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DEMONSTRATION OF A CONFORMATIONAL ISOTOPE EFFECT IN DEUTERIUM SUBSTITUTED CYCLOPENTANONES†

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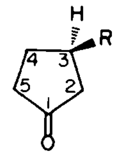
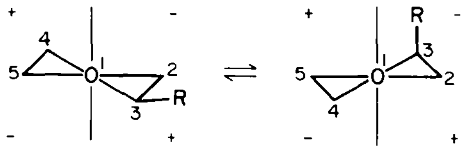
Abstract The synthesis and chiroptical properties of three chiral, deuterium-substituted cyclopentanones are reported which shed light on subtle conformational changes. Thus, the CD spectra of (3*R*)-3-deuteriocyclopentanone (**1**), (3*S*,4*S*)-3,4-dideuteriocyclopentanone (**2**) and (3*S*,4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**) are found to undergo an increase (in the absolute sense) of the rotational strength on lowering the temperature. This change is associated with a shift in the conformational equilibrium towards the twist conformation with the deuterium in the quasi-axial position. Using literature estimates for the rotational strength of the involved twist conformation, enthalpy differences of approximately −1, −4 and −6 cal/mol were calculated for the respective conformational equilibria of **1**, **2** and **3**. Empirical force field calculations were found to be in qualitative agreement with the experimental results when weaker non-bonded interactions for deuterium were used. The gas-phase spectra of **1** and **2** are reported which reveal a surprisingly well resolved vibrational fine structure. Two superimposed main progressions with a spacing of 1250 cm^{-1} extending up to the sixth overtone are identified. It is suggested that they represent progressions in the excited state carbonyl stretch mode built upon two pseudo origins.

(3*R*)-3-Deuteriocyclopentanone (**1**) was the first reported[2] ketone, which owes its chirality solely to isotopic substitution and exhibits a clearly measurable Cotton effect for the CO n-π^* transition. Originally this compound had been chosen in the anticipation that it might show a particularly large rotational strength since in general chiral cyclopentanones (e.g. 3-methylcyclopentanone) exhibit much stronger Cotton effects than other alicyclic (e.g. 3-methylcyclohexanone) or aliphatic ketones.[3] More recent work in our laboratory has shown this assumption to be oversimplified, since the subsequently synthesized 6-membered ring analog, (3*S*)-deuteriocyclohexanone,[4] showed a three times larger Cotton effect amplitude. The explanation is clear: cyclopentanone exists predominantly in an equilibrium of the two possible twist conformations,[5,6] A (R=H) and B (R=H) and in contrast to the chair conformations of cyclohexanone, the twisted ring gives rise to a large rotational strength[3b,f] which is positive for A and negative for B (as predicted by the octant rule).[7]

A bulky substituent such as a Me group, will shift the conformational equilibrium towards A(R = Me, quasi-equatorial position) and consequently lead to a large (in this example positive) observed rotational strength (associated with C-3 and C-4). In contrast, when R represents deuterium, the equilibrium will be affected only very slightly resulting in the almost complete cancellation of the chiral ring contributions (due to C atoms 3 and 4 in A *vs* B). *The observed rotational strength results then predominantly from the difference between the contributions of deuterium in the quasi-axial* (*B*) *and quasi-equatorial* (*A*) *positions* and this value turns out to be smaller compared to the equivalent difference in 3-deuteriocyclohexanone.[4] In two recent communications[8,9] we have presented experimental evidence that the temperature-dependent CD spectra of various mono-deuterium substituted cyclohexanones can be used to calculate the energy difference between the conformations with the deuterium in the equatorial and axial positions, provided that through the presence of a geminal α-dimethyl group (i.e. a "chiral probe") the rotational strengths of both chair conformations become large numbers of opposite sign. This concept is demonstrated with the octant diagram representation



1 R=D



A (+) B (-)

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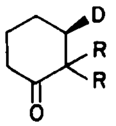
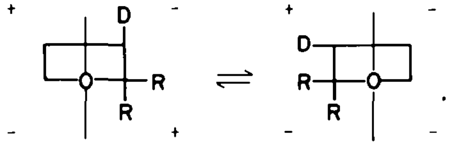
†This contribution commemorates our collaborative research in the late 1950's with R. B. Woodward which led to the development of the octant rule (Ref. 7).



4 R=CH$_3$



4A(+) **4B**(−)

of (3*R*)-2,2-dimethyl-3-deuteriocyclohexanone (**4**) whose temperature-dependent CD spectrum has been reported earlier.[8]

As pointed out above both twist conformations (**1A** or **1B**) of **1** possess large rotational strengths of opposite sign due to the ring C atoms C-3 and C-4 (which now serve as "chiral probes" similar to the gem-dimethyl group in **4**) and consequently even small temperature-induced shifts in the equilibrium position can be expected to lead to measurable changes in the observed rotational strength. Therefore, we felt encouraged to repeat the measurement of **1** at various temperatures in order to determine whether the energy difference between the conformations with the deuterium in the quasi-equatorial and quasi-axial positions can be detected through this method. In addition we report the synthesis and temperature-dependent CD spectra of (3*S*, 4*S*)-3,4-dideuteriocyclopentanone (**2**) and its perdeuterated analog (3*S*, 4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**). A quantitative comparison of the temperature dependency of the rotational strength for compounds **1**, **2** and **3** was of particular interest since they were not expected to be of equal magnitude. Such a comparison required a precise knowledge of the enantiomeric excess of these compounds. In order to verify the previously reported[2] rotational strength of **1** we have resynthesized this compound by a different synthetic route from an intermediate of known optical purity.

