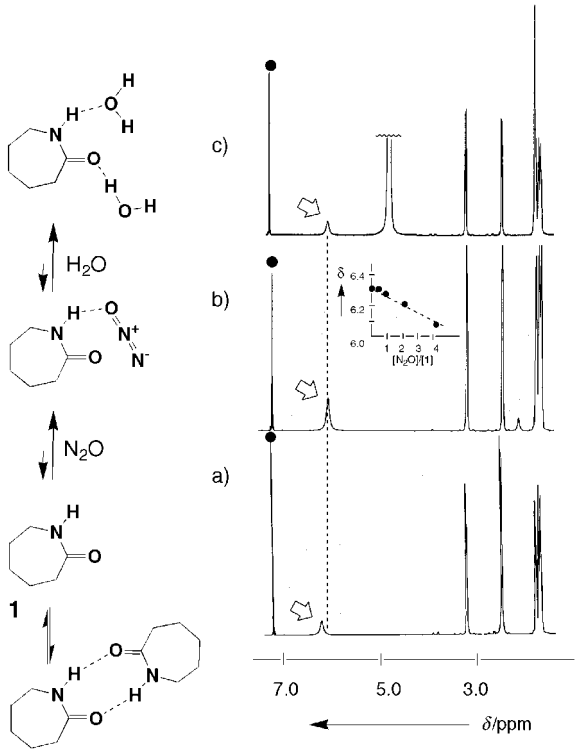
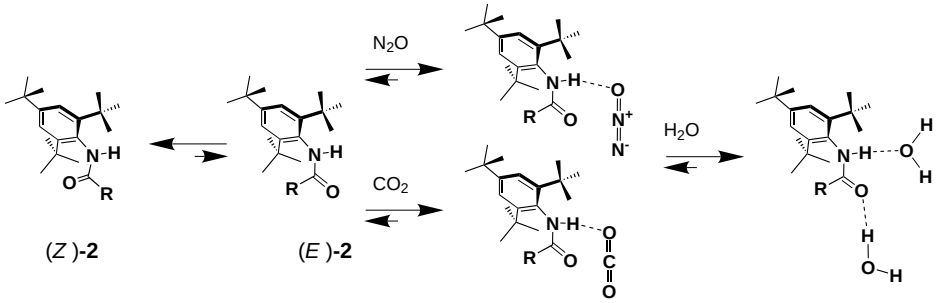


Figure 1. Complexation-induced changes in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 295 ± 2 K) of ε-caprolactam **1**: a) solution of **1**, 5×10^{-2} M; b) same, after saturation with N_2O; c) same, after saturation with H_2O. In two independent experiments, saturation of both **1** and **1**·N_2O solutions with H_2O gave identical spectra. An arrow marks the NH signal. The residual $CHCl_3$ signal is marked ●.

The rational explanation of the binding events and the differences between *cis* and *trans* amides may be obtained from molecular modeling, ab initio and semi-empirical calculations,[21] and the limited literature data on the gas-phase noncovalent aggregates of N_2O.[22] A complementary receptor site for N_2O should contain both a hydrogen donor and an acceptor separated by ~2 Å, and the *cis* amide HN–C=O fragment satisfies such a requirement (Figure 3).

Cis amides exhibit amphiphilic properties in both dipolar and hydrogen-bonding interactions. The C=O oxygen atoms are dipole donors and hydrogen acceptors, whereas the NH groups are dipole acceptors and hydrogen donors. Ab initio, MP2/6-31 + G* calculations of the complex between simple



Scheme 1. Complexation of N_2O, CO_2, and H_2O by *cis* amide (*E*)-**2**.

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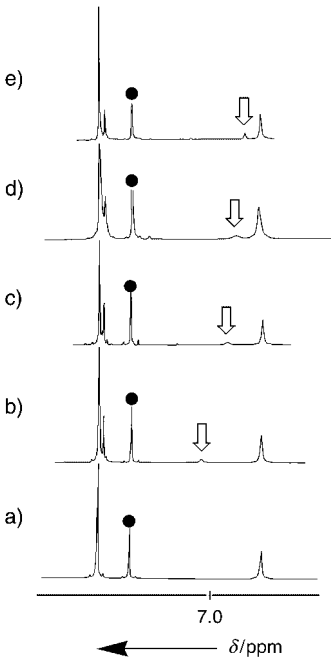

