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# Molecular structure and ultrasound-assisted synthesis of the diazacrown derivative containing 2,3,4,6-tetraaryl-γ-piperidone

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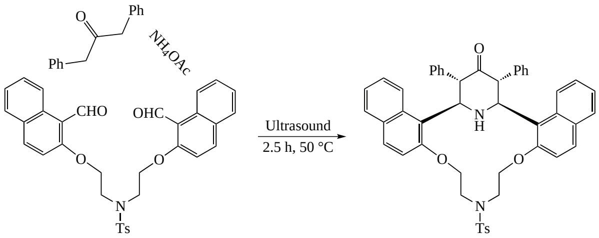
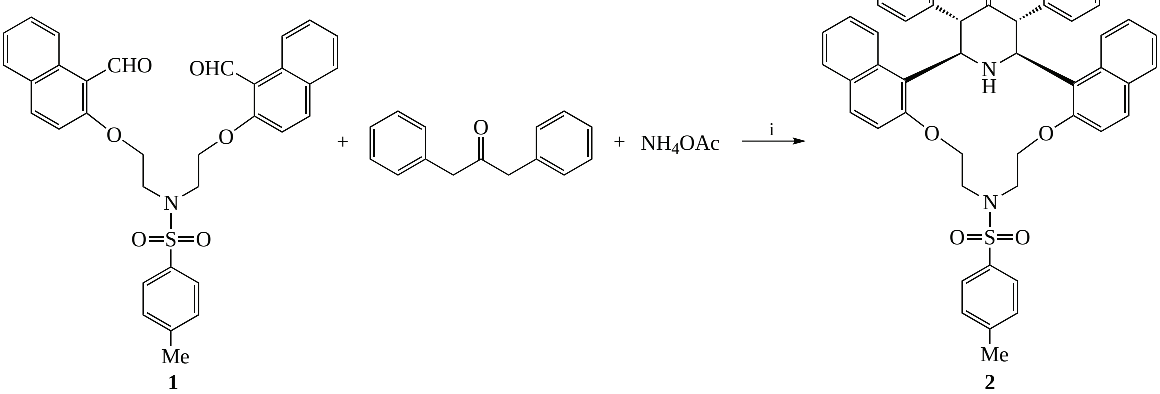
**A 14-membered azacrown ether, namely, $2^3$,$2^5$-diphenyl-7-tosyl-4,10-dioxa-7-aza-2(2,6)-piperidina-1(2,1),3(1,2)-dinaphthalenacyclodecaphan-$2^4$-one, was successfully synthesized in a short period of time and with a reasonable yield using ultrasonic vibration. The obtained compound containing a polyether chain, an *N*-tosyl group and a piperidone ring seems promising biologically active substance and ligand for chelating with metal ions.**



*Keywords*: azacrownophane, ultrasonic vibration, polyether chain, *N*-tosyl, X-ray, piperidone.

Piperidones are reported to possess various biological properties such as antimicrobial,[1] anticancer and antioxidant,[2] anti-inflammatory and anti-proliferation,[3] and human DNA ligase I inhibition.[4] Piperidone is also an important template for further conversion into candidate drugs.[5] A classical method for the synthesis of piperidones is based on the Petrenko-Kritschenko reaction,[6] in which a dialkyl acetone-1,3-dicarboxylate is combined with benzaldehyde and an amine or ammonia to furnish the 4-piperidone derivative. As part of our ongoing research,[7–13] we present a modification of the Petrenko-Kritschenko method to synthesize a 4-piperidone compound by the introduction of naphthalene-linked crown ether groups at the 2,6 positions and phenyl groups at the 3,5 positions of piperidone ring. Three agents, 1,5-bis(2-formylnaphthalen-1-yloxy)-3-tosyl-3-azapentane **1**, dibenzyl ketone and ammonium acetate reacted in the presence of acetic acid as catalyst to give the target $2^3$,$2^5$-diphenyl-7-tosyl-4,10-dioxa-7-aza-2(2,6)-piperidina-1(2,1),3(1,2)-dinaphthalenacyclodecaphan-$2^4$-one **2** (Scheme 1).