Synthesis

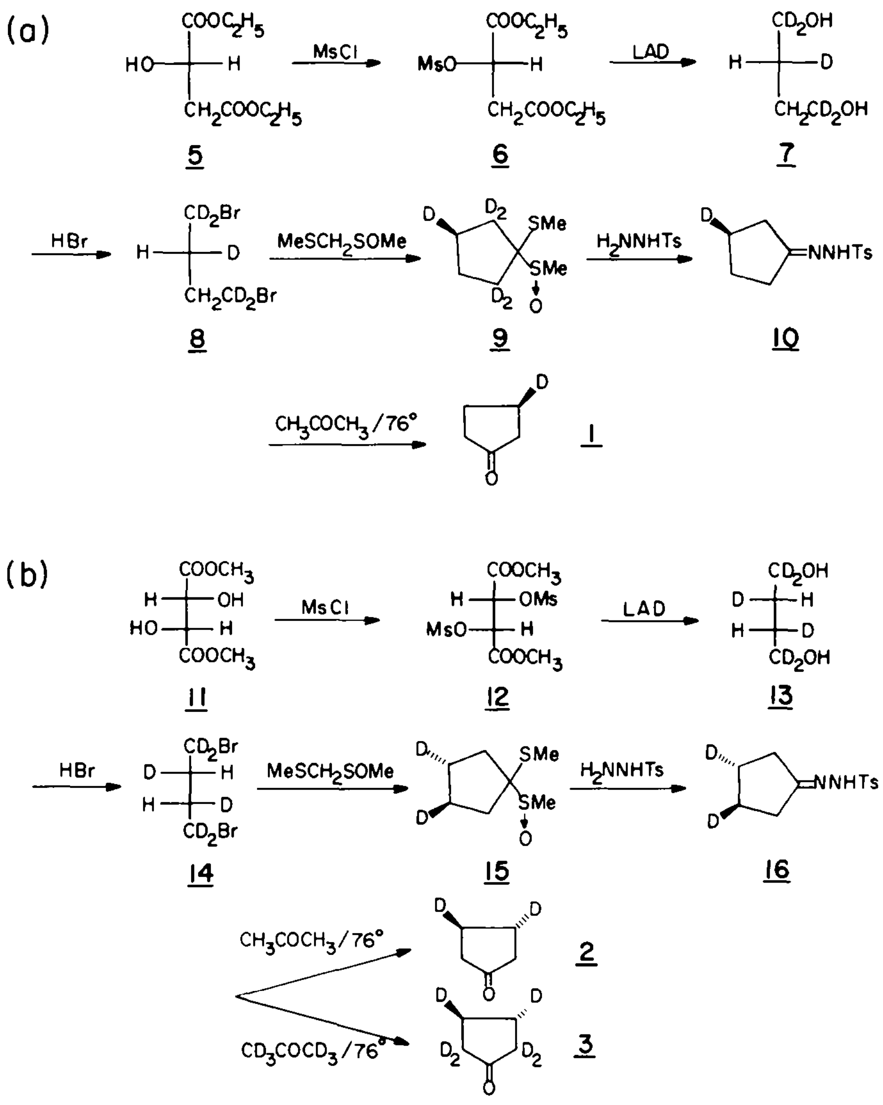
The monodeuterium substituted cyclopentanone (**1**) was synthesized according to Scheme 1a. The diethyl ester of L-malic acid (**5**) was converted via the mesylate **6** and LAD reduction to pentadeuteriobutanediol (**7**) and thence to the dibromide **8**.[10] Cyclization of **8** with methyl methylsulfonylmethylide[11] gave **9** which was transformed into the tosylhydrazone **10** and then hydrolyzed by the procedure of Maynez *et al.*[12] to **1**.

Using dimethyl-L-tartrate (**11**) as starting material, the 3,4-dideuterio analog **2** was synthesized using the same reaction steps (Scheme 1b) as outlined for the synthesis of **1**. The hexadeuterio analog **3** was obtained from **2** by perdeuteration of the CO α-positions using a D_2O-pretreated gas chromatographic column.[13] The enantiomeric excess of **1**, **2** and **3** is assumed to be equal to that of the starting material, i.e. 100%, since the LAD reduction of the mesylates **6** and **12** proceeds with nearly complete stereoselectivity and all other reaction steps in the sequence leave the chiral center(s) unaffected. It was gratifying to note that the rotational strength of **1**, as prepared by this new method, was found to be within 5% of the value reported for a sample[2] prepared by a totally different method. Compound **1** has recently[14] been synthesized also by microbiological reduction and the reported [θ] value of 62 is in close agreement with that reported in this and the previous study,[2] thereby leaving little doubt about its optical purity.

