Supplemental information:

Combining density functional theory (DFT) and collision cross-section (CCS) calculations to analyze the gas-phase behaviour of small molecules and their protonation site isomers

Jasper Boschmans[1], Sam Jacobs[2], Jonathan P. Williams[3], Martin Palmer[3], Keith Richardson[3], Kevin Giles[3], Cris Lapthorn[4], Wouter A. Herrebout[2], Filip Lemière[1], Frank Sobott[1]

[1]Biomolecular & Analytical Mass Spectrometry group, Department of Chemistry, University of Antwerp, Antwerp, Belgium, [2]Molecular Spectroscopy group, Department of Chemistry, University of Antwerp, Antwerp, Belgium, [3]Waters Corporation, Stamford Avenue, Wilmslow, SK9 4AX, UK, [4]Faculty of Engineering & Science, University of Greenwich, Medway Campus, Chatham, ME4 4TB, UK

1. Calculation of CCS values

The used version of MobCalPARSER was modified in order to be compatible with the new MobCal code and Gaussian 09. In order to correctly refer to the chlorine atom, defined in the MobCal code, the integer mass of chlorine was corrected in the configuration file. In contrast to previous Gaussian versions that refer to a structure's charge distribution as the 'Mulliken atomic charge', Gaussian 09 refers to the 'Mulliken charge'. Therefore, the term 'atomic' was omitted from the MobCalPARSER code. When starting MobCalPARSER and prior to CCS calculation, the correct charge distribution was selected.

MobCal POTENT parameters are: 1000 (ipr). MOBIL4 (PA) was not used. MOBIL2 (TM) parameters: 10 (itn), 40 (inp) and 1000 (imp). Temperature was set at 301 K. Typical run time for the MobCal code using Method C is more than 12 hours (2.3 GHz Intel Core i5, 4GB RAM, 2 cores).

Figure S.1

3D-visualisation of the 5 lowest-energy structures of each of the three possible melphalan protomers after conformational analysis and subsequent standard-level DFT optimisation. CCS values were calculated using MobCal. Note the relatively large CCS difference between protomers, when compared to the smaller variation for different structures of the same protomer.
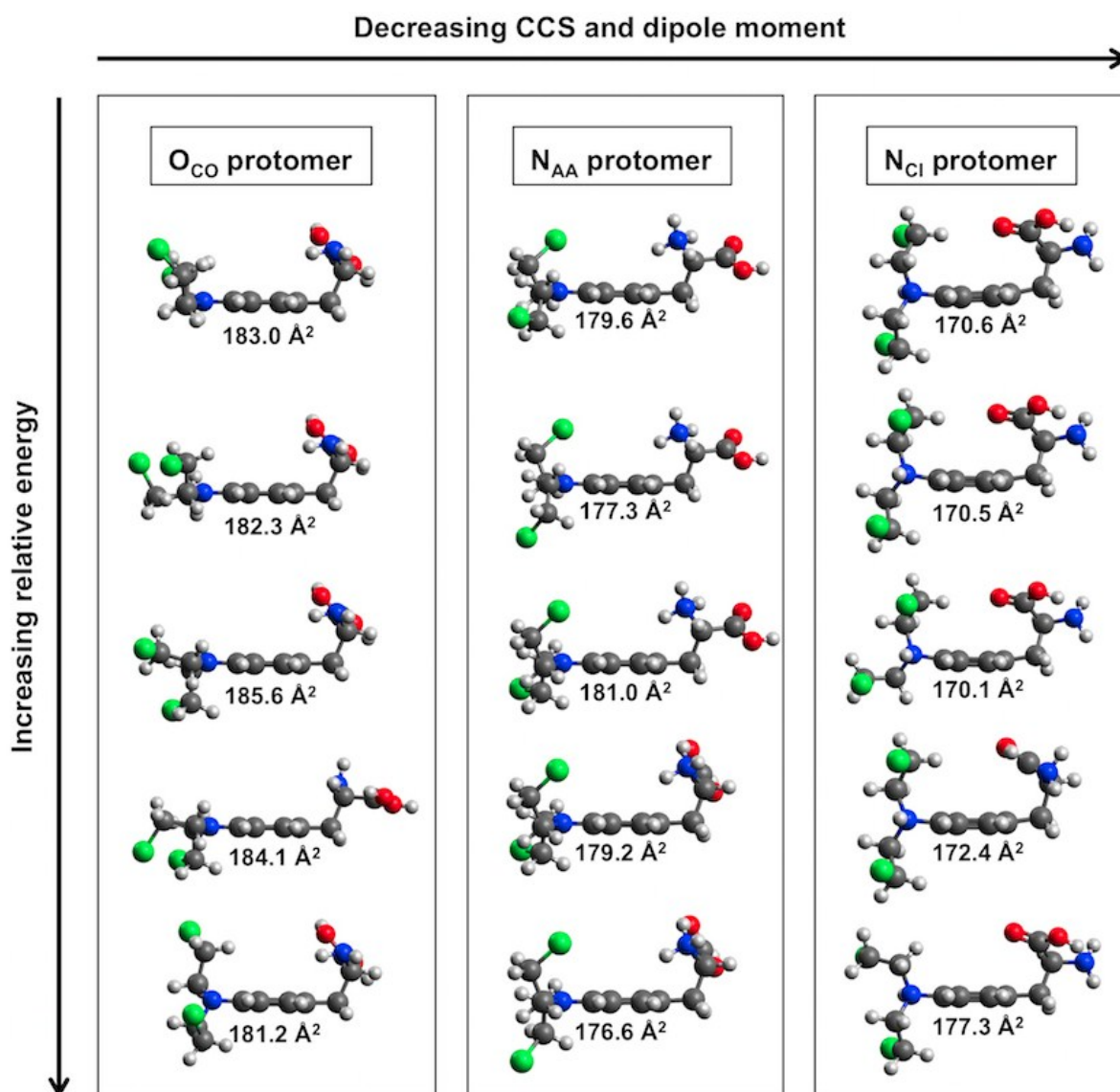
Figure S.2