Our experiments showed that the reaction was completed in 24 h of heating and stirring in a water bath at 70 °C to afford product **2** in a moderate yield of 36%. Since ultrasound irradiation is known to generally improve the reaction yields,[14] we herein attempted to perform the synthesis under sonication. In fact, the sonication allowed us to reduce the reaction time about 12-fold (from 24 to 2.5 h), saved energy by running at lower temperature (50 °C), and improved the yield to 45% (for synthetic details, see Online Supplementary Materials).



**Scheme 1** *Reagents and conditions:* i, AcOH, MeCN, sonication, 50 °C, 2.5 h.

The structure of product **2** was identified by NMR, HRMS and X-ray single crystal diffraction. In the $^1$H NMR spectrum, protons for the $CH_3$ group showed a sharp singlet at 2.48 ppm, hydrogen atoms of polyether chain resonated as multiplets at 3.39–4.67 ppm. Proton for NH located at 4.75 ppm as a triplet.

Furthermore, we performed single crystal X-ray diffraction of compound **2** (Figure 1).† The calculations were carried out using the SHELXTL program.[15–17] Overall, the molecule possesses idealized Cs (m) intrinsic symmetry. However, in the crystal the geometry of **2** is differentiated from the idealized one by the asymmetric intramolecular N–H···O and C–H···O hydrogen bonds as well as the crystal packing effects. Molecule of **2** comprises a fused hexacyclic system containing the diaza-14-crown-4-ether macrocycle, piperidone and two naphthalene rings. The diaza-14-crown-4-ether ring adopts a bowl conformation, which is stabilized by the intramolecular N–H···O and C–H···O hydrogen bond. The configuration of the C(11)–O(12)–C(13)–C(14)–N(15)–C(16)–C(17)–O(18)–C19 aza-ether chain is t–g$^-$–g$^-$–g$^+$–g$^+$–t (t = *trans*, 180°; g = *gauche*, ± 60°). The central piperidone ring has a slightly distorted *chair* conformation. The two phenyl substituents and the two naphthalene fragments occupy the sterically more favorable equatorial positions. The dihedral angles between the basal C(1)/C(29)/C(30)/C(32) plane of the piperidone ring and planes of the two naphthalene fragments fused to the diaza-14-crown-4-ether moiety are 80.79(5) and 80.68(5)°. The nitrogen N(15) and N(33) atoms have trigonal pyramidal configurations [sums of the valent angles are 348.2(4) and 329.9(4)°, respectively].

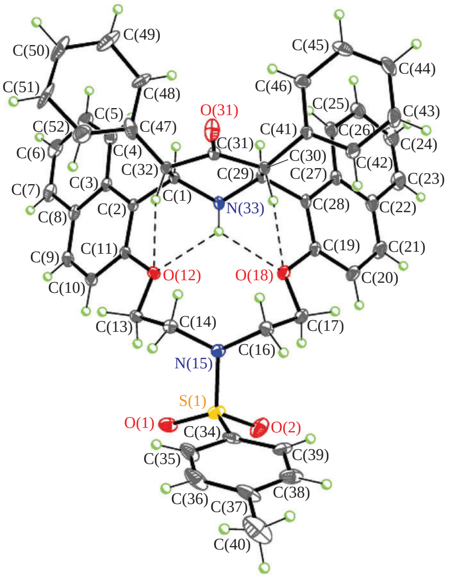


**Figure 1** Molecular structure of **2** (30% ellipsoids). The alternative positions of the disordered carbonyl, tolyl and phenyl substituents with the minor occupancies are not shown. Dashed lines indicate the intramolecular N–H···O and C–H···O hydrogen bonds.

As shown in Figure 1, there are four hydrogen bonds in total that really differ from a crownophane in which naphthalene rings are replaced by phenyl rings, only two N–H···O hydrogen bonds were detected.[10] Molecule of **2** possesses four asymmetric centers at the C(1), C(29), C(30) and C(32) carbon atoms and can potentially have sixteen diastereomers. The crystal of **2** is racemic and consists of enantiomeric pairs with *rac*-1*RS*,29*SR*,30*RS*,32*SR* relative configuration.