RESULTS AND DISCUSSION

The CD spectra of **1**, **2** and **3** in EPA (ether, i-pentane, ethanol 5:5:2 vv) at various temperatures together with the octant diagram representation of both twist conformations are shown in Fig. 1. In all three examples the rotational strength increases (in the absolute sense) with lowering the temperature. In order to associate these changes with a shift in the conformational equilibria of **1**, **2** and **3** as shown in Fig. 1, one has to exclude alternative possibilities like the presence of conformations other than the twist forms and/or solvent-solute interactions which also can give rise to temperature-dependent CD spectra.[15] The envelope form of cyclopentanone has been calculated[16] to be 3.22 kcal/mol higher in energy and therefore participates to the extent of less than 0.5% to the equilibrium at room temperature. Furthermore the interpretation of the microwave[5] and ^{1}H NMR[6] spectra was only consistent with the exclusive presence of the twist conformation. We also note that the main intensity changes of the CD spectra (Fig. 1) take place below *ca* 150 K; even if one assumes an energy difference as low as 1 kcal/mol between twist and envelope forms the equilibrium would already be shifted practically completely toward the twist conformations (97%) at this temperature.

In view of this evidence it appears very unlikely that the observed intensity changes are associated with a "freezing out" of the envelope conformations. The presence or absence of solvent-solute related intensity changes of the rotational strength can usually be assessed through measurements in solvents of different polarity.[15] The measurements of **1**, **2** and **3** in IPM (i-pentane, methylcyclohexane 4:1 vv), a non-polar solvent as compared to EPA, resulted in virtually identical intensity changes with temperature. However, it was observed that, while the room temperature spectra showed a well-resolved vibrational fine-structure (see spectra in i-octane in Fig. 2), the spectra at 77 K displayed no distinct vibrational structure and in addition were shifted by *ca* 10 nm to lower wavelengths. We suggest that this behavior results from a solute-solute interaction which takes place in the non-polar solvent IPM but not in EPA. Nevertheless the similarity of the temperature dependency of [R] in both solvent systems can be taken as an indication that they are not related to a solvational effect. Inspection of the octant diagram representation of the twist conformations (Fig. 1) therefore allows the qualitative conclusion that in all three examples *the twist conformation with the deuterium substituent(s) in the quasi-axial position*



Scheme 1.

increases in population on lowering the temperature. This is precisely the same conclusion obtained for the mono-deuterio substituted cyclohexanone analogs,[8,9] i.e. *the isotope of "smaller size" (deuterium) tends to preferentially occupy the position of larger strain namely the quasi-axial and axial positions in cyclopentanone and cyclohexanone respectively.*

For the quantitative determination of the energy differences one requires good estimates for the rotational strengths of both conformers.[17] Experimentally, such values are not directly available since in contrast to the cyclohexanone ring any substituent which locks the cyclopentanone ring in one or the other twist conformation will contribute by itself to the observed rotational strength. From the CD spectra of various reported cyclopentanone derivatives, Kirk[3f] has estimated the rotational strength of the twisted cyclopentanone ring to be $[R] = \pm 17$. In view of the uncertainty of such estimates we have carried out the calculations with reference values of different magnitude to give an indication of the associated range for ΔH°. In addition, the contributions from the D substituents have not been included in these estimates since they remain unknown. From the results of previous studies[19–21] in the cyclohexanone series these contributions must be assumed to be very small ($[R]$ *ca* $\leq \pm 0.3$) and their neglect will not affect significantly the calculated energy differences. The results of these calculations are given in Table 1.

Comparatively few experimental data for the quasi-axial/quasi-equatorial energy differences of substituted cyclopentanones are reported in the literature and the majority of them have been determined by circular dichroism measurements.[3f] For example an energy difference of −500 cal/mol has been reported for 3-methylcyclopentanone[3f,22] and −600 cal/mol for 3-methylcyclohexanone.[23] This comparison indicates that the energy differences between axial and equatorial Me substituents are of comparable magnitude in both ring systems which also is born out by the values found by us for D (−2 to −7 cal/mol for the mono-D substituted cyclohexanones).[8,9]

The notion that D is of "smaller size" as compared to H is most likely related to the somewhat shorter C–D