3D-visualisation of the 5 lowest-energy structures of each of the three melphalan protomers after conformational analysis and subsequent "high" level DFT optimisation. CCS values were calculated using MobCal. Note the relatively large inter-protomer CCS variation, when compared to the smaller intra-protomer CCSs.
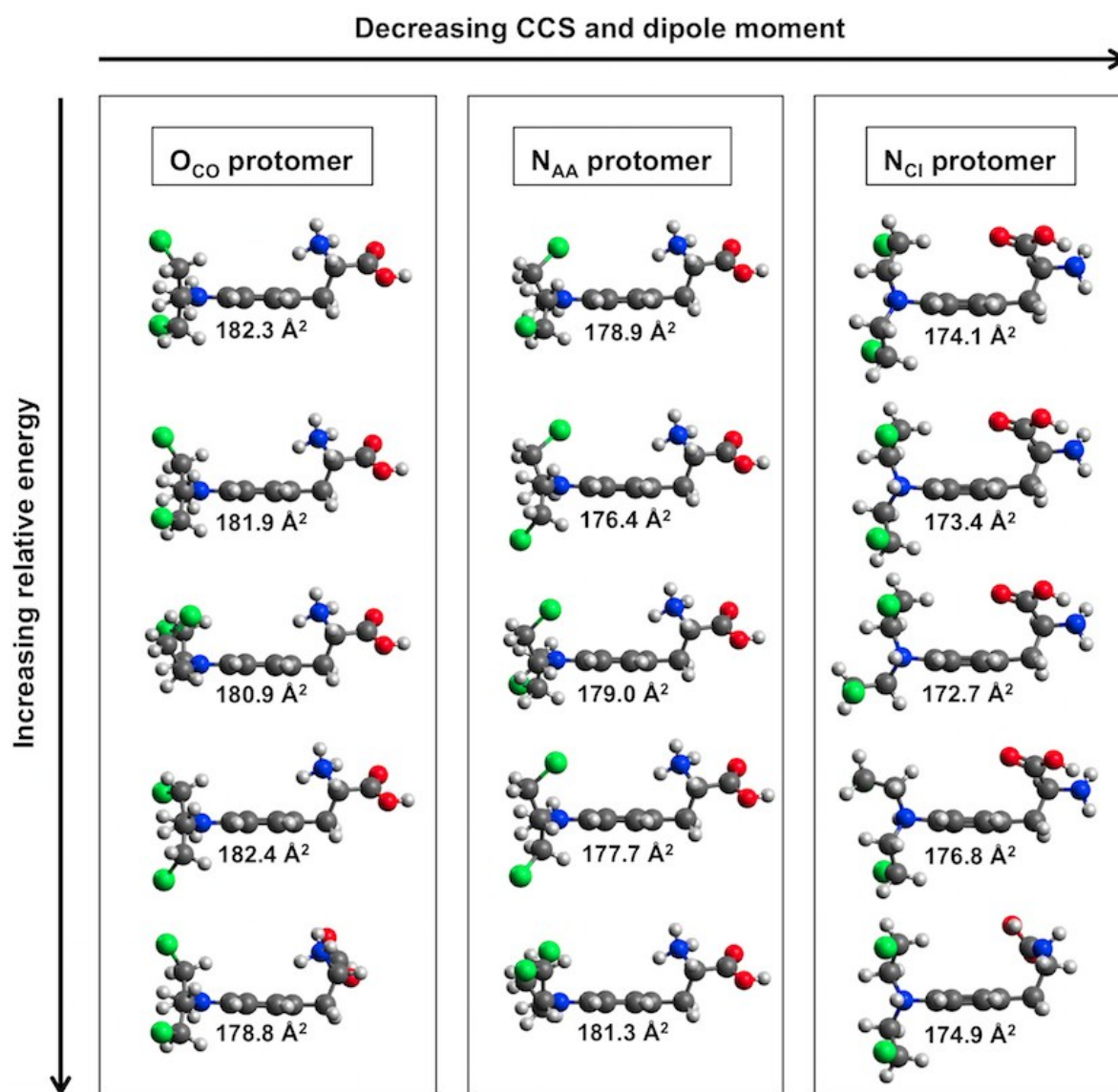

