

Structure Analysis of Two Conformationally Flexible Sapidants, *o*- and *p*-Tolylurea

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Abstract. *o*-C₈H₁₀N₂O, $M_r = 150.18$, monoclinic, $P2_1/c$, $a = 4.652$ (6), $b = 5.999$ (2), $c = 27.55$ (2) Å, $\beta = 94.90$ (7)°, $Z = 4$, $D_x = 1.30$ Mg m⁻³, $R = 0.052$ for 848 observed reflections. *p*-C₈H₁₀N₂O, $M_r = 150.18$, monoclinic, $P2_1/c$, $a = 4.6270$ (3), $b = 5.449$ (1), $c = 31.991$ (2) Å, $\beta = 99.653$ (6)°, $Z = 4$, $D_x = 1.25$ Mg m⁻³, $R = 0.052$ for 959 observed reflections. Both isomers have similar molecular parameters with the amide bonds in *trans* conformation and the aryl rings forming angles of about 50° with the plane of the urea moiety, a conformation that may allow for interaction with the sweet-taste-receptor site. Extensive networks of intermolecular hydrogen bonds dominate the two crystal packings.

Introduction. The tastes of tolylureas show a remarkable dependence on positional isomerism, that is the *p*-isomer elicits a sweet taste whereas the *m*-isomer tastes bitter and the *o*-isomer is tasteless (Moncrieff, 1967).

Correlation between structure and biological activity can be based on a detailed model of the receptor site for sweet molecules proposed by some of us (Temussi, Leij & Tancredi, 1978) but is hampered by the conformational flexibility of arylureas. Conformational preferences around the amide bond are well studied and can be tackled with the aid of spectroscopic methods but the torsion of the aryl ring around the N–aryl bond can only be studied with the aid of empirical and quantum chemical calculations. Rather than using literature data on related compounds, we have undertaken the X-ray study of the crystal structures of the *o*- and *p*-isomers mainly with the aim of obtaining reliable molecular parameters for subsequent semi-empirical calculations. It is also worth noting that although solid-state structural data are not directly transferable, in general, to studies of structure–activity relationship, in this particular case even a rough knowledge of the overall shape of the two molecules is potentially useful, in view of the fact that the active-site model requires a rather flat shape of the putative tastants.

Experimental. Both compounds were prepared according to standard organic-chemistry recipes (Vogel, 1961) and recrystallized from ethanol by slow evaporation.

The lattice parameters were obtained by least-squares refinement of 25 accurately centered reflections. Intensity data were collected on a CAD-4 Enraf–Nonius automatic single-crystal diffractometer of the Centro di Metodologie Chimico Fisiche of the University of Naples in the 2θ – ω mode (radiation used Cu $K\alpha$, $\lambda = 1.54178$ Å). 1137 reflections were collected for the *o*-isomer and corrected for polarization and Lorentz factors. 289 of these reflections having $I < 3\sigma(I)$ were not considered in the refinement. 1157 reflections were collected for the *p*-isomer and corrected likewise. 198 of these reflections having $I < 3\sigma(I)$ were not considered in the refinement. Both structures were solved by means of direct methods using the program *MULTAN* (Germain, Main & Woolfson, 1971) included in the Enraf–Nonius structure determination package for a PDP-11 computer. The Fourier maps, calculated with the set of phases presenting the highest combined figure of merit given by *MULTAN*, revealed all the non-H atoms. Refinement was achieved by least-squares procedures for all except the H atoms.

All H-atom positions were revealed by Fourier difference maps for both isomers and isotropic thermal factors equal to those of the carrier atoms were assigned to them. The conversion of all non-H atoms to anisotropic thermal parameters and further refinement yielded R values of 0.052 for both the *o*- and *p*-isomers. Refinement with weights $w = 1/\sigma(F_o)^2$ was continued until the maximum shifts in the atomic coordinates were less than $\frac{1}{3}$ of the corresponding standard deviations.