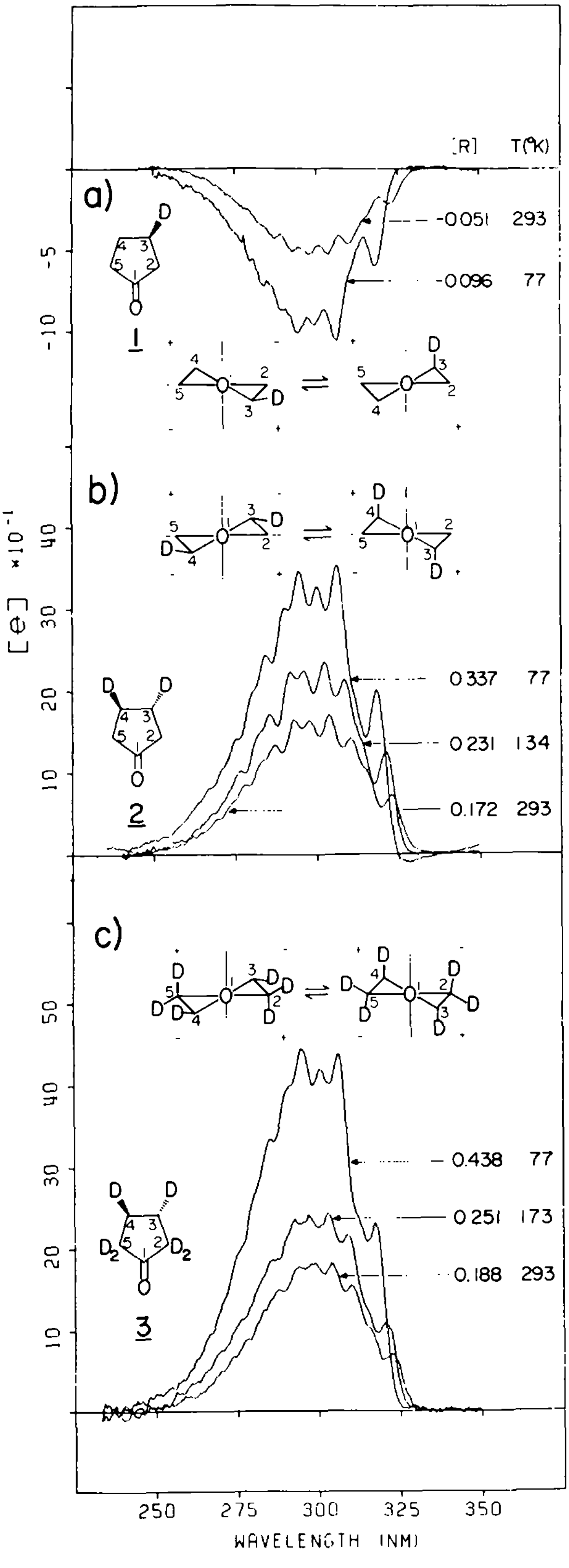


Fig. 1. Circular dichroism spectra at various temperatures and octant diagrams of both twist conformations of (a) (3*R*)-3-deuteriocyclopentanone (**1**), (b) (3*S*, 4*S*)-3,4-dideuteriocyclopentanone (**2**) and (c) (3*S*, 4*S*)-2,2,3,4,5,5-hexadeuteriocyclopentanone (**3**) in EPA (ether, i-pentane, ethanol 5:5:2 vv) as solvent. The concentrations were ca. 0.04 mol/L.

