A Detailed Study Defining the Extent of Preorganization of an Aza Macrocycle containing the Phenyldinaphthomethane Subunit (a Three Bladed Propeller) Using Dynamic NMR and Molecular Dynamics

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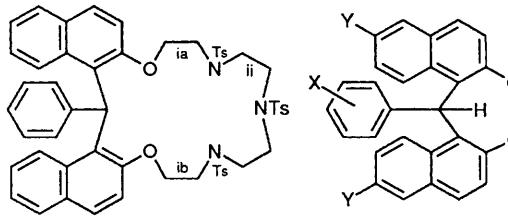
The aza-propeller crown 4,7,10-tritosyl-4,7,10-triaza-1,13-dioxacyclooctadecane **1** has been examined by variable temperature ^{13}C NMR studies, and the movement of each segment of the molecule (ArOCCN, NCCN, propeller) was determined kinetically. Several sets of coalescences were found to occur at the same activation energy, which was also that found for the flip of the propeller segment. This movement of the macrocycle as a whole is a relatively slow process (ms scale) compared to the torsional movements round the crown ether ring (ps scale). These torsional movements were explored by molecular dynamics (MD) modelling; the macrocyclic ring is mobile when simulated at 200 K. The tosyl groups are in permanent motion although none twists by more than a few degrees round the N–S torsion. The segments next to the propeller (which are both *gauche* in the crystal structure) converted from *gauche* to *anti*, while the TsNCCNTS segments remained *anti* throughout.

The new aza-propeller crowns, *e.g.* **1**,† have proved useful as reporters of their own fluxional state,[1] and show promise like the propeller crown ethers, **2**, of providing detailed insight into the fluxionality of the free ligand.[2] This paper is a fundamental study of the nature of conformational change in one aza crown, with reporter groups on each section of the structure, which have enabled activation energies for an observed process to be correlated all round the molecule. In **2**, the propeller flip has earlier[2] been correlated with the movement of ether segment *i* (seen in formula **2**). With **1**, we have added the further probe of the tosyl groups, with which we can monitor the movement of segment *ii* (see **1**). The crystal structure shows for the single isomer isolated (enantiomeric pair), that there are three non-equivalent tosyl groups, but the ^1H NMR shows two sets, in the ratio 2:1 at room temperature. The structure thus undergoes a rapid symmetrisation process at room temperature on the relevant NMR timescale (s to ms at 200–250 K), which makes two of the tosyl groups equivalent, the unique tosyl being that on the central N of the –N–C–C–N–C–C–N– string. Decoalescence at 230–240 K ($\Delta G^{\ddagger}$ = 52.3 ± 1.7 kJ mol^{-1}, at 230–240 K) of tosyl methyl signals was consistent with the hypothesis that the process of which the kinetics are being observed is actually the 'locking' of the propeller at low temperatures. Since this reaction is actually slightly slower than that for the compounds **3** and **4**, it may indicate that the steric bulk of three adjacent tosyl groups is a factor in the flipping observed. In this paper we present an analysis of decoalescence in the ^{13}C NMR spectra for this uniquely labelled crown, which enables us to confirm that exchanges of the same rate are observed in each section of the molecule, and to assign the propeller flip as the controlling process for these exchanges. The torsional movements of **1** on a ps timescale have been simulated with molecular dynamics (MD) techniques and the results are discussed in relation to the overall conformational movements of **1**.



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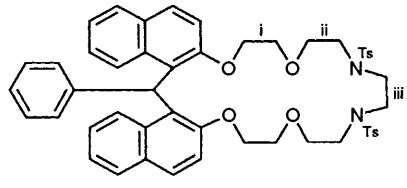

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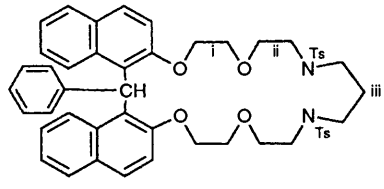

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Experimental

Tosylated macrocycle **1** was available.[1] NMR spectra were obtained in CD_2Cl_2 solvent at variable temperatures on a Bruker WM300-WB. The 1D ^{13}C VT spectra were acquired at 75.459 MHz. The 2D ^1H spectrum at 230 K and 300.132 MHz was obtained with the Bruker CONOESY sequence; comparison of COSY and NOESY plots showed interactions through space between different sections of the molecule. Molecular modelling studies were performed using the protocol of Lockhart and Tomkinson[3] with version 21.3 of CHARMm[4] on a Silicon Graphics IRIS 4D20 and the Molecular Editor of Quanta,[5] as described in earlier studies.[3]

† 26-Phenyl-10,13,16-tritosyl-8,9,11,12,14,15,17,18-octahydro-26*H*-10,13,16-triaza-7,19-dioxadinaphtho[2,1-*n*,1′,2′-*q*]cyclooctadecene.