Table 1 contains the final positional parameters.* The nomenclature for the atoms of the asymmetric

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36945 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final atomic coordinates and equivalent isotropic thermal parameters

E.s.d.'s, in units of the last significant figure, are given in parentheses.

| o-Isomer | | | | p-Isomer | | | | | |
|----------|---------------|---------------|--------------|--------------------------------|------|---------------|---------------|--------------|--------------------------------|
| | x | y | z | B_{eq} (\AA^2) | | x | y | z | B_{eq} (\AA^2) |
| C(1) | 0.16251 (60) | 0.06428 (50) | 0.13420 (11) | 2.75 (6) | O | -0.14369 (29) | 0.07067 (32) | 0.20518 (5) | 3.68 (3) |
| C(2) | -0.01996 (71) | 0.22799 (57) | 0.14968 (12) | 3.62 (7) | N(1) | 0.24306 (37) | 0.18362 (41) | 0.17378 (6) | 3.90 (4) |
| C(3) | -0.15462 (77) | 0.37578 (58) | 0.11651 (13) | 4.17 (8) | N(2) | 0.30829 (37) | -0.07546 (42) | 0.23013 (6) | 4.18 (5) |
| C(4) | -0.09956 (76) | 0.36402 (57) | 0.06802 (13) | 4.12 (8) | C(1) | 0.08367 (46) | 0.33318 (45) | 0.14141 (7) | 3.58 (5) |
| C(5) | 0.08790 (73) | 0.20417 (60) | 0.05324 (12) | 3.73 (7) | C(2) | 0.12424 (62) | 0.29937 (58) | 0.10020 (8) | 5.53 (7) |
| C(6) | 0.21841 (60) | 0.04918 (50) | 0.08561 (11) | 2.86 (6) | C(3) | -0.01901 (65) | 0.44785 (65) | 0.06852 (8) | 5.75 (7) |
| C(7) | 0.41275 (72) | -0.12728 (60) | 0.06847 (12) | 3.95 (8) | C(4) | -0.20476 (57) | 0.63147 (50) | 0.07647 (8) | 4.63 (6) |
| C(8) | 0.16535 (61) | -0.21316 (52) | 0.20023 (11) | 2.66 (6) | C(5) | -0.24508 (66) | 0.66089 (56) | 0.11758 (9) | 5.51 (7) |
| N(1) | 0.30304 (49) | -0.08572 (45) | 0.16872 (9) | 3.07 (5) | C(6) | -0.10289 (60) | 0.51557 (52) | 0.15030 (8) | 4.55 (6) |
| N(2) | 0.33559 (51) | -0.34985 (48) | 0.22851 (10) | 3.53 (6) | C(7) | -0.34971 (75) | 0.79253 (63) | 0.04107 (10) | 6.94 (9) |
| O | -0.09975 (40) | -0.20296 (38) | 0.20327 (8) | 3.39 (4) | C(8) | 0.12241 (44) | 0.05923 (45) | 0.20316 (7) | 3.09 (5) |

Table 2. Bond lengths (\AA), angles ($^\circ$) and internal rotation angles ($^\circ$)

E.s.d.'s, in units of the last significant figure, are given in parentheses.