Decreasing CCS and dipole moment

Increasing relative energy

O_{CO} protomer

182.3 Å²
181.9 Å²
180.9 Å²
182.4 Å²
178.8 Å²

N_{AA} protomer

178.9 Å²
176.4 Å²
179.0 Å²
177.7 Å²
181.3 Å²

N_{Cl} protomer

174.1 Å²
173.4 Å²
172.7 Å²
176.8 Å²
174.9 Å²

Figure S.3

3D-visualisation of the lowest-energy structures of melphalan (Mel; **I**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimisation. CCS values were calculated using MobCal. Molecular electrostatic potentials (MEPs) are also shown.
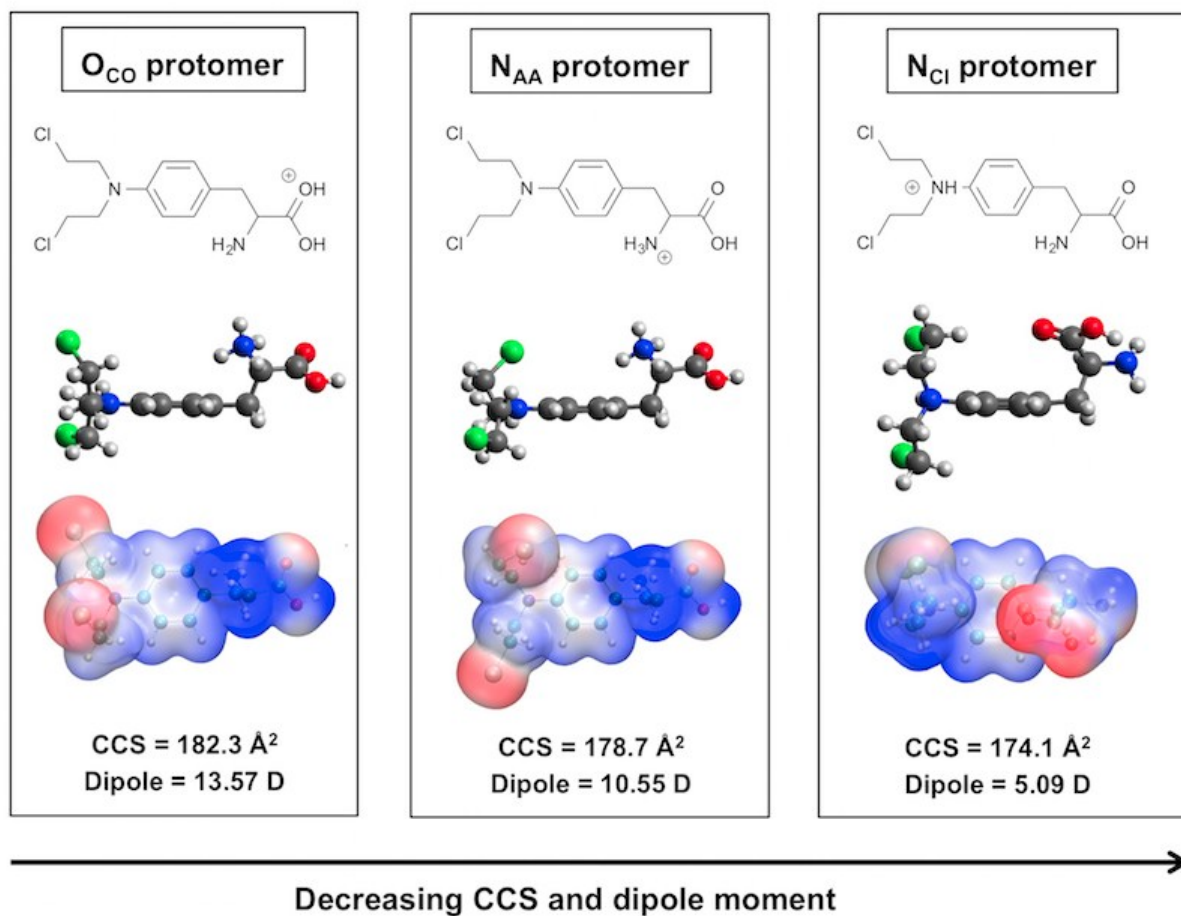
Figure S.4

