Proton-Driven Conformational Switch of a Cyclohexyl Skeleton Coupled with NH···O Hydrogen-Bond Formation

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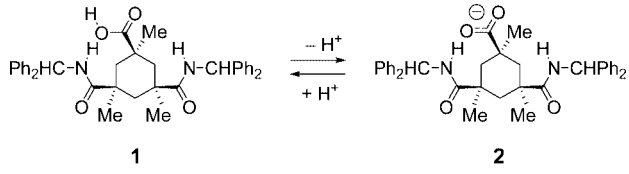
We report an unprecedented, proton-driven ring transformation from a chair to a twist-boat conformation in the doubly amide-derived Kemp's acid compounds *r*-1,*c*-3,*c*-5-$(CH_3)_3$-3,5-$(Ph_2CHNHCO)_2C_6H_6$-1-COOH (**1**) and (NMe_4)\{*r*-1,*c*-3,*c*-5-$(CH_3)_3$-3,5-$(Ph_2CHNHCO)_2C_6H_6$-1-COO^-\} (**2**) with a protonated and deprotonated carboxyl group, respectively. Each conformation was determined by X-ray analyses and ^1H NMR spectroscopy.

Introduction

cis,*cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic acid, Kemp's acid,[1] along with its *cis*,*trans* epimer and their various derivatives, has been used for molecular recognition[2–4] or metal complexation.[5–7] Previous studies have shown that the chair conformation, with the three acid groups in axial positions, predominates for Kemp's acid and that the trianion has the acid groups in the equatorial positions due to electrostatic repulsion.[1,8] Intermediate states in this chair-to-chair transition, such as half-chair, boat, and twist-boat conformations, have been isolated with various substituted cyclohexane skeletons. Systematic research has been done by Biali et al. and they reported that some of the alkyl-substituted cyclohexane compounds give a twist-boat conformation.[9,10] A similar twist-boat conformation has also been observed in an alkynylcyclohexanol upon coordination to $Co_2(CO)_6$.[11] A twist-boat conformation has also been reported for the *cis*,*trans* epimer of Kemp's acid.[12] The conformation of cyclohexane derivatives having intramolecular OH···O hydrogen bonds has been studied.[13] We report herein an unprecedented, proton-driven ring transformation from a chair to a twist conformation in the doubly amide-derived Kemp's acid compound *r*-1,*c*-3,*c*-5-$(CH_3)_3$-3,5-$(Ph_2CHNHCO)_2C_6H_6$-1-COOH (**1**), with a protonated/deprotonated carboxyl group.

We have reported hydrogen-bond formation in benzoic acid derivatives with amide groups previously.[14–18] Even though the amide NHs are located within hydrogen-bonding distance, these compounds do not form NH···O hydrogen bonds with the carboxyl group in the acid state; they form strong hydrogen bonds only in the carboxylate anion state. Thus, we were motivated to investigate the formation of hydrogen bonds between the carboxyl group and amide groups linked to a less fixed cyclic alkane skeleton, such as **1**, both in the carboxylic acid and the carboxylate anion state (Scheme 1).



Scheme 1

Results and Discussion

Compound **1** was synthesized by amidation of Kemp's triacid. The corresponding carboxylate anion, (NMe_4)\{*r*-1,*c*-3,*c*-5-$(CH_3)_3$-3,5-$(Ph_2CHNHCO)_2C_6H_6$-1-COO^-\} (**2**), was prepared from the reaction of **1** with $(NMe_4)(OAc)$.

