for the two peptides were very similar, κ = 0.016 cm/dyn for MCT-I and 0.02 cm/dyn for SCT-I, while A_0 = 362 Å^2 for the model peptide and A_0 = 322 Å^2 for the natural analogue. However, the collapse pressure of 24 dyn/cm found for the monolayer of MCT-I was much higher than the value of 14 dyn/cm observed for SCT-I.

In order to study the receptor binding properties of both peptides, ^{125}I-SCT-I was prepared by the method of Hunter and Greenwood.[7] The iodinated hormone was purified by ion-exchange chromatography on SP-Sephadex C-25. Competitive binding experiments with rat brain homogenates were carried out as described by Nakamuta et al.[8] The binding curves obtained (Figure 2) gave IC_{50} values for SCT-I of about 1 nM, in agreement with the value reported earlier,[8] and 20 nM for MCT-I, which compares to the value of 17 nM found for PCT.[8]

The biological potency of MCT-I was assessed in vivo by the method of Kumar et al.[9] The dose-response curve in Figure 3 summarizes the results. As with the binding studies, MCT-I is about 10-fold less potent than SCT-I, or approximately as active as PCT, the most potent mammalian analogue.

Although the sequence of amino acids in MCT-I differs from that in SCT-I from positions 8 to 22, the model peptide exhibited chemical and biological properties similar to those of the natural hormone. Like SCT-I, MCT-I was monomeric in aqueous solution. The model peptide showed somewhat more α-helical character than the natural one did under these conditions, and at the air–water interface, an amphiphilic environment, it formed a much more stable monolayer than did SCT-I. Moreover, MCT-I displaced a specifically bound ligand from calcitonin receptors in vitro and effected a potent hypocalcemic response in the rat bioassay. Taken together, these results provide strong evidence that the region from residues 8 to 22 of the calcitonins has a primarily structural role, providing an amphiphilic surface in the α-helical conformation for binding interactions with its receptor. Further studies are now in progress to determine what structural features might be altered to provide calcitonins with enhanced biological activity.

Acknowledgment. This research was supported by a grant from the Dow Chemical Co. Foundation (E.T.K.), United States Public Health Service Grant DA-0212 (R.J.M.), and a United States Public Health Service Predoctoral Traineeship AM-07011-09 (G.R.M.). We thank Dr. J. W. Taylor for his help in the synthesis of MCT-I and in the initial experiments on this peptide. We are grateful to Dr. R. L. Orlowski and J. Geever for the HF cleavage performed in connection with the preparation of MCT-I.

(7) Hunter, W. M.; Greenwood, F. C. *Nature* (London) **1962**, *194*, 495.
(8) Nakamuta, H.; Furukawa, S.; Koida, M.; Yajima, H.; Orlowski, R. C.; Schlueter, R. *Jpn. J. Pharmacol.* **1981**, *31*, 53.
(9) Kumar, M. A.; Slack, E.; Edwards, A.; Soliman, H. A.; Baghdiantz, A.; Foster, G. V.; MacIntyre, I. *J. Endocrinol.* **1965**, *33*, 469.

Jump Rope Enantiomerization of 1,5-Naphthalenophanes as a Probe of Polymethylene Chain Conformational Dynamics

Moon Ho Chang and Dennis A. Dougherty*

Contribution No. 6788 from the Crellin Laboratory of Chemistry California Institute of Technology Pasadena, California 91125

Received February 2, 1983

Interest in the structures, properties, and conformational dynamics of polymethylene chains remains intense because of the crucial role of such structures in biological membranes and related bilayer systems, micelles, and synthetic polymers.[1] A wide variety of techniques has been applied to probe chain dynamics, but relatively few studies involving the direct observation of an unambiguously defined conformational process involving a polymethylene chain have been reported.[1b,c] In the present work, we use dynamic NMR spectroscopy (DNMR) to study the interconversion of the enantiomers of 1,5-naphthalenophanes **1**. Such

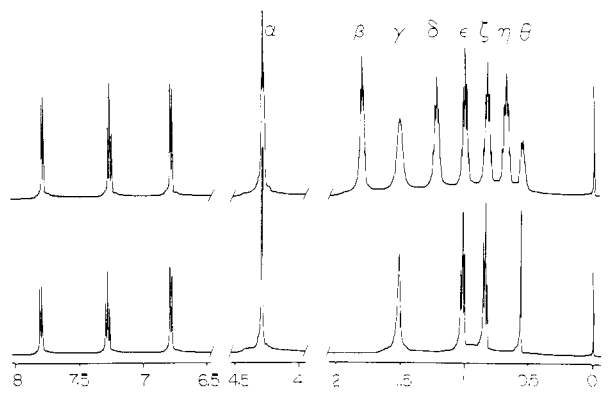
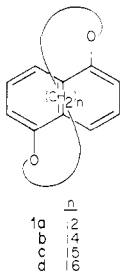


Figure 1. 500-MHz ^{1}H NMR spectra of **1c** (top) and **2** (bottom) at 49 °C in CCl_4 + 10% $CDCl_3$ (Me_4Si). Decoupling experiments on **1c** and the labeling pattern in **2** unambiguously led to the assignments shown.



	n
a	2
b	4
c	5
d	6

a process involves substantial conformational changes along the aliphatic chain of **1** and can thus provide a general method for probing substituent, solvent, and conformational effects in polymethylene chains.

Structures such as **1** are chiral, having at most C_2 symmetry. All methylene groups when n is even and all but the central methylene group when n is odd consist of a diastereotopic pair of protons. The enantiomers can interconvert by simply moving the polymethylene chain around to the other face of the naphthalene system[1c] in what has been termed[2] a "jump rope" reaction. This process also interconverts the diastereotopic protons of each methylene group, thus providing a potential DNMR probe of the enantiomerization.