In the crystal, molecules of **2** form centrosymmetric H-bonded dimers by the intermolecular C–H···O hydrogen bonds (Table 1, Figure 2). The H-bonded dimers are arranged at van-der-Waals distances (Figure 3).

It is well known that one of the outstanding properties of crown ethers is the ability to chelate with metal ions, the metal ions nature depending mainly on the size of the internal cavity of

**Table 1** Hydrogen bonds for compound **2** (Å and °).

| D–H···A$^a$ | d(D–H) | d(H···A) | d(D···A) | ∠(DHA) |
|---|---|---|---|---|
| C(14)–H(14A)···O(31)$^b$ | 0.97 | 2.33 | 3.234(3) | 155.5 |
| C(14)–H(14A)···O(31A)$^b$ | 0.97 | 2.39 | 3.147(11) | 134.2 |
| C(16)–H(16B)···O(31)$^b$ | 0.97 | 2.47 | 3.376(3) | 156.0 |
| C(16)–H(16B)···O(31A)$^b$ | 0.97 | 2.47 | 3.258(11) | 138.4 |
| C(30)–H(30)···O(18) | 0.98 | 2.38 | 3.033(2) | 123.5 |
| C(32)–H(32)···O(12) | 0.98 | 2.37 | 3.014(2) | 122.3 |
| N(33)–H(33)···O(12) | 0.87(2) | 2.21(2) | 2.810(2) | 126.4(17) |
| N(33)–H(33)···O(18) | 0.87(2) | 2.23(2) | 2.828(2) | 125.9(17) |

$^a$ D – proton donor; A – proton acceptor. $^b$ Symmetry transformations used to generate equivalent atoms: $–x+1, –y+1, –z+1$.