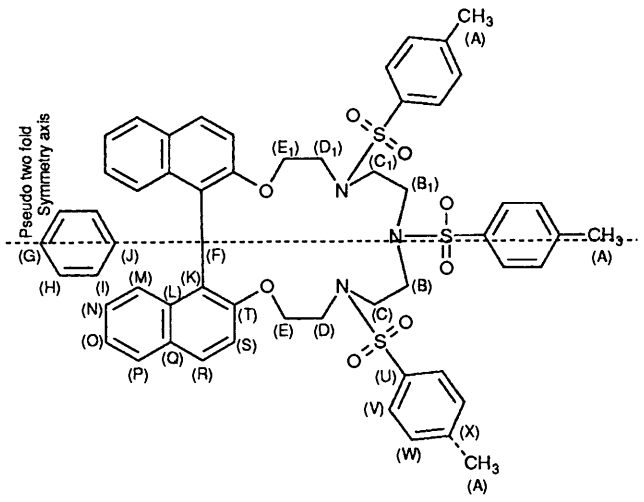

Fig. 1 Labelling of carbon atoms of **1** as assigned in ^{13}C NMR spectra

Results and Discussion

The 1D ^{13}C spectra of this crown have now been examined in detail and show several instances of the effect of conformation freezing out on cooling. The decoalescence temperatures differ for several of these signals but all give approximately the same free energy of activation ($\Delta G^{\ddagger}$ = 53.0 ± 2.0 kJ mol^{-1}). Opportunity is thus presented to analyse the complete movement of each section of the crown, and to show which is the controlling movement.

Detailed descriptions of the relative rates of movement of different sections of the propeller crown ether molecules **2** were made available following lengthy NMR and crystallographic studies of ligands and their complexes.[2,6] It was discovered for example that one of the two Ar-OCCO crown ether segments chelated to a potassium ion nevertheless dechelated rapidly on the relevant ms NMR scale (since the coupling constants for the segment's ABCD protons were actually averages, representing an AA'BB' system), yet the whole ligand remained attached to the cation throughout (since the other ArOCCO segment exhibited static coupling characteristic of an ABCD system with *gauche* oxygens). In recent work the crystal structure of the tritosyltriaza crown **1** was obtained.[1] NMR-Viable reporter groups on **1** (see Fig. 1) have now provided means to examine the relative movement of all sections of the molecule and to define the role of the propeller flip in this overall process more clearly.

The carbons assigned in the ^{13}C spectrum of **1** at room temperature are indicated in Fig. 1. Observation of only 17 signals out of the expected aromatic signals is consistent with the molecule being mobile at room temperature and apparently symmetrical about a pseudo twofold symmetry axis as shown previously.[1] At 230 K most of these signals have split into two signals and 29 out of the 38 aromatic signals expected for a static molecule are seen; all eight carbon signals expected for the ether and amine carbons of the macrocycle ring are observed (see Fig. 2). It was thus expedient to carry out further ^{13}C variable temperature studies, to gain further insight into the role of the propeller unit in the overall movement of the molecule.