3D-visualisation of the lowest-energy structures of dimethoxymelphalan (DOCH$_3$; **II**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimisation. Two possible protomers are shown including MEPs: N$_{AA}$ (top) and N$_{OCH3}$ (bottom). The dipole moments are relatively similar, which results in similar CCS. As a result, no IM separation is expected. This is confirmed by the ATD plot (see Figure 2).
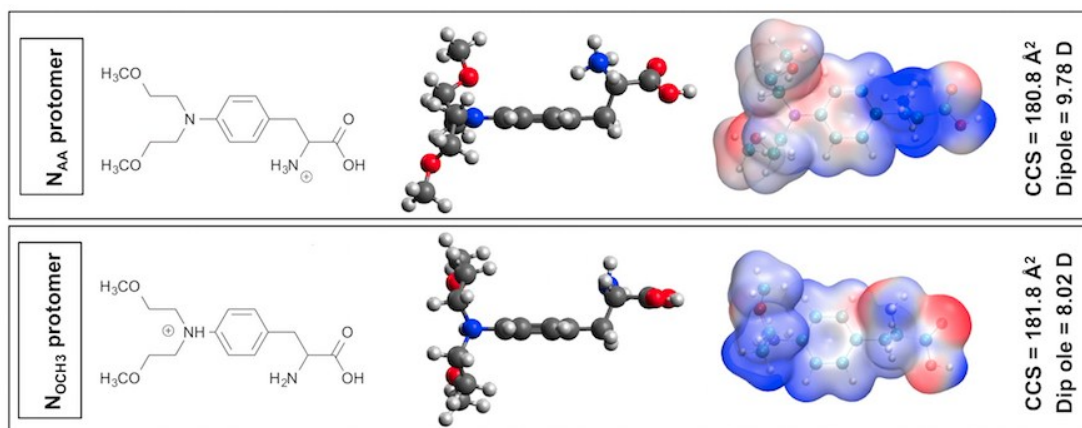
Figure S.5