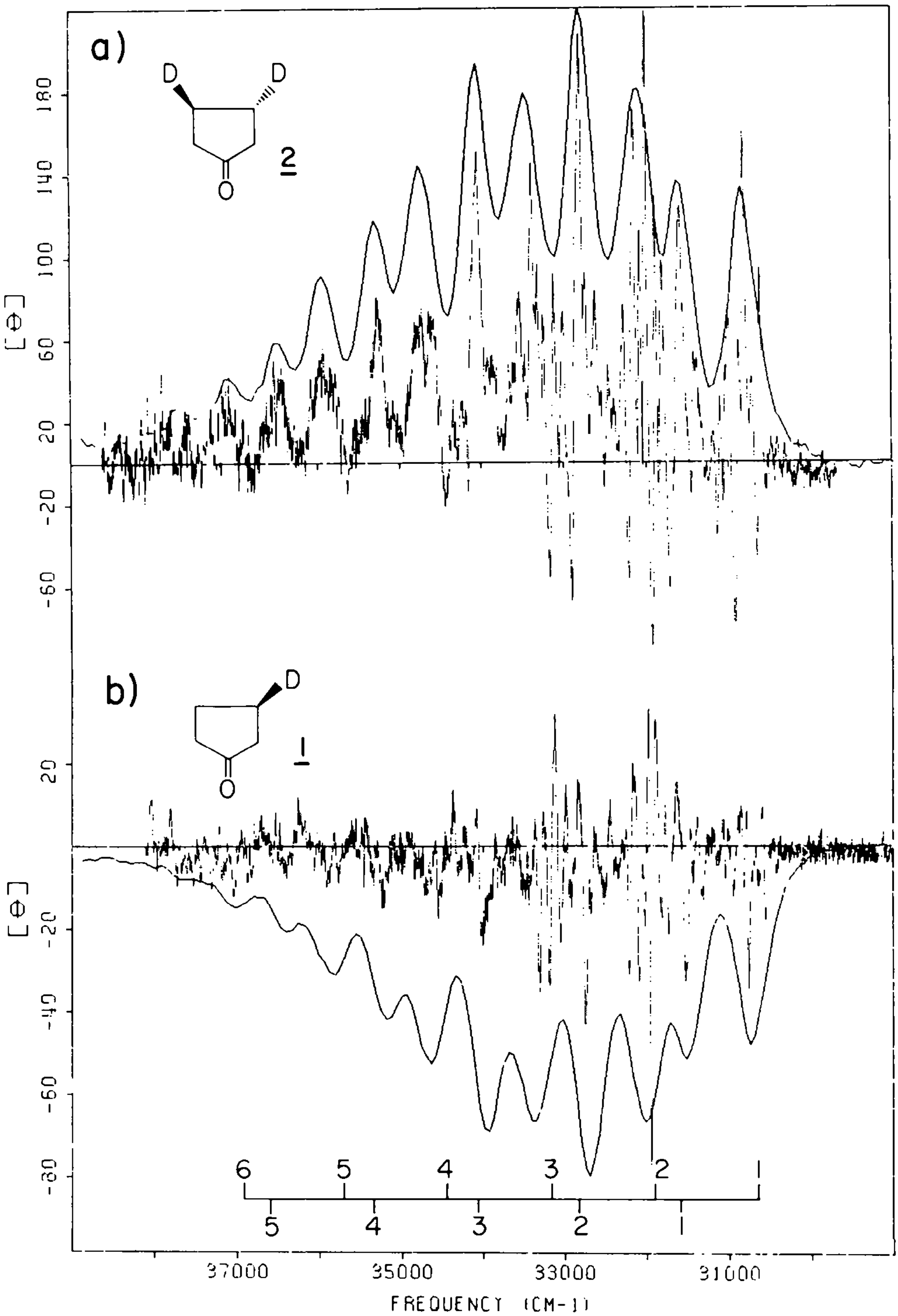


Fig. 2. Solution (in i-octane as solvent) and gas-phase spectra (at room temperature) of (a) (3S, 4S-3,4-dideuteriocyclopentanone (**2**) and (b) (3*R*)-3-deuteriocyclopentanone (**1**). The gas-phase spectra are not normalized.

bond distance (0.004 Å) and smaller vibrational amplitudes (0.01 Å) as determined through electron diffraction[24] and Raman spectroscopic[25] studies. However, from model inspections it is not immediately clear how this concept of the "size difference" between D and H can be used to explain the energy relationship of *ca* 1:4:6 as calculated for **1**, **2**, and **3** respectively (Table 1). To obtain a more quantitative idea for this steric isotope effect we have carried out empirical force field (EFF) calculations[26] on the various twist conformations with the deuterium in the quasi-equatorial and quasi-axial positions, since this method has been shown[16,27] to predict quite accurately energy differences of conformational equilibria. Although we

Table 1. Estimated energy differences for compounds **1**, **2** and **3**[1]

Estimate for $[R]^2$ of the quasi-equatorial and quasi-axial conformers	Enthalpy differences in cal/mol for the equilibria of compounds		
	1	2	3
± 19	-0.99	-3.62	-5.51
± 17	-1.11	-4.04	-6.15
± 15	-1.26	-4.58	-6.98

1) The experimental uncertainty of the $[R]^T_{obs}$ values is approximately ±0.002. The error assocated with the linear least square fit of the data in the Arrhenius diagram was approximately 10%. The overall error associated with the ΔH^{o} values is therefore estimated to be 15%.

2) [R] is the reduced rotational strength.

did not expect that these calculations would reproduce the very small energy differences found experimentally, it was hoped that trends would become discernible by exaggerating the "size" difference between D and H.

The employed force field is usually broken down into bond-deformation (i.e. bond-stretch, -bend and torsional modes) and non-bond interactions.[26] The bond-stretch potential U_{st} is most frequently represented by equation 1 where the parameters A and B represent the bond force constant and equilibrium distance respectively and R_{ij} is the internuclear distance between atoms i and j.

$$U_{st}(\text{kcal/mol}) = 144{*}0.5{*}A{*}(R_{ij} - B)^2. \qquad (1)$$

The non-bond potential U_{nb} is described by a three parameter Buckingham equation (2) where A, B and C are empirically chosen parameters.

$$U_{nb}(\text{kcal/mol}) = 144{*}[A{*}\text{EXP}(-BR_{ij}) - C/R_{ij}^{6}]. \qquad (2)$$

Reducing the magnitude of B in eqn (1) leads to a shorter equilibrium bond length and reduction of A in 2 results in a "softer" non-bond interaction i.e. to a reduction of the potential energy for a given atomic distance R_{ij}. The chosen parameters for hydrogen and deuterium and the calculated energy differences for **1**, **2** and **3** are summarized in Table 2. As indicated above we place no particular physical significance on the

Table 2. EEF calculations[a] for the twist conformations of **1**, **2** and **3**