The carbon signals chosen for kinetic study were singlets at room temperature, and were well separated from other carbon signals, both at room temperature and at the temperature of decoalescence, and had the following shifts; δ 72.85, 120.69, 124.88 and 156.30. These carbon signals can be assigned to the ether and triaryl segments of the compound, see Fig. 1. The signal at δ 72.85 which is assigned as the carbon E next to the oxygen atom (see Figs. 1 and 2) decoalesces at 258 K with free energy of activation $\Delta G^{\ddagger}$ = 52.3 kJ mol^{-1}. Fig. 2 shows the

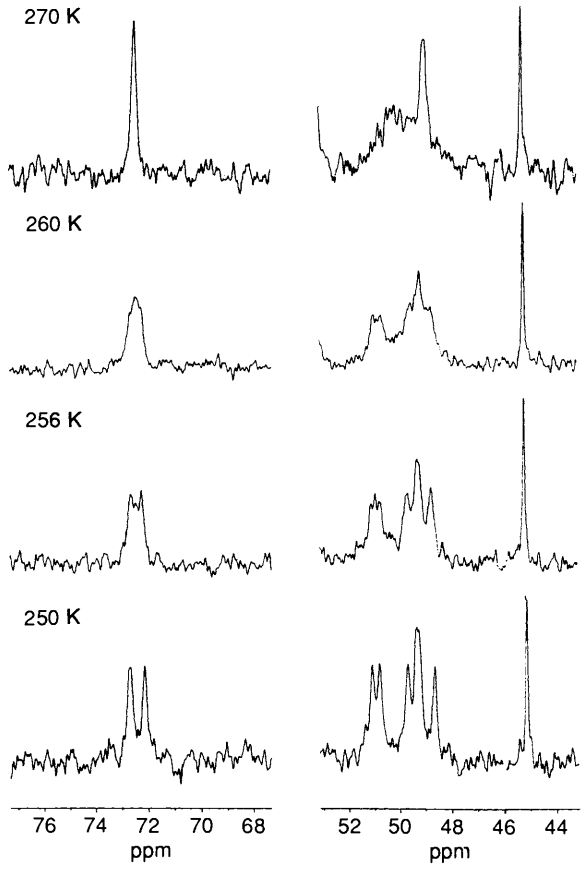

Fig. 2 VT ^{13}C NMR spectra of ligand **1** showing coalescence of the aliphatic ether carbon signals, and the aliphatic carbons next to the tosylamine residues

carbon spectra of the aliphatic carbons of the ether and amine links at temperatures between 250 and 270 K where the gradual decoalescence of the signal(s) for carbon E and also D, C and B can be observed. We were unable to assign the D, C, B spectra individually, but the E spectra gave one coalescence point. The signals at δ 120.69 (assigned as a C–H of the phenyl ring), 124.88 (assigned as a C–H of the phenyl or naphthyl rings), and 156.30 (assigned as a quaternary carbon of a naphthyl ring), are all from the triaryl section of the molecule. The two signals due to C–H carbons, δ 120.69 and 124.88 decoalesce at approximately 270 and 258 K respectively, giving activation energies of 53.1 kJ mol^{-1} and 53.1 kcal mol^{-1}.* The signal due to the naphthyl quaternary carbon at δ 156.30 decoalesces at approximately 254 K giving an activation energy of 54.0 kJ mol^{-1}. These are estimated within ±2.0 kJ mol^{-1} and the average is 53.1 kJ mol^{-1}.

These results together with the activation energy previously obtained[1] for **1** from the coalescence of CH_3 signals of the two outer tosyl groups are reviewed in Fig. 3; we have calculated the free energy of activation from several different segments of the molecule, the phenyl and naphthyl rings of the propeller, the ether segment *i* as well as the tosyl groups adjacent to segment *ii* (and whose position is dependent on movement of segment *ii*). Similar values have been obtained in each case, indicating that one process is controlling the entire observed movement of the molecule. Since it is already known that the propeller flip in other molecules occurs with similar activation energy to that found, it is clear that the controlling process is indeed the propeller flip, the slowest process present. The macrocycle