3D-visualisation of the lowest-energy structures of dihydroxymelphalan (DOH; **III**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimisation. Two possible protomers are shown including MEPs: N_{AA} (top) and N_{OH} (bottom). Minor differences in dipole moments are observed between the protomers, which result in small differences in CCS. Nonetheless, no IM separation is observed (see Figure 2).
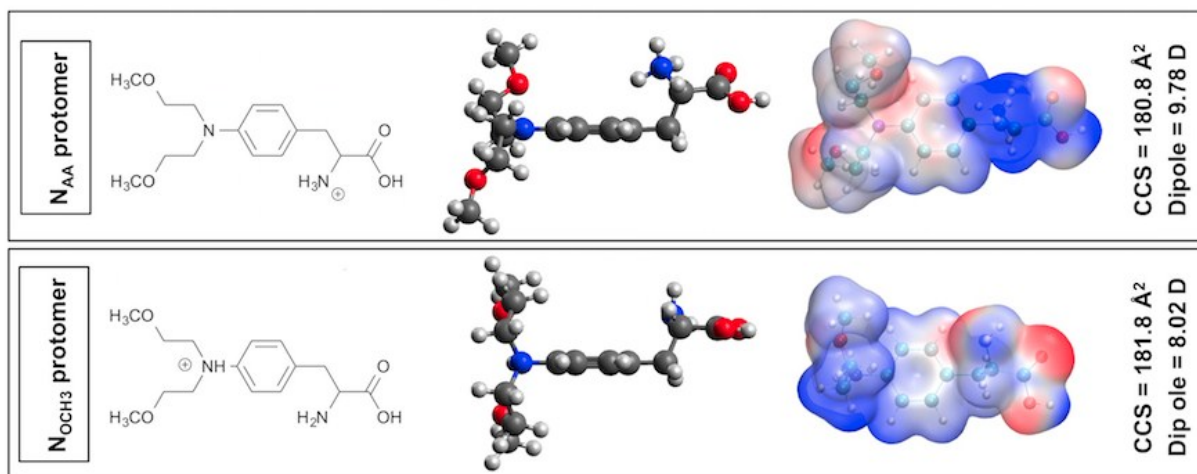
Figure S.6

3D-vizualization of the lowest-energy structures of *para*-benzocaine (**IV**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimisation. Two possible protomers are visualized: N_{NH2} (top) and O_{CO} (bottom). MEPs are also given. A larger difference in dipole moments between both protomers is observed in comparison to melphalan. As a result, well-separated ATDs are observed (see Figure 3).
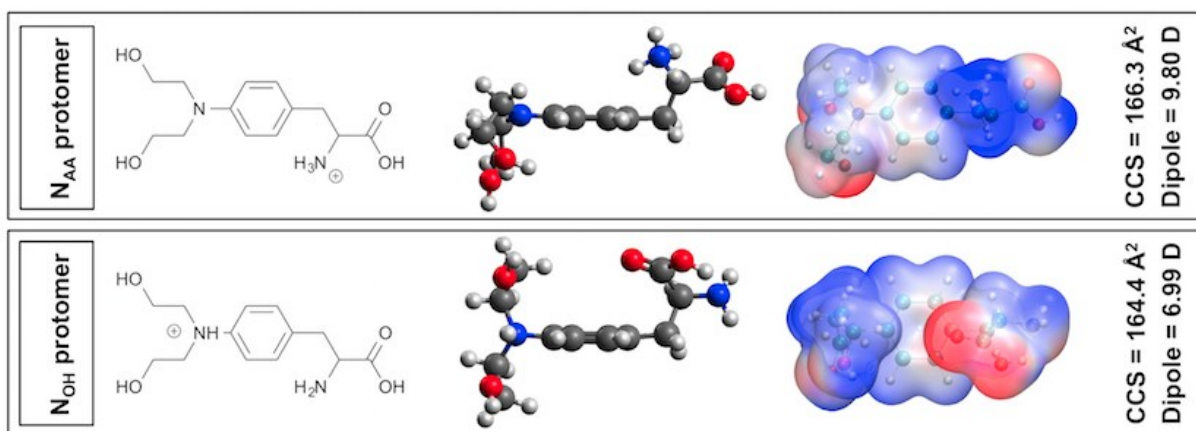
Figure S.7