| o-Isomer | | | p-Isomer | | | | |
|---------------------|------------|---------------------|------------|---------------------|-----------|---------------------|------------|
| C(1)-C(2) | 1.389 (4) | C(2)-C(1)-C(6) | 120.8 (5) | O-C(8) | 1.245 (2) | C(1)-N(1)-C(8) | 124.7 (3) |
| C(1)-C(6) | 1.388 (4) | C(2)-C(1)-N(1) | 119.9 (5) | N(1)-C(1) | 1.423 (3) | N(1)-C(1)-C(2) | 118.9 (4) |
| C(1)-N(1) | 1.426 (4) | C(6)-C(1)-N(1) | 119.2 (4) | N(1)-C(8) | 1.353 (3) | N(1)-C(1)-C(6) | 122.0 (4) |
| C(2)-C(3) | 1.383 (5) | C(1)-C(2)-C(3) | 120.3 (5) | N(2)-C(8) | 1.332 (3) | C(2)-C(1)-C(6) | 119.1 (4) |
| C(3)-C(4) | 1.383 (5) | C(2)-C(3)-C(4) | 119.6 (5) | C(1)-C(2) | 1.375 (3) | C(1)-C(2)-C(3) | 120.1 (4) |
| C(4)-C(5) | 1.381 (5) | C(3)-C(4)-C(5) | 119.6 (5) | C(1)-C(6) | 1.377 (4) | C(2)-C(3)-C(4) | 122.1 (5) |
| C(5)-C(6) | 1.390 (4) | C(4)-C(5)-C(6) | 121.8 (5) | C(2)-C(3) | 1.377 (4) | C(3)-C(4)-C(5) | 117.0 (4) |
| C(6)-C(7) | 1.495 (4) | C(1)-C(6)-C(5) | 117.8 (5) | C(3)-C(4) | 1.370 (4) | C(3)-C(4)-C(7) | 120.2 (4) |
| C(8)-N(1) | 1.358 (4) | C(1)-C(6)-C(7) | 121.3 (5) | C(4)-C(5) | 1.368 (3) | C(5)-C(4)-C(7) | 122.8 (4) |
| C(8)-N(2) | 1.341 (4) | C(5)-C(6)-C(7) | 120.9 (5) | C(4)-C(7) | 1.499 (4) | C(4)-C(5)-C(6) | 122.3 (4) |
| C(8)-O | 1.246 (3) | N(1)-C(8)-N(2) | 115.3 (4) | C(5)-C(6) | 1.387 (4) | C(1)-C(6)-C(5) | 119.4 (4) |
| | | N(1)-C(8)-O | 122.7 (5) | | | O-C(8)-N(1) | 122.5 (3) |
| | | N(2)-C(8)-O | 122.0 (5) | | | O-C(8)-N(2) | 122.0 (3) |
| | | C(1)-N(1)-C(8) | 124.5 (4) | | | N(1)-C(8)-N(2) | 115.4 (3) |
| C(4)-C(3)-C(2)-C(1) | -2.0 (5) | C(8)-N(1)-C(1)-C(2) | 54.4 (5) | C(4)-C(3)-C(2)-C(1) | -0.2 (5) | C(7)-C(4)-C(5)-C(6) | -178.0 (5) |
| C(4)-C(5)-C(6)-C(1) | -2.2 (5) | C(8)-N(1)-C(1)-C(6) | -127.8 (5) | C(4)-C(5)-C(6)-C(1) | -0.7 (4) | C(8)-N(1)-C(1)-C(2) | -130.0 (4) |
| C(5)-C(4)-C(3)-C(2) | 0.3 (6) | N(1)-C(1)-C(2)-C(3) | 179.3 (6) | C(5)-C(4)-C(3)-C(2) | -0.5 (4) | C(8)-N(1)-C(1)-C(6) | 52.1 (4) |
| C(5)-C(6)-C(1)-C(2) | 0.5 (5) | N(1)-C(1)-C(6)-C(5) | -177.2 (6) | C(5)-C(6)-C(1)-C(2) | -0.1 (4) | N(1)-C(1)-C(2)-C(3) | -177.6 (5) |
| C(6)-C(1)-C(2)-C(3) | 1.5 (5) | N(1)-C(1)-C(6)-C(7) | 2.7 (4) | C(6)-C(1)-C(2)-C(3) | 0.5 (4) | N(1)-C(1)-C(6)-C(5) | 177.9 (5) |
| C(6)-C(5)-C(4)-C(3) | 1.8 (6) | N(2)-C(8)-N(1)-C(1) | 177.5 (6) | C(6)-C(5)-C(4)-C(3) | 0.9 (5) | N(2)-C(8)-N(1)-C(1) | 178.4 (4) |
| C(7)-C(6)-C(1)-C(2) | -179.6 (6) | O-C(8)-N(1)-C(1) | -3.3 (5) | C(7)-C(4)-C(3)-C(2) | 178.4 (5) | O-C(8)-N(1)-C(1) | -2.1 (4) |
| C(7)-C(6)-C(5)-C(4) | 177.9 (6) | | | | | | |

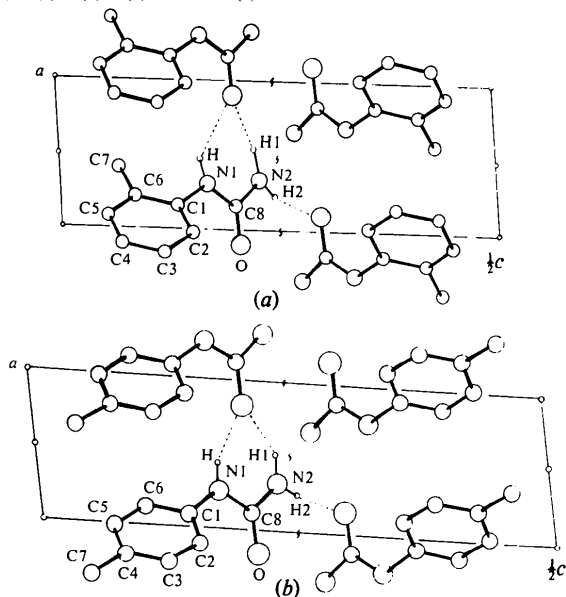


Fig. 1. Mode of packing for (a) o- and (b) p-tolylurea along the [010] direction. Some hydrogen bonds are indicated as dashed lines.

units is given in Fig. 1. Calculated bond lengths, bond angles and internal rotation angles are given in Table 2.