* 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

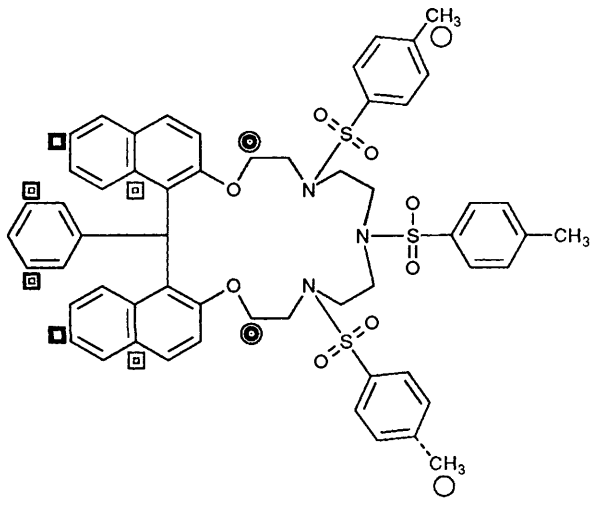

Fig. 3 Line drawing of **1** to show the sections used in determining free energies of activation from the ^{13}C NMR spectra: ⧈, $\Delta G^{\ddagger}_{270} = 12.7$; ■, $\Delta G^{\ddagger}_{258} = 12.7$; ⧈, $\Delta G^{\ddagger}_{254} = 12.9$; ◎, $\Delta G^{\ddagger}_{258} = 12.5$; ○, $\Delta G^{\ddagger}_{230-240} = 12.5 \pm 0.4$ kcal mol^{-1}

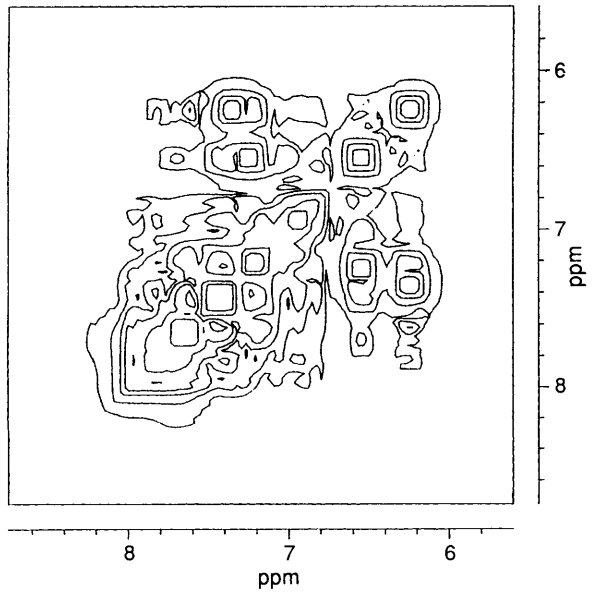

Fig. 4 Part of the NOESY spectrum (magnitude mode) of **1** showing NOE effects between certain aromatic protons

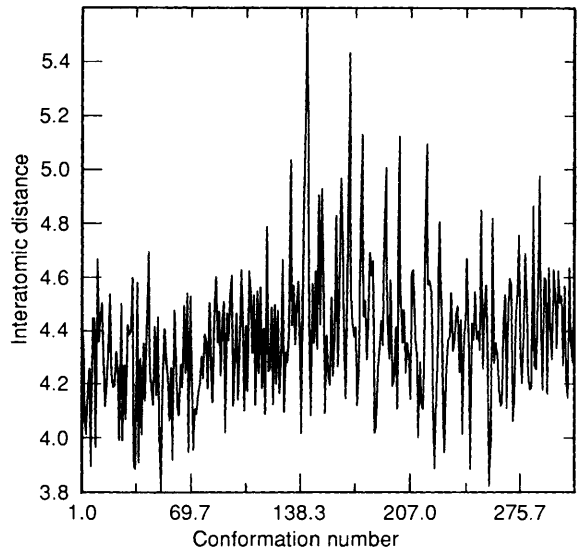

Fig. 5 Time evolution of the non-bonded distance between the two unsubstituted *peri* positions of the naphthyl rings (carbons labelled M on Fig. 1) during 200 K simulation of azacrown **1**