The crystal structures of **1** and **2** are shown in Figure 1. In the carboxylic acid state, the amide NH1 is directed towards the C=O oxygen atoms of the carboxyl group and the other amide carbonyl O-atom is intermolecularly hydrogen-bonded to the -COOH proton. The two amide groups position themselves in an antiparallel fashion. In the carboxylate anion **2**, both amide NHs are involved in strong intramolecular NH···O(COO^-) hydrogen bonds. The ν(NH) stretching bands appear at 3462 and 3282 cm^{-1} for **1** and

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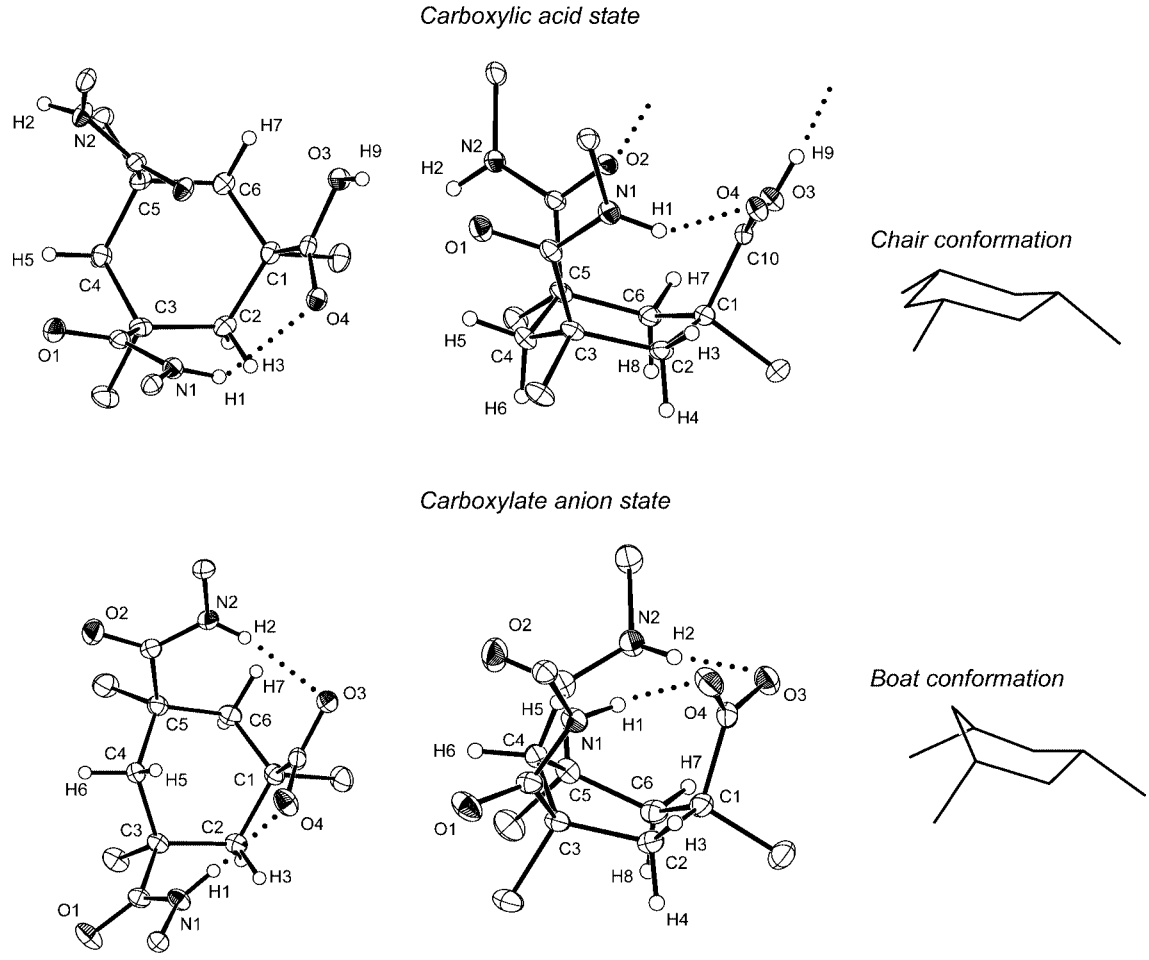