Assumption	Energy difference (cal/mol) between the twist conformations with the deuterium in the quasi-equatorial and quasi-axial positions (see Fig. 1) 1	2	3
shortening of C-D bond length only[b]	18	38	38
reduction of non-bond interactions for D only[c]	-68	-135	-135
C-D bondlength shortening plus reduction of D non-bond interactions	-51	-99	-99

a) the calculations were carried out with the program MOLBD2 described by R.H. Boyd J. Chem. Phys., 49, 2574 (1968).

b) the parameters for the bond deformation modes were taken from ref. 16 and D.H. Wertz, and N.L. Allinger, Tetrahedron, 30, 1579 (1974). The C-D stretch mode parameter B in equation (1) was set to 1.070 vs. 1.095 for the C-H bond.

c) the non-bond parameters for equation 2 were taken from S. Fitzwater and L.S. Bartell J. Amer. Chem. Soc., 98, 5107 (1976). The chosen parameters for the D interactions were: D...D; A=11.8; D...H, A=13.25; C...D, A=121.9.

absolute magnitude of the calculated values but rather wish to emphasize the relationship between them. First it is interesting to note that the reduction of the C–D bond length alone leads to a contradiction with experiment—the conformations with the D in the quasi-equatorial positions are calculated to be of lower energy. However, the use of weaker non-bond interactions leads to a qualitative agreement with experiment, i.e. the twist conformations with the D in the quasi-axial position are found to be lower in energy. It should be noted that the calculations predict that the ratio of the energy differences of **1**, **2** and **3** is 1:2:2 (rather than the observed 1:4:6), i.e. they confirm what one might have predicted intuitively: the introduction of a second D in **2** leads to a doubling of ΔH° as compared to **1** and that the perdeuteration of the α-positions in **3** has no further effect on the energy difference. Whether this discrepancy between calculation and experiment results from deficiencies in the chosen model or whether effects other than purely steric ones contribute to the stabilization of the conformation with the D in the quasi-axial positions cannot be decided at present.

Although not directly related to the conformational problem, we wish to take the opportunity to present the remarkable gas phase CD spectra of (3*R*)-deuteriocyclopentanone (**1**) and (3*S*,4*S*)-3,4-dideuteriocyclopentanone (**2**) which are shown in Fig. 2 together with their spectra in i-octane as solvent. The solution spectra appear to be analyzable in terms of two superimposed progressions with a nearly uniform spacing of 1250 cm^{-1} and origins at 30380 and 30826 cm^{-1} respectively as schematically indicated in Fig. 2. In the gas phase spectra each of these bands is resolved into a large number of vibrational sub-levels, the resolution becoming more diffuse toward the blue end of the spectrum. The vibration involved in the two main progressions is undoubtedly the carbonyl stretch mode in the excited state (totally symmetric a_1 symmetry). From the analysis of the high resolution absorption spectrum of cyclopentanone Howard Lock and King[28] have concluded that the n $\rightarrow \pi^*$ transition gains intensity via two different vibronic pathways. One based on a hot pseudo-origin involving the ground state ring puckering mode (a_2 symmetry) and a cold pseudo-origin involving the excited state ring puckering and CO out-of-plane bend mode (b_1 symmetry). These two origins serve as starting points for the a_1 C=O stretch mode. This analysis appears to offer an explanation for the presence of two progressions in ν_{1250} as observed in the CD spectrum. That the CD spectra are considerably better resolved than the corresponding absorption spectrum (see Fig. 1 in Ref. 28) indicates that the CO stretch mode is particularly effective in inducing optical activity compared to other totally symmetric modes whose presence cause the absorption spectrum to be more diffuse. Another interesting observation is the presence of various bands of opposite sign in the gas phase spectra (Fig. 2). As Weigang[29] has pointed out, vibrational bands of opposite sign can be expected within the n $\rightarrow \pi^*$ transition depending on which higher electronic state is vibronically coupled by a particular vibration.[30] Alternatively the presence of negative bands could also result from a small frequency shift of the vibrational bands between both conformations of **1** and **2** (diagrams in Fig. 1) one having positive and the other negatively signed bands.

CONCLUSION

In conclusion, the temperature dependency of the CD spectra of **1**, **2** and **3** reveal the presence of a conformational isotope effect. The D substituent behaves as if it were of "smaller size", thereby shifting the conformational equilibrium towards the conformation where it occupies the site of larger non-bond strain i.e. the quasi-axial position in cyclopentanone. This result is consistent with that obtained previously for the deuterium substituted cyclohexanones[8,9] (where the chair conformation with the deuterium in the axial position was found to be energetically more stable) and again demonstrates the remarkable utility of chiroptical methods for quantitative studies of subtle conformational changes.