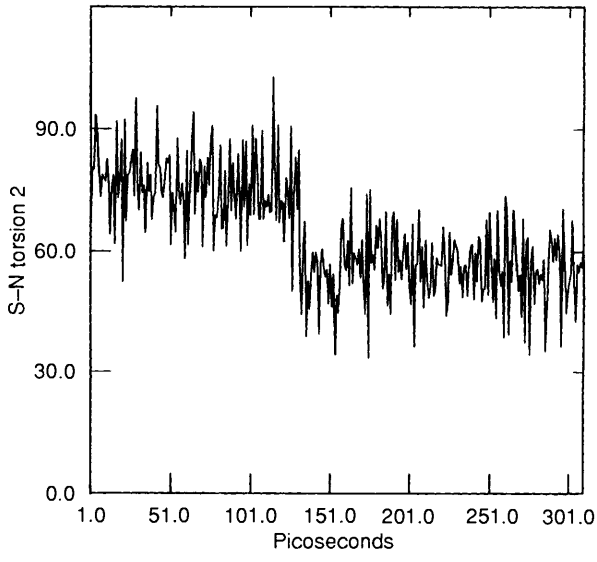

Fig. 6 Time evolution of one S–N torsion for one tosyl group showing the rapid but restricted rotation of the tosyl groups at 200 K in the simulation of **1** at 200 K

carbons are exchanging between two sites in the overall asymmetric crown, resulting in an averaged structure which is apparently symmetric about a pseudo twofold axis of symmetry.

However, even at the temperature of slow exchange reached in the ^{13}C spectra for the macrocycle, NOE data on this crown indicated the solution structure to be at variance with the observed crystal structure.[1] In the ^{1}H NMR spectrum taken at 230 K, several aromatic proton signals are clearly resolved and individually identifiable. The further upfield (doublet at δ 6.15) can be assigned as the proton on phenyl carbon I (I′) and the next (triplet at δ 6.5) as the proton on carbon H (H′). These two signals showed clear NOESY correlations. Comparison of 2D COSY and NOESY spectra taken for ^{1}H NMR at 230 K indicated clearly through-space correlation between the doublet signal at δ 6.16 and a signal at δ 7.3 (an apparent triplet, assigned as the proton on carbon N or O), while the triplet signal at δ 6.5 may be correlated with the naphthyl signal at δ 7.2, which is clearly resolved as a doublet at 210 K. A section of the NOESY spectrum is shown in Fig. 4. Analysis of the crystal structure geometry of **1** showed that the only ArH–ArH contacts less than 4 Å would be between protons attached to M and I. Thus the apparent structure of the molecule at low temperature in solution did not match that of the crystal structure. A partial reason for this may be that the molecule is still mobile, which was investigated further. Still faster processes were clearly operational, which could not be reached experimentally in this study, but which it was desirable to analyse further. Thus a MD study was performed to determine general molecular mobility on the ps–ns scale.

Coordinates from the crystal structure were used as the starting point for MD simulations of the macrocycle, **1**, following the methods of Lockhart and Tomkinson.[4] Simulations were made initially at 300 K, when the macrocycle segments were found to be very mobile, and subsequently at 200 K, which corresponds to the lowest temperatures reached in the NMR work. Simulation was carried out for 300 ps. Out of the vast amount of information available from these simulations, it was necessary to select key geometrical features which convey the structural variations observed. The propeller segment itself did

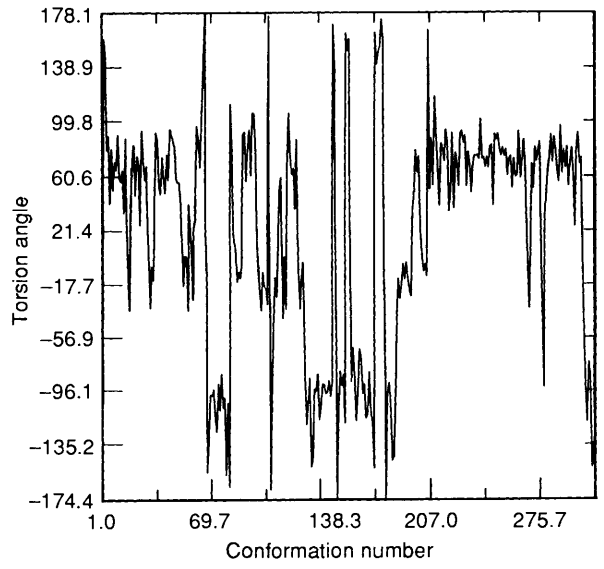

Fig. 7 *Time evolution of the most mobile Ar–S torsion of an outer tosyl group in* **1** *during simulation at 200 K*