Figure 1. ORTEP drawings of (a) **1** and (b) **2**; phenyl groups have been omitted for clarity; selected bond distances [Å] for **1**: N1···O1 2.854(2), O2···O3 2.860(2); for **2**: N1···O1 2.795(2), N2···O2 2.793(2); the ring conformations are also shown

3285 cm^{-1} for **2** in the solid state. These IR results are coincident with the crystal structures. The strong hydrogen bonds in **2** force the angle between the two amide groups to be widened (C3–C11/C5–C12 from 31.6° to 99.2°). Surprisingly, the hydrogen bond interaction also induces a conformational change of the cyclohexyl ring from a chair to a twist form, which can be confirmed by the dihedral angles of the ring [the angles C1–C2–C3–C4, C2–C3–C4–C5, C3–C4–C5–C6, C4–C5–C6–C1, C5–C6–C1–C2, and C6–C1–C2–C3 are 45.8(2)°, –52.3(2)°, 53.5(2)°, –48.0(2)°, 41.4(2)°, and –40.3(3)° for **1** and –7.8(3),° 49.9(2)°, –36.4(2)°,–17.7(3)°, 56.9(2)°, and –42.2(2)° for **2**].

The formation of hydrogen bonds in **1** and **2** was investigated by ^1H NMR spectroscopy in 10 mM CD_3CN solution (Figure 2). The amide NH signal appears at δ = 7.59 ppm in the carboxylic acid state and shifts downfield to δ = 11.14 (+3.55) ppm in the anion. The temperature coefficients of the NH signals are –2.9 and –1.5 ppb K^{-1} for the acid and anion, respectively. A similar downfield shift is also observed in less-polar $CDCl_3$ solution (δ = 7.05 ppm for COOH and δ = 9.49 ppm for COO^-). The ν(NH) stretching bands for **1** appear in the region that suggests no hydrogen bonds (3449 cm^{-1}) in 2 mM chloroform solution, while the NH bands of the carboxylate anion **2** are shifted to 3282 cm^{-1}.

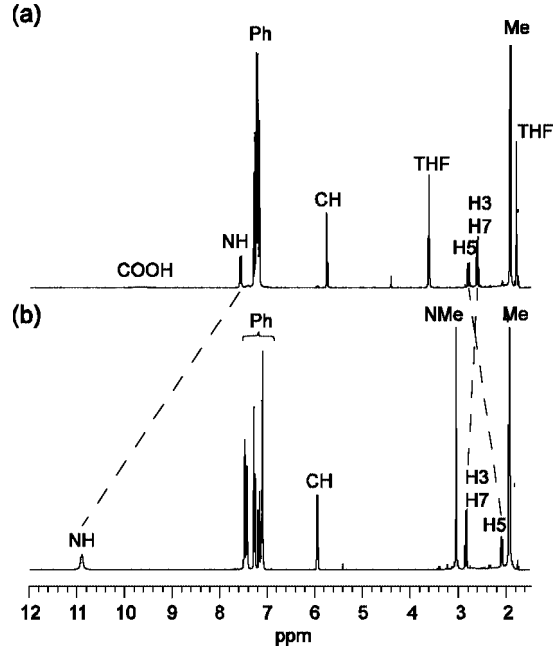

Figure 2. ^1H NMR spectra of (a) **1** and (b) **2** in 10 mM CD_3CN solution at 30 °C

Thus, only the COO^- anion forms strong intramolecular NH···O hydrogen bonds with amide NHs in solution as well.

The strong hydrogen bonds maintain the *twist* conformation of the ring in the carboxylate anion in solution. In the carboxylic acid **1**, the equatorially positioned ring protons H5 and H3 (H7) (as labeled in Figure 1), are observed at δ = 2.87 and 2.63 ppm, respectively. Both protons shift, to δ = 2.05 ppm (–0.76 ppm) for H5 and δ = 2.81 ppm (+0.24) for H3 (H7), in the carboxylate anion **2**. This is presumably because the shielding of H5 and H3 (H7) is changed by a flipping of the amide plane. The separated signals of the aromatic protons in **2** suggest that one phenyl ring of the diphenylmethyl group is positioned above the ring; this is consistent with the X-ray structural analysis. We also found an NOE correlation between the H5 ring proton and the phenyl proton at the *o*-position (H_{a1}) only in the carboxylate anion; this indicates that the cyclohexyl ring obviously exists in a twist conformation (Figure 3).