EXPERIMENTAL

Magnetic resonance spectra were determined on Varian T-60 and Bruker HXS-360 spectrometers. IR spectra were recorded on a Perkin–Elmer 700A spectrometer. Mass spectra were recorded on an AEI-MD 9 mass spectrometer and a Hewlett–Packard 7610A High Efficiency gas chromatograph interfaced through an all-glass dual-stage Watson–Bieman molecular separator to a Varian MAT-711 high resolution mass spectrometer. The CD spectra were measured with a JASCO J-40 circular dichrometer using an earlier described[31] cell for the low temperature measurements. The accessible temp range was 77–293 K, the accuracy of the temp control is estimated to be ±5 degrees. The gas-phase spectra of **1** and **2** were measured at room temp using a 10 cm cell. The instrumental slit-width for these measurements was 18 μm, corresponding to a spectral resolution of 0.07 nm (*ca* 8 cm^{-1} in the 350–250 nm wavelength region). The wavelength scale was calibrated with a soln of holmium perchlorate[32] to an accuracy of *ca* 0.2 nm (*ca* 20 cm^{-1} in the 350–250 nm wavelength region). Elemental analyses were performed by the Microanalytical Laboratory at the Department of Chemistry of Stanford University.

(2*R*)-1,1,2,4,4-*Pentadeuteriobutane*-1,4-*diol* (**7**). To a soln of **5** in 500 mL of CH_2Cl_2 was added 20 mL Et_3N (dist. over CaH_2). The mixture was cooled to 0° and 10 mL methanesulfonyl chloride was added dropwise. The mixture was stirred at 0° for 10 min and then poured into ice and HCl and extracted with ether. The ether soln was washed to neutrality with $NaHCO_3$, dried over $MgSO_4$ and evaporated to yield 26 g (yield 100%) of **6** ^{1}H NMR ($CDCl_3$, δ ppm) 1.30 (t, 3 H, J = 7), 1.33 (t, 3 H, J = 7), 3.0 (d, 2 H, J = 6), 3.26 (s, 3 H), 4.26 (q, 2 H, J = 7), 4.30 (q, 2 H, J = 7), and 5.40 (t, 1 H, J = 6); IR (neat) 1700, 1380, 1190, 980, 940 and 740 cm^{-1}. A soln of the crude **6** (26 g, 0.1 mol) in dry THF (50 mL) was added dropwise to a stirred and ice-cooled suspension of lithium aluminum deuteride-d_4 (30 g) in dry THF (100 mL). The mixture was stirred at 0° for 2 hr, followed by 10 hr at 25° and then heated under reflux for 24 hr. Standard workup and tlc analysis of the residual oil indicated one major component which was purified by column chromatography (silica gel; EtOAc/MeOH 9:1) to give 4.5 g (50%) of **7**. ^{1}H NMR ($CDCl_3$, δ ppm) 1.66 (br s), 4.0 (br s, OH); IR (neat) 3300, 2170, and 2070 cm^{-1}.

(2*R*)-1,1,2,4,4-*Pentadeuterio*-1,4-*dibrobutane* (**8**). This compound was prepared in 80% yield by using the procedure described by Goldsworthy[10] for the nondeuterated analog. The dibromo compound **8** is a colorless liquid b.p., 110°/40 mm, ^{1}H NMR ($CDCl_3$, δ ppm) 2.08 (s); IR (neat) 2950, 2170 and 970 cm^{-1}, which was used directly in the next step.

(3R)-3-Deuteriocyclopentanone p-toluenesulfonylhydrazone (**10**). To a suspension of 3.44 g potassium hydride (24% content, dispersed in mineral oil) in 50 mL dry THF at −10° under an atmosphere of N_2 was added 0.92 g (7.39 mmol) methyl methylsulfinylmethyl sulfide. After the mixture was stirred at −10° for 1 h, 2 g of **8** was added dropwise and the mixture kept stirring at −10° for 1 hr and then at room temp for 17 hr. After addition of CH_2Cl_2 (200 mL) the deposited solid was filtered off. Evaporation of the solvent left a light yellow oil, to which was added 30 mL abs EtOH and 2.27 g (9.32 mmol) p-toluenesulfonylhydrazide. The mixture was heated to reflux and 10 drops 36 N HSO_4 were added and refluxing continued for another 4 hr. After the solvent was removed under reduced pressure, the residue was washed with cold pentane and then recrystallized twice from EtOH to give 0.9 g (40%) of **10** as white needles. The mother liquor was concentrated and purified by column chromatography (silica gel; EtOAc/hexane 1:1) followed by recrystallization from EtOH to give additional 0.5 g of **10**; m.p. 186-187° (lit. m.p.[33] of the undeuterated analog 183°). ^1H NMR ($CDCl_3$, δ ppm) 2.43 (s, 3 H), 7.26 (d, 2 H, J = 8), 7.81 (d, 2 H, J = 8); mass spectrum, *m/z* (rel. intensity) 64(55), 65(90), 67(75), 68(100), 98(50), 99(50), 155(20), 157(30), 253 (M^+, < 1).