Discussion. All molecular parameters are similar in the two isomers, including the internal rotation angles around the C(8)-N(1) bonds that correspond to an antiperiplanar conformation in both compounds, and around the N(1)-C(1) bonds that correspond to the synclinal conformation.

The bond lengths and angles of the urea moiety are in excellent agreement with those of unsubstituted urea (Worsham, Levy & Peterson, 1957) with only slight deviations in the bond angles owing to the influence of the substituent.

Comparison with polysubstituted arylureas (Lepore, Castronuovo, Ganis, Germain & Goodman, 1976) on the other hand shows that the substituted N in our compounds is purely trigonal, with no hint of pyramidalization. All the molecular parameters of the tolyl moieties are in good agreement with standard values for aromatic compounds (Harmony *et al.*, 1979).

Fig. 1 shows the projections of the two structures along the *b* axis. In both cases the molecular packing is dominated by an extensive network of hydrogen bonds. Rows of molecules along the *a* axis form hydrogen bonds involving the two *trans* H atoms and the O atom of the adjacent molecule of the same height. The lengths N(1)⋯Oⁱ and N(2)⋯Oⁱ [(i) 1 + *x*, *y*, *z*] for the *o*-isomer are 2.944 (2) and 2.913 (2) Å [N(1)–H⋯Oⁱ = 140.0 (2), N(2)–H(1)⋯Oⁱ = 142.7 (2)°]. The corresponding distances for the *p*-isomer are 2.913 (1) and 2.895 (1) Å respectively [N(1)–H⋯Oⁱ = 156.7 (2), N(2)–H(1)⋯Oⁱ = 145.7 (2)°]. Another type of hydrogen bond is formed along the screw axes and involves the *cis* H. The lengths of the N(2)⋯Oⁱⁱ [(ii) \bar{x} , $y - \frac{1}{2}$, $\frac{1}{2} - z$] distances are 3.094 (2) Å for the *o*- [N(2)–H(2)⋯Oⁱⁱ = 176.2 (3)°] and 3.018 (2) Å for the *p*- compound [N(2)–H(2)⋯Oⁱⁱ = 174.5 (7)°]. These arrangements are reminiscent of the structure of urea (Vaughan & Donohue, 1952), in which one O is linked to four H atoms of adjacent molecules.

The presence of pairs of hydrogen bonds between moieties of the same height influences the relative orientation, and hence the conformation, of the aromatic rings. In fact a smaller value of the internal rotation angle around the N(1)–C(1) bond would induce very close intermolecular distances between adjacent tolyl rings, that could only be accommodated by weakening the hydrogen bonds. Thus, it can be anticipated that the isolated molecules may have a smaller equilibrium value for this torsion angle (larger values on the other hand would completely offset the contribution to resonance energy). Preliminary calculations with PCILO methods (Malrieu, 1977) show in fact most probable values around 30° for both isomers. As mentioned in the *Introduction*, the ac-

cessibility of fairly low values for this angle (*i.e.* a flat overall molecular shape) is crucial for a good interaction with the sweet-taste-receptor site. Complete internal-energy calculations based on the present molecular parameters will shortly be published elsewhere, together with a detailed discussion on the possible interactions of our model with the sweet-taste-receptor site.

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Structure of Anthralin Dimer*

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Abstract. C₂₈H₁₈O₆, *M_r* = 450.45, monoclinic, *C*2/*c*, *a* = 17.708 (2), *b* = 7.566 (1), *c* = 16.263 (1) Å, β = 106.60 (1)°, *V* = 2088.08 Å³, *D_x* = 1.433, *D_m* =

1.43 (1) Mg m⁻³, *Z* = 4, *F*(000) = 936, μ(Cu *Kα*) = 0.790 mm⁻¹, λ(Cu *Kα*) = 1.54056 Å. The crystal structure has been determined and refined with 778 observed reflexions, *I* > 1.5σ(*I*), to *R* = 0.041 and *R_w* = 0.052. The structural formula has been established

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