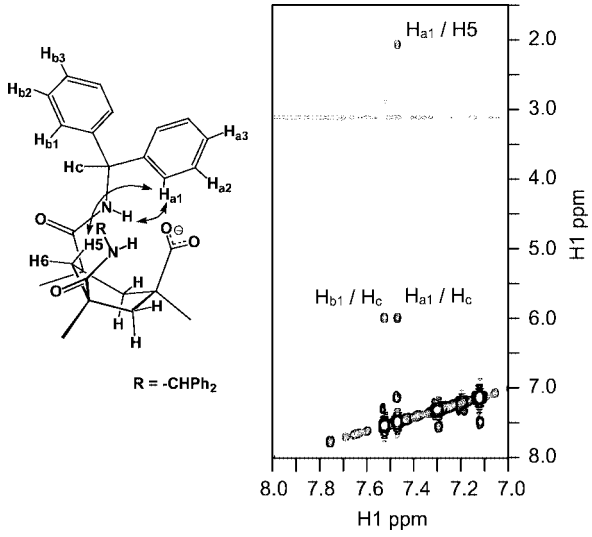

Figure 3. Selected region of the NOESY spectrum of **2** in 10 mM CD_3CN solution at 30 °C; the left side shows a schematic drawing that shows the characteristic NOE correlations originating from the twist conformation

The twist form in **2** is fairly stable in different solvent and high-temperature environments. We investigated the stability of the twist conformation in **2** by using the ^1H NMR signals of H5 and H3 (H7) as a fingerprint. The NMR result reveals that the boat form is conserved in MeOH and DMSO, both of which strongly disrupt hydrogen-bonding interactions. In addition, the twist conformation is present in DMSO solution at high temperature (90 °C). These results indicate that the energy barrier of the chair form in the carboxylate anion is relatively high due to the strong hydrogen bonds.

We performed a total energy calculation of model systems of **1** and **2** lacking phenyl groups based on the X-ray structures using the MP2/6-31G basis set to estimate the effect of the hydrogen bonding. Compared with the chair and twist forms with the amide groups, intramolecular NH···O hydrogen-bond formation in the carboxylate stabilizes the twist conformation (–6.3 kcal mol^{-1}). In contrast, when the calculation is performed with only the ring part, the twist conformation in **2** has a higher energy than the chair conformation in **1** by +4.3 kcal mol^{-1}. In general, the conformational energies of the idealized boat and half-chair states are 6.5 and 10 kcal mol^{-1} higher, respectively, when compared with the chair state (Figure S1, see Supporting Information). Thus, the NH···O^- hydrogen bonds actually contribute to the stabilization of the twist conformation of the ring.

The transition between the cyclohexyl ring conformers only depends on the protonation and deprotonation of the carboxyl group. We estimated the pK_a value of COOH group for **1** by a titrative proton-exchange reaction with $(NMe_4)(2,3,4,5,6\text{-}Cl_5C_6O)$. The p$K_a$ value of the corresponding phenol, $2,3,4,5,6\text{-}Cl_5C_6OH$, is 4.75. The ratio of **1** and **2** was calculated from the ^1H NMR chemicals shifts of the H5 and H3 (H7) ring protons in $CDCl_3$. The pK_a value of **1** was determined as 5.9. When **2** reacts with one equiv. of PhOH (pK_a in aqueous solution: 10.9) and $3\text{-}NO_2\text{-}C_6H_4OH$ (8.29) in $CDCl_3$ solution, the twist conformation persists in the carboxylate anion. On the other hand, the twist form is transformed into the chair form upon the addition of $2,6\text{-}(NO_2)_2C_6H_3OH$ (3.17) and $2,4,6\text{-}(NO_2)_3\text{-}C_6H_2OH$ (0.33) to give the carboxylic acid form of **2**.