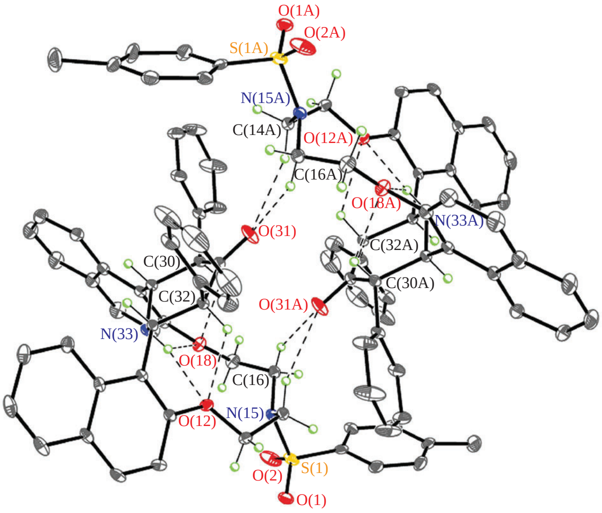


**Figure 2** The centrosymmetric H-bonded dimers of compound **2** (30% ellipsoids).

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† *Crystal data for* **2**. The colorless prismatic crystal of **2** ($C_{48}H_{42}N_2O_5S$, $M = 758.90$) is triclinic, space group $P\bar{1}$, at $T = 100$ K: $a = 11.9057(10)$, $b = 14.2125(14)$ and $c = 14.2658(13)$ Å, $\alpha = 62.714(5)°$, $\beta = 74.391(5)°$, $\gamma = 68.364(5)°$, $V = 1979.5(3)$ Å$^3$, $Z = 2$, $d_{calc} = 1.273$ g cm$^{-3}$, $F(000) = 800$, $\mu = 0.133$ mm$^{-1}$. Data were collected on a Bruker D8 QUEST instrument at 100 K with MoKα radiation ($\lambda = 0.71073$ Å) using a TRIUMPH monochromator. Structure solution and refinement were performed with the SHELXT and SHELXL 2014/7 programs.[15–17] A total of 92037 reflection intensities (12149 independent reflections, $R_{int} = 0.0658$) were measured using a Bruker D8 QUEST diffractometer [$\lambda$(MoK$\alpha$)-radiation, graphite monochromator, ω and φ scanning mode] and corrected for absorption using the SADABS program ($T_{min} = 0.953$, $T_{max} = 0.986$). The structure was determined by direct methods and refined by a full-matrix least squares technique on $F^2$ with anisotropic displacement parameters for non-hydrogen atoms. The carbonyl, tolyl and one of the two phenyl substituents are disordered over two sites each with the occupancies of 0.857(6)/0.143(6), 0.647(5)/0.353(5), and 0.726(16)/0.274(16), respectively. The crystal contained two solvate water molecules, which were strongly disordered. Unfortunately, all attempts to model and refine positions of the solvate molecules were unsuccessful. Therefore, their contribution to the total scattering pattern was removed by use of the utility SQUEEZE in PLATON15. The hydrogen atom of the NH-group was localized in the difference-Fourier map and included into the refinement with fixed positional and isotropic displacement parameters [$U_{iso}(H) = 1.2\,U_{eq}(N)$]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [$U_{iso}(H) = 1.2\,U_{eq}(C)$]. The final divergence factors were $R_1 = 0.0655$ for 7285 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1525$ for all independent reflections, $S = 1.030$.

CCDC 2213231 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

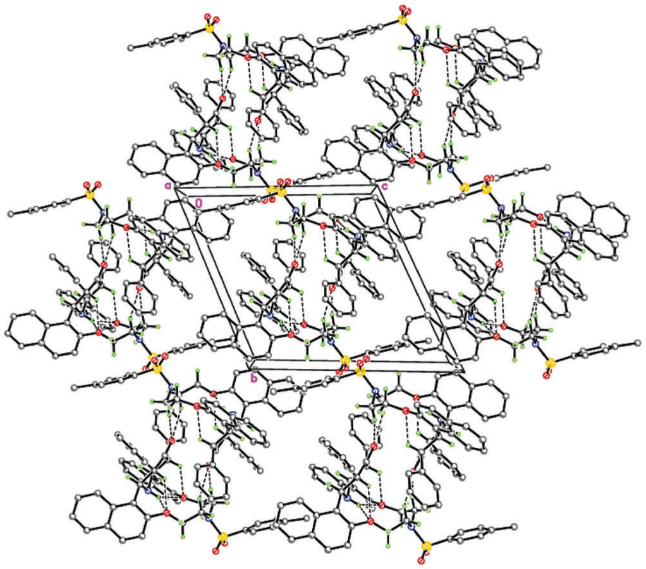

**Figure 3** Crystal packing of **2** along the crystallographic *a* axis.

the crown compound. This value could be determined as the double average distance between the cyclic n-electron donor heteroatoms and the centroid of the crown ring.[13,18] For compound **2**, this value is 4.16 Å, relatively smaller than that for compound in which naphthalene groupings are replaced by phenyl rings (4.24 Å)[10] but longer than for $2^3$,$2^5$-diphenyl-4,7,10-trioxa-2(2,6)-piperidina-1(2,1),3(1,2)-dinaphthalenacyclodecaphan-$2^4$-one (4.051 Å), a very similar structure in which the *N*-tosyl group is replaced by oxygen atom[9,19] (see Online Supplementary Materials, Table S6). The steric effect of the naphthalene grouping as well as the structure of polyether chain have contributed to this value. This result demonstrates that these compounds are potent candidates for forming complexes with alkali metals.

In summary, this study introduces the synthesis of $2^3$,$2^5$-diphenyl-7-tosyl-4,10-dioxa-7-aza-2(2,6)-piperidina-1(2,1),3(1,2)-dinaphthalenacyclodecaphan-$2^4$-one **2** using an ultrasonic bath. With an internal cavity of 4.16 Å, this compound is anticipated to be a good ligand for complexing with alkali metals.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.038.

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