(3R)-3-Deuteriocyclopentanone (**1**). A lit[12] procedure of regeneration of cyclopentanone from its *p*-toluenesulfonylhydrazone was adapted to give **1**. A soln of **10** (0.356 g, 1.4 mmol) in 4 mL reagent grade acetone in a sealed tube was heated at 76° for 20 hr. Upon addition of 30 mL pentane, white needles precipitated and were removed by filtration. The filtrate was carefully concentrated by distillation through a 6" Vigreux column. The distillation was terminated as soon as the temp at the column head reached 37°, at which stage a residue of colorless liquid and white solid remained in the distillation flask. The residual liquid was decanted and purified by preparative gas chromatography (10% Carbowax 20 M on Chromosorb W, 150°) to give 70 mg of **1** as a colorless liquid (58%); mass spectrum, *m/z* (rel. intensity) 29(100), 31(27), 32(27), 33(13), 42(17), 55(11), 56(51), 85(M^+, 20); isotopic purity > 99%.

Dimethyl (2R, 3R)-2,3-dimesyloxysuccinate (**12**). A soln of **11** (Aldrich Chemical Company, Inc.) (5 g, 28.1 mmol) in pyridine (50 mL) was stirred at −20° and treated dropwise with methanesulfonyl chloride (6.88 g, 60 mmol). After stirring at −20° for 3 hr, a light brown milky mixture was obtained. With stirring, the entire mixture was poured into ice (100 g) and the white ppt was filtered off, washed with water, dried *in vacuo* at room temp, and recrystallized from acetone/pentane to give 6 g of white needles (75% yield): m.p. 133-134°; ^1H NMR ($CDCl_3$, δ ppm) 3.25 (s, 3 H), 3.90 (s, 3 H), 5.70 (s, 1 H): IR (Nujol) 1765 cm^{-1}; $[\alpha]_{578}$ +51.1° (*c* = 1.58, acetone). Found: C, 29.12; H, 4.14. Calc. for $C_8H_{14}O_{10}S_2$: C, 28.74; H, 4.22%).

(2S, 3S)-1,1,2,3,4,4-Hexadeuteriobutane-1,4-diol (**13**). Synthesis as described for **7**. ^1H NMR (acetone-d_6, δ ppm): 1.58 (br s), 3.9 (br s, OH); IR (neat): 3300, 2170 and 2070 cm^{-1}. (Found C, 49.75. Calc. for $C_4H_4D_6O_2$: C, 49.96%).

(2S, 3S)-1,1,2,3,4,4-Hexadeuterio-1,4-dibromobutane (**14**). Synthesis as described for **8**. ^1H NMR ($CDCl_3$, δ ppm) 2.08 (s). IR (neat) 2950, 2170 and 970 cm^{-1}. Mass spectrum, *m/z* (rel. intensity) 60.08690 (100, $C_4H_2D_5$), 61.09283 (67.49, C_4HD_6), 141.01613 (94.00, $C_4H_2D_6{}^{79}Br$), 143.01379 (93.29, $C_4H_2D_6^{81}Br$), 219.93701 (1.77, $C_4H_2D_6^{79}Br_2$), 221.93578 (4.89, $C_4H_2D_6^{79}Br^{81}Br$), 223.93667 (1.77, $C_4H_2D_6^{81}Br_2$).

(3S, 4S)-3,4-Deuteriocyclopentanone p-toluenesulfonylhydrazone (**16**). Synthesis as described for **10**. ^1H NMR: (acetone-d_6, δ ppm) 1.65 (m, 2 H), 2.15 (m, 4 H), 2.36 (s, 3 H), 7.27 (d, J = 8 Hz, 2 H), 7.49 (d, J = 8 Hz, 2 H); IR (Nujol) 3210, 1070, and 1600 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 69 (100), 71 (90), 99 (45), 124 (34), 254 (M^+, 3).

(3S, 4S)-3,4-Dideuteriocyclopentanone (**2**). Synthesis as described for **1**. ^1H NMR ($CDCl_3$, δ ppm) 2.15 (s), 2.17 (s); IR (Nujol) 1740, 2150, and 2200 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 31(100), 32(73), 56(23), 57(60), 58(2), 85(1), 86(M^+, 6), 87(M^+ + 1, 1); isotopic purity > 99%.

(3S, 4S)-2,2,3,4,5,5-Hexadeuteriocyclopentanone (**3**). Compound **3** was prepared similarly to **2** by using acetone-d_6 instead of reagent grade acetone in the regeneration from the *p*-toluenesulfonylhydrazone **16**. After purification by preparative gas chromatography, **3** was obtained as a colorless liquid (37% yield): mass spectrum, *m/z* (rel. intensity) 57(100), 87(2), 88(8), 89(24), 90(M^+, 32). The isotopic purity at the α-position is only 52% based on mass spectral analysis, which can be effectively increased to 89% by three successive passes through a D_2O pretreated gas chromatographic column[13] (10 ft 10% Carbowax 6000, with 10% KOH, pretreated with 3 × 1 mL of D_2O, oven temp 150°, t_R = 4 min). ^1H NMR ($CDCl_3$, δ ppm) 1.92 (s); IR ($CDCl_3$) 1739, 2130, and 2180 cm^{-1}; mass spectrum, *m/z* (rel. intensity) 31(100), 57(97), 59(30), 88(2), 89(7.5), 90(M^+, 39), 91(M^+ + 1, 2).

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