Conclusions

In conclusion, we have demonstrated that the twist-boat conformation of an amide-derived cyclohexyl ring can be strongly stabilized by strong NH···O^- hydrogen bonds between the amide NHs and the carboxylate group. Protonation converts the twist form of the ring to the chair form both in the solid state and in solution.

Experimental Section

***r*-1,*c*-3,*c*-5-$(CH_3)_3$-3,5-$(Ph_2CHNHCO)_2C_6H_6$-1-COOH (1):** 5-(Chloroformyl)-*cis*,*cis*-1,3,5-trimethylcyclohexane-1,3-dicarboxylic anhydride was synthesized by a slightly modified literature method.[1] The precipitate was washed with dry toluene, dried under vacuum, and used without further purification. 5-(Chloroformyl)-*cis*,*cis*-1,3,5-trimethylcyclohexane-1,3-dicarboxylic anhydride (1.05 g 4.07 mmol) in 30 mL of dry THF was added dropwise to a mixture of triethylamine (1.2 mL, 8.4 mmol) and aminodiphenylmethane (1.4 mL, 8.4 mmol) in an ice-water bath under argon. The mixture was heated to 50 °C and stirred overnight. All the solvent was removed under reduced pressure and the precipitate was dissolved in CH_2Cl_2. The organic phase was washed with water, a 2% aq. HCl, solution, a sat. aq. NaCl solution, and dried with Na_2SO_4. The organic layer was evaporated and the crude products were recrystallized from THF/hexane to give colorless crystals. Yield: 1.93 g (69%). $C_{36}H_{68}N_2O_4$: calcd C 72.92, H 11.56, N 4.72; found C 71.92, H 11.63, N 4.65. ESI (MS): calcd. (found) for $\{r\text{-}1,c\text{-}3,c\text{-}5\text{-}(CH_3)_3\text{-}3,5\text{-}(Ph_2CHNHCO)_2C_6H_6\text{-}1\text{-}COO\}^{1-}$ *m*/*z* = 587.7 (587.7). ^1H NMR (400 MHz, CD_3CN, 30 °C): δ = 10.2 (br., COOH), 7.60 (d, ^3J = 6.8 Hz, 2 H, CONH), 7.19–7.34 (m, 20 H, ArH), 5.78 (d, ^3J = 6.8 Hz, CH), 2.81 (d, ^2J = 15.2 Hz, 1 H, CH), 2.63 (d, ^2J = 15.3 Hz, 2 H, 2CH), 1.24 (s, 3 H, CH_3), 1.21

(d, ^2J = 15.3 Hz, 2 H, 2CH), 1.20 (s, 6 H, $2CH_3$), 1.12 (d, ^2J = 15.2 Hz 1 H, CH) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 179.10, 176.39, 142.54, 128.06, 128.30, 127.41, 127.34, 126.56, 56.88, 41.59, 41.04, 30.78, 30.04 ppm.