Figure 2. Complexation-induced changes in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 295 ± 2 K) of amides **2** at 3×10^{-2} M: a) (*Z*)-**2** obtained immediately after dissolution; b) a mixture of (*Z*)-**2** and (*E*)-**2** (8:1), equilibrated over 20 h; c) solution of (*Z*)-**2** and (*E*)-**2** after saturation with N_2O; d) solution of (*Z*)-**2** and (*E*)-**2** after saturation with CO_2; e) solution of (*Z*)-**2** and (*E*)-**2** after saturation with H_2O. The signal for the NH proton of the (*E*)-**2** amide is marked by an arrow. The signal for NH of the (*Z*)-**2** amide is at $\delta = 6.66$ ppm. Both singlets for the aromatic H atoms (~8:1 ratio) are situated at $\delta \sim 7.4$ ppm. The residual $CHCl_3$ signal is marked ●.

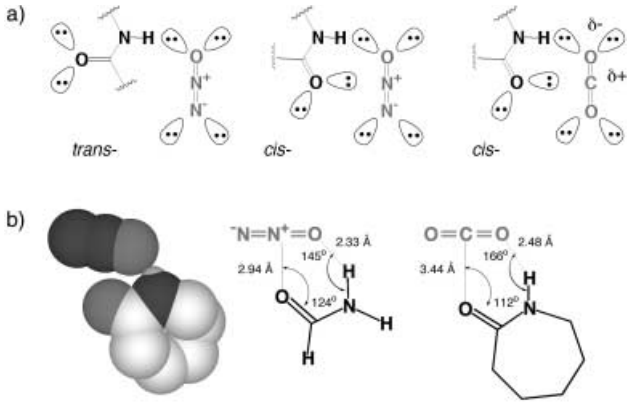

Figure 3. a) Proposed binding motif between a secondary *cis* amide and N_2O and CO_2. b) Computer-generated structures of: **1**·N_2O (PM3), H-C(O)-NH_2·CO_2 (MP2/6-31 + G*), and **1**·CO_2 (MP2/6-31 + G*). The CH hydrogen atoms and long alkyl chains are omitted for clarity.

formamide (HC(O)-NH_2, which possesses a *cis* amide arrangement) and N_2O indicates that a hydrogen bond is possible between the amide N–H hydrogen atom (+0.43 e) and the partially negatively charged (−0.62 e) oxygen atom of the gas molecule. The N–H···O=N$^+$=N:$^-$ distance is 2.33 Å, and the N–H···O and N$^+$=O···H angles are 145° and 119°, respectively (Figure 3). This places the basic C=O oxygen atom of the amide group (−0.58 e) directly in front of the central, electron-deficient nitrogen (+0.68 e) of the N_2O molecule. There is an electrostatic attraction between the former lone pair and the latter partial positive charge. The C=O···N$^+$ distance is 2.94 Å, and the C=O···N$^+$ angle is 124°. Taken together, a two-point noncovalent interaction occurs. Semi-empirical, PM3 calculations with caprolactam (**1**) and N_2O gave similar results. The C=O···N$^+$ distance appeared to be 3.26 Å, and the C=O···N$^+$ angle is 128°. The N–H···O=N$^+$=N:$^-$ distance is 1.9 Å, and the N–H···O angle is 165°.

As saturation with N_2O interrupts dimerization of *cis* amides ($K_D = 5\,M^{-1}$), this sets the lower limit for the described N_2O complexation to be $\Delta G^{295} \sim 0.9$ kcal mol^{-1}, which is typical for weak interactions in apolar solutions. This estimate was further confirmed by dilution experiments with amides **1** and (*E*)-**2**, and N_2O in $CDCl_3$. The association constant values of $K_{ass} = 5 \pm 3\,M^{-1}$ were obtained for 1:1 complexes **1**·N_2O and (*E*)-**2**·N_2O; $\Delta G^{295} = 0.8 \pm 0.4$ kcal mol^{-1}.[23,24]

Similar conclusions can be drawn from the modeling and calculations with CO_2, which is isoelectronic with N_2O (Figure 3). Indeed, we confirmed this experimentally. When the 3×10^{-2} M solution of (*E*)-**2** amide was saturated with CO_2, the NH singlet shifted from $\delta = 7.04$ ppm to $\delta = 6.77$ ppm ($\Delta\delta = 0.27$, 295 ± 2 K). Neither amide (*Z*)-**2** nor any other *trans* amides interacted with CO_2.[25,26]

Addition of H_2O to the $CDCl_3$ solutions of complexes **1**·N_2O, (*E*)-**2**·N_2O and also (*E*)-**2**·CO_2 destroyed them, and the formation of **1**·H_2O and (*E*)-**2**·H_2O species was clearly observed (for example, Figure 2e). The latter complexes were also independently obtained upon addition of H_2O to the $CDCl_3$ solutions of **1** and (*E*)-**2**.