3D-vizualization of the lowest-energy structures of *ortho*-benzocaine (**V**), after conformational analysis of the protonated molecules and subsequent high-level DFT optimization. MEPs are also given. Two possible protomers are visualized: N_{NH2} (top) and O_{CO} (bottom). For *ortho*-benzocaine, only one ATD is observed (see Figure 3). Unlike for the other two benzocaine isomers, the difference between the calculated dipole moments of the protomers is much smaller.
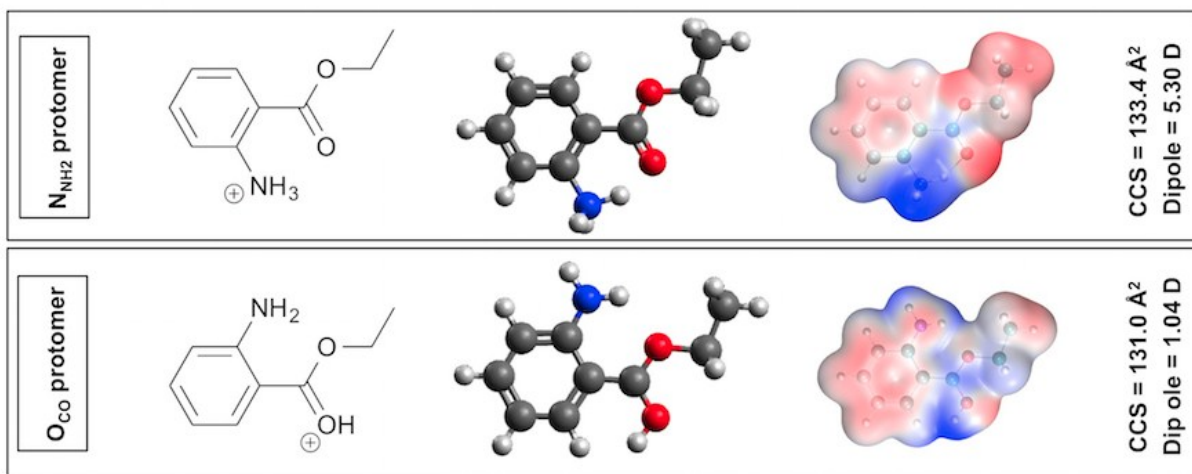
Figure S.8

3D-vizualization of the lowest-energy structures of *meta*-benzocaine (**VI**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimization. MEPs are also given. Two possible protomers are visualized: N_{NH2} (top) and O_{CO} (bottom). It is thought that the large difference in dipole moment, calculated for the lowest-energy protomers, results in the observation of two distinct ATDs (see Figure 3).
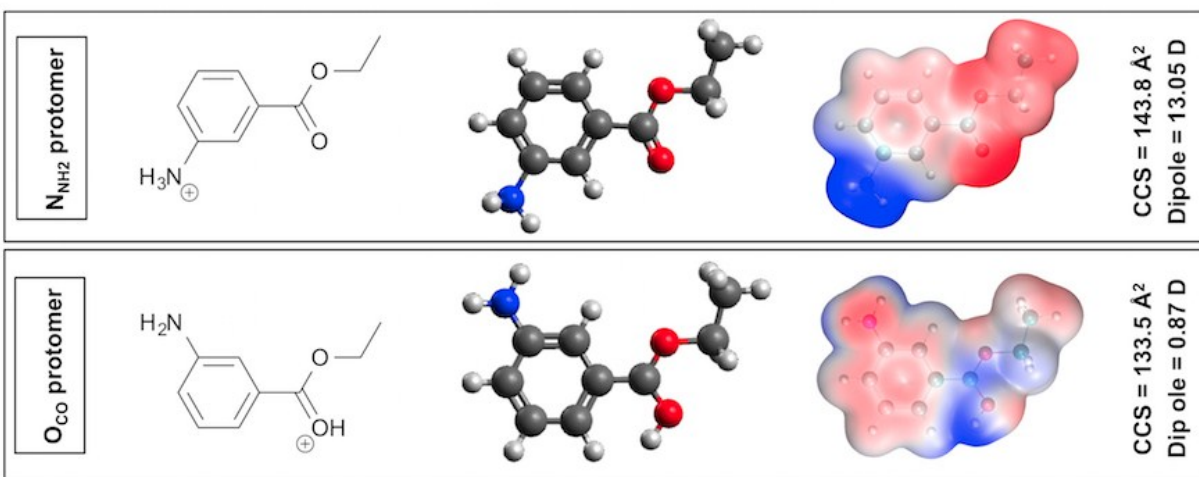
Figure S.9

3D-vizualization of the lowest-energy structures of aniline (**VII**) after conformational analysis of the protonated molecules and subsequent high-level DFT optimization. MEPs are also given. Two possible protomers are visualized: N_{NH2} (top) and the ring protomer (*para*-; bottom). Figure 3 also shows two ATDs for aniline, although less resolved than those of benzocaine. This is reflected in the calculated dipole moment values.