(NMe$_4$){*r*-1,*c*-3,*c*-5-(CH$_3$)$_3$-3,5-(Ph$_2$CHNHCO)$_2$C$_6$H$_6$-1-COO$^-$} (2): Carboxylate anion **2** was synthesized by a ligand-exchange reaction in methanol. Carboxylic acid **1** (150 mg, 2.55 × 10^{-4} mmol) in 5 mL of MeOH was added (NMe$_4$)(OAc)·H$_2$O (33 mg, 2.55 × 10^{-4} mmol) in 2 mL of aqueous solution. The mixture was stirred for 3 h and the solvent was then removed under reduced pressure to yield a white powder. The crude product was recrystallized from hot CH_3CN to give colorless crystals. Yield: 105 mg (62%). $C_{42}H_{51}N_3O_4(H_2O)_2$: calcd. C 72.28, H 7.94, N 6.02; found C 72.46, H 7.67, N 5.99. ^{1}H NMR (400 MHz, CD_3CN, 30 °C): δ = 11.14 (d, ^3J = 9.00 Hz, 2 H, CONH), 7.55–7.12 (m, 20 H, 4 Ph), 5.98 (d, ^3J = 9.00 Hz, CH), 3.09 (s, 12 H, NMe$_4$), 2.87 (d, ^2J = 14.8 Hz, 2 H, CH), 2.04 (d, ^2J = 14.4 Hz, 1 H, CH), 1.25 (s, 6 H, 2 CH_3), 1.13 (d, ^2J = 14.4 Hz 1 H,CH), 1.12 (d, ^2J = 14.8 Hz, 2 H, CH), 1.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 181.30, 178.03, 144.13, 143.65, 128.19, 127.97, 127.32, 126.70, 126.40, 125.90, 57.30, 54.49, 43.12, 42.06, 31.42, 30.55 ppm.

X-ray Crystallography: The X-ray data for **1** were collected in 3.0° oscillation at 200 K on a Rigaku Raxis RAPID image plate diffractometer. A sweep of data was performed using ω oscillations from 130.0 to 190.0° in 5.0° steps at φ = 0.0° and χ = 45.0°, and from 0.0 to 160.0° in 5.0° steps at φ = 180.0° and χ = 45.0°. The structures were solved by direct methods and expanded using Fourier techniques with the *teXsan* [19] and SHELXL-97[20] crystallographic software packages. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically for **1**. Crystal data: $C_{42}H_{46}N_2O_4$, triclinic, $P\bar{1}$, a = 12.438(5) Å, b = 13.104(5) Å, c = 13.272(4) Å, α = 65.84(3)°, β = 77.02(3)°, γ = 77.75(3)°, V = 1905.7(12) Å^3, Z = 2, ρ_{calc} = 1.169 g cm^{-1}, 8589 independent reflections, 4425 reflections $F > 2\sigma(F)$, $R1$ = 0.059, $wR2$ = 0.150, GOF = 1.009. The X-ray data for **2** were collected in 4.0° oscillation at 200 K on a Rigaku Raxis RAPID image plate diffractometer. A sweep of data was performed using ω oscillations from 130.0 to 190.0° in 5.0° steps at φ = 0.0° and χ = 45.0°, and from 0.0 to 160.0° in 5.0° steps at φ = 180.0° and χ = 45.0°. The structures were solved by direct methods and expanded using Fourier techniques with the *teXsan* [19] and SHELXL-97[20] crystallographic software packages. Disordered carbon atoms of the tetramethylammonium cation and of one phenyl group, and the hydrogen atoms for **2**, were refined isotropically. Other non-hydrogen atoms were refined anisotropically. Crystal data: $C_{44}H_{54}N_4O_4$, monoclinic, $P2_1/n$, a = 11.9278(7) Å, b = 16.5045(11) Å, c = 20.7986(15) Å, β = 102.9740(10)°, V = 1 3989.9(5) Å^3, Z = 4, ρ_{calc} = 1.170 g cm^{-1}, 8990 independent reflections, 5739 reflections $F > 2\sigma(F)$, $R1$ = 0.063, $wR2$ = 0.202, GOF = 1.091. CCDC-257346 (for **1**) and -257347 (for **2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Calculations: Ab initio calculations for the ring part and the whole structure of **1** and **2** were performed with atom coordinates taken from the crystallographic data using the Gaussian 98 program suite.[21] Phenyl groups were omitted to save computational time. The carboxyl group for **1** was set as a carboxylate anion for comparison with the corresponding anion form **2**. Single point calculations at the HF and MP2 levels of theory were performed using the 6-31G and 6-31+G* basis sets. DFT calculations using Becke's three-parameter hybrid functional with the correlation functional of Lee, Yang, and Parr (B3LYP)[22–24] were also performed with similar basis sets.

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