In conclusion, noncovalent interactions between *cis* amides and N_2O (and CO_2) have been detected in apolar solutions for the first time. It is proposed that both hydrogen bonding and electrostatic interactions play a role in the binding event. This finding opens novel possibilities to construct receptors, sensors, and membranes for N_2O (and CO_2) that are based on the molecular recognition principles. Synthesis of fluorescent and UV/vis-active hydrogen-bonding receptors for N_2O, and also *cis*-amide-functionalized catalytic systems for its chemical fixation is underway. In the meantime we are also looking at the complexation between *cis* peptide bonds and N_2O in biological systems. In the absence of strong self-aggregation and competing water molecules, such interactions could be responsible for a certain biological activity of this important gas.

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[15] In a typical procedure, N_2O vapor was passed through the NMR samples for 2 h at 295 ± 2 K. To compensate for losses caused by evaporation, the solvent level was adjusted with $CDCl_3$ saturated with N_2O. The ^1H NMR spectra were recorded immediately and also after standing for 12, 24, and 48 h. All experiments were performed at least in triplicate. The solubility of N_2O in $CHCl_3$ is 2.2×10^{-1} M at 293 K; see: W. Gerrard, *Solubility of Gases and Liquids*, Plenum, New York, **1976**, chap. 8. Commercial $CDCl_3$ was used in all experiments. Saturation of $CDCl_3$ with N_2 prior to measurements did not affect the reported chemical shifts. Solubility of N_2 in $CDCl_3$ is 6×10^{-3} M.

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[18] **2**: *n*-Octanoyl chloride (1.1 mmol) was added to a magnetically stirred solution of 2,4,6-tri-*tert*-butylaniline (0.26 g, 1 mmol) and a catalytic amount of DMAP in pyridine (10 mL). The reaction mixture was heated at reflux for 48 h, cooled down, and poured onto ice water (50–100 mL). The pH value was adjusted to 2, and the product was extracted with EtOAc (3×50 mL). The organic layer was washed twice with water, then with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was treated with hexanes (40 mL), and the formed precipitate was filtered off, washed with hexane, and dried. Upon dissolving in $CDCl_3$, *exclusively* (*Z*)-**2** isomer is detected by NMR spectroscopy, which slowly equilibrates over 12 h. (*Z*)-**2** (*trans*-isomer): yield 60%; mp 240 °C (hexane); ^1H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.39$ (s, 2H; arom), 6.66 (br s, 1H; NH), 2.35–2.4 (m, 2H; CH_2), 1.7–1.8 (m, 2H; CH_2), 1.38 (s, 2×9H; CH_3), 1.3–1.4 (m, 10H; CH_2), 1.29 (s, 9H; CH_3), 0.88 ppm (t, $^3J(H,H) = 6.8$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 172.9$, 149.5, 148.3, 130.9, 123.3, 38.1, 36.4, 35.1, 32.1, 31.8, 31.5, 29.7, 29.1, 25.1, 22.7, 14.2 ppm; MS (EI): *m*/*z* $[M-t\mathrm{Bu}]^+$: calcd: 330.5; found: 330.3. (*E*)-**2** (*cis*-isomer): ^1H NMR ($CDCl_3$): $\delta = 7.38$ (s, 2H; arom), 7.04 (br s, 1H; NH), 2.3–2.35 (m, 2H; CH_2), 1.38 (s, 2×9H; CH_3), 1.3–1.4 (m, 10H; CH_2), 1.17 (s, 9H; CH_3), 0.82 ppm (t, ^3J (H,H) = 6.9 Hz, 3H; CH_3). Experiments with gases were performed only *after* the equilibration.