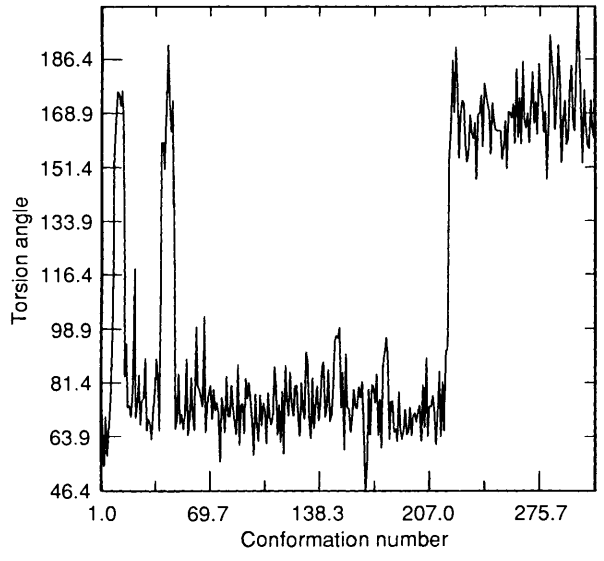

Fig. 8 Time evolution of one segment *i* torsion O(13)C(12)C(11)N(10) showing the *gauche–anti* transitions during 200 K simulation of azacrown **1**

not flip; the naphthyl and phenyl rings, although not fixed, nevertheless twisted by small amounts round their bonds to the apex carbon of the triarylmethane. This is displayed in Fig. 5 as a plot of separation of the two carbons on position 8 of each naphthyl residue. The separation changes by ± 0.5 Å on a 300 ps scale. The torsion of each tosyl against the macrocycle ring changed constantly, however, the S–N torsions changed by roughly ± 20° and the Ar–S by ± 40°, except for one outer tosyl group which showed several ± 180° rotations of its Ar–S torsion within 300 ps. Traces of one Ar–S and one S–N torsion are shown as Figs. 6 and 7. Sections in which the OCH_2CH_2N segment *i* changed *anti* to *gauche* are shown in Fig. 8 for one segment, while Fig. 9 illustrates that the segment *ii* stayed essentially *anti* at 200 K. Three possible conformers for segment *i* (*aa*, *ga* and *gg*) were observed. Of these three possibilities, the relative CHARMm

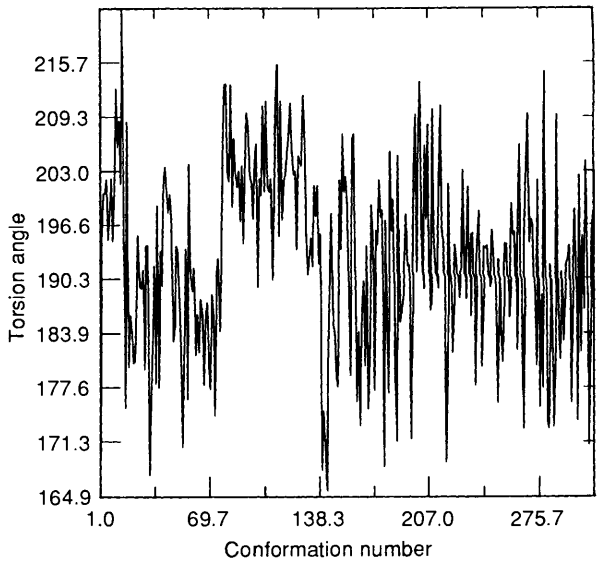

Fig. 9 Time evolution of one segment *ii* torsion N(4)C(5)C(6)N(7) showing the *anti* conformation preserved at 200 K for azacrown **1**

energies were 399.36, 389.32 and 406.14 kJ mol^{-1}, respectively. Thus segment *i* is mobile, and the tosyl groups are mobile in a very restricted region at this temperature, but the propeller and segment *ii* may definitely be said to be preorganized.

Conclusions

These results indicate that the overall symmetrisation process observed in the NMR spectra was controlled by the propeller flip. It is instructive that the torsional movements remained rapid during simulation at 200 K, and essentially on the ps timescale for segment *i*, but where segment *ii* is concerned, little torsional movement is observed. This study represents one of the fullest pictures of conformational movement yet obtained for any macrocycle, and has been possible because of the highly differential labelling of different segments of the molecule resulting from ring current shifts. The extent of preorganization in this molecule has also been specified in detail.

Acknowledgements

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