[19] For the discovery of the *cis–trans* equilibrium of related *N*-acetyl-2,4,6-tri-*tert*-butylaniline, see: H. Kessler, A. Rieker, *Liebigs Ann. Chem.* **1967**, *708*, 57 – 68. We successfully reproduced their results. In the same way as (*E*)-**2**, *cis*-*N*-acetyl-2,4,6-tri-*tert*-butylaniline also binds N_2O.

[20] Upon dilution of (*E*)-**2** from 2×10^{-1} M to 3×10^{-3} M, the singlet for the NH group shifted upfield from $\delta = 8.1$ ppm to $\delta = 6.8$ ppm, with significant broadening; the dimerization constant of $K_D \sim 5\,M^{-1}$ was obtained.

[21] Commercially available software packages: MacroModel 7.1; MP2/6-31 + G*; PM3.

[22] a) M. D. Marshall, H. O. Leung, *J. Mol. Spectrosc.* **1999**, *196*, 149 – 153; b) H. O. Leung, A. M. Osowski, O. A. Oyeyemi, *J. Chem. Phys.* **2001**, *114*, 4829 – 4836, and references therein; c) J. Sadlej, M. Sicinski, *J. Mol. Struct. (Theochem)* **1990**, *204*, 1 – 14.

[23] In principle, upon hydrogen bonding, a downfield shift of the signal for the amide NH proton should result. The basicity of the N_2O and CO_2 oxygen atoms is low: a) J. E. Szulejko, T. B. McMahon, *J. Am. Chem. Soc.* **1993**, *115*, 7839 – 7848; b) M. H. Abraham, F. Martins, R. C. Mitchell, C. J. Salter, *J. Pharm. Sci.* **1999**, *88*, 241 – 247. It is therefore expected that in the N–H···ON_2 and N–H···O_2C complexes, the signals for the amide NH proton are not significantly shifted relative to those for the free amides. On the other hand, under the experimental conditions, ~20% of the amides are aggregated. The amide oxygen atom is much more basic than that of N_2O and CO_2, and the difference between $\Delta\delta$ of the free amide NH and their dimers are at least $\Delta\delta = 3$ ppm. Complexation with the gases leads to the dissociation of dimers **1**·**1** or (*E*)-**2**·(*E*)-**2**, and the signals for the NH protons shift upfield. These shifts are significant and simply mask the opposite-direction shifts caused by the gas complexes themselves. Indeed, even small residual amounts (~5%) of dimers give pronounced, $\delta \sim 0.2$–0.3 ppm, downfield shifts of the signal for NH. Overall, the signals for NH shift *upfield* relative to gas-free but self-associated **1** and (*E*)-**2** upon saturation with N_2O and CO_2.

[24] Preliminary binding studies were performed at 295 ± 2 K with a constant concentration of amides **1** (5×10^{-2} M) and (*E*)-**2** (3×10^{-2} M) and varied (0–2×10^{-1} M) concentration of N_2O. The association constants were estimated from the changes in the chemical shifts for the amide NH at different concentrations of N_2O considering ~20% loss of the amide concentration as a result of dimerization. Nonlinear regression gave a fit for a 1:1 model. Detailed thermodynamic studies will be published in a full paper.

[25] For an unsuccessful attempt to use amide macrocycles for hydrogen bonding with CO_2 (no evidence of CO_2 complexation was obtained), see: A. G. Johnston, D. A. Leigh, A. Murphy, J. P. Smart, *Bull. Soc. Chim. Belg.* **1996**, *105*, 721 – 727. Hydrogen bonding studies between carboxylic acids and amides have been performed in supercritical CO_2, but the influence of CO_2 on this hydrogen bonding has not been addressed; see, for example: a) M. A. Kane, S. Pandey, G. A. Baker, S. A. Perez, E. J. Bukowski, D. C. Hoth, F. V. Bright, *Macromolecules* **2001**, *34*, 6831 – 6838; b) Q. Xu, B. Han, H. Yan, *J. Phys. Chem. A* **1999**, *103*, 5240 – 5245.

[26] The Lewis basic C = O group is known as a "CO_2-phile". While this manuscript was under review, the two-point interaction between sugar acetates and CO_2 was proposed, which involved *both* the acetate C=O···CO_2 electrostatic interactions and C–H···O_2C hydrogen bonding; see: P. Raveendran, S. L. Wallen, *J. Am. Chem. Soc.* **2002**, *124*, 7274 – 7275.

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