Both CPK molecular models and molecular mechanics calculations[3] indicate that structures **1a–d** are essentially strain free and possess many low-energy conformations with varying numbers and locations of gauche interactions. These conformations are expected to interconvert rapidly on the NMR time scale by C–C bond rotations over relatively small barriers. We anticipated that in the enantiomerization transition state such torsions would be severely restricted, and the chain would adopt a relatively extended conformation in order to pass around the naphthalene system. If this were the case, the enantiomerization would provide a direct

(1) (a) For a recent review, see: Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491–524. (b) For studies of large ring cycloalkanes, see: Dale, J. *Top. Stereochem.* **1976**, *9*, 199–270. Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 7166–7171; 7810–7814. (c) The process studied in the present work is, of course, precisely analogous to the enantiomerization of *trans*-cycloalkenes. See, for example, Binsch, G.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 5157–5162. For studies on systems related to **1**, see: Whitesides, G. M.; Pawson, B. A.; Cope, A. C. *Ibid.* **1968**, *90*, 639–644. Brown, H. S.; Muenchausen, C. P.; Sousa, L. R. *J. Org. Chem.* **1980**, *45*, 1682–1686. Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1983**, *105*, 838–844.
(2) Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213–218.
(3) Details will be provided in the full account of this work. The program BIGSTRN (Andose, J. D.; et al. *QCPE* **1979**, *11*, 348) was used. See: Mislow, K.; Dougherty, D. A.; Hounshell, W. D. *Bull. Soc. Chim. Belg.* **1978**, *87*, 555–572.

0002-7863/83/1505-4102$01.50/0

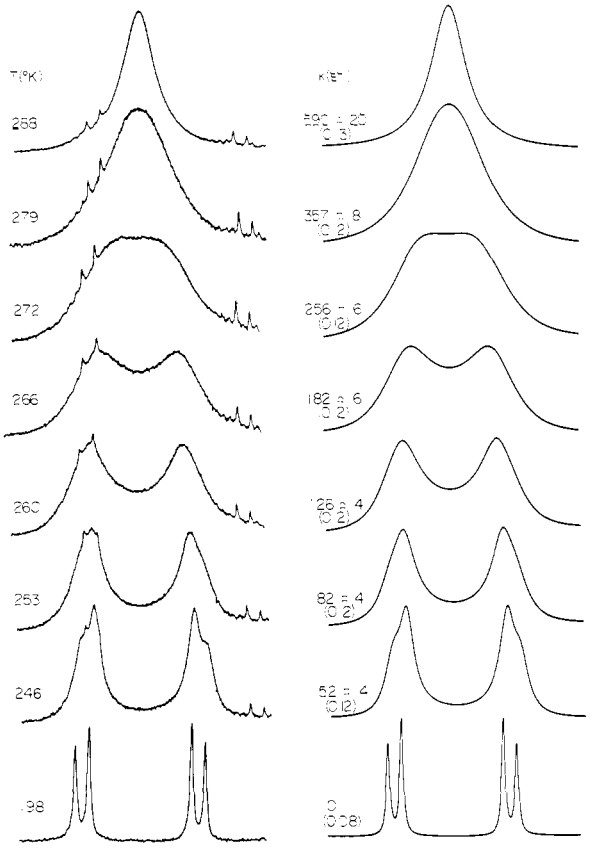
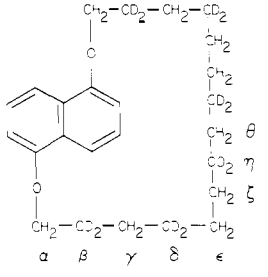


Figure 2. Variable-temperature ^{2}H-decoupled 500-MHz ^{1}H NMR spectra for the γ protons of **2** in CD_2Cl_2. Temperatures are considered accurate to ±1 K. Error limits for rate constants were determined as the maximum deviation from the value listed that still gave a tolerable fit between observed and calculated spectra. T_2 values (s) for the Θ protons (i.e., $1/(\pi \cdot \omega_{1/2})$) are listed in parentheses below the rate constants.

probe of the enthalpic and entropic cost of freezing out torsional motions along the chain.

We have thus far concentrated on the structure with $n = 15$. Figure 1 shows the 500-MHz ^{1}H NMR of **1c**[4] and of **2**. For **1c**



2

one observes eight base-line-resolved methylene signals, indicating that the jump rope reaction is rapid on the NMR time scale at ambient temperatures and that the molecule has real or time-averaged C_2 symmetry. Decoupling experiments allow the assignments shown and reveal that the middle CH_2's of the chain lie over the naphthalene ring and are substantially shielded. Preliminary studies of **1c** revealed a decoalescence of signals as the temperature was lowered, and by far the largest effect was seen with the γ protons. We therefore prepared structure **2**, which is specifically deuterated so as to isolate the α, γ, and θ protons, for quantitative studies of the DNMR effect.

Figure 2 shows the results of the DNMR study on the γ protons of **2** and simulated spectra with appropriate rates.[5] Using the seven rate constants of Figure 2, application of the Eyring equation gives $\Delta H^{\ddagger} = 7.6 \pm 0.8$ kcal/mol, $\Delta S^{\ddagger} = -20 \pm 4$ eu, and $\Delta G^{\ddagger}_{298} = 13.4 \pm 0.1$ kcal/mol, with a correlation coefficient of 0.9998. The error limits were estimated by inserting into the Eyring equation the worst possible combinations of rate and temperature data within the estimated error limits of the measurements. We believe these represent very generous error bars—the standard deviations for the original Eyring plot are ±0.05 kcal/mol and ±0.2 eu.

We are well aware of the hazards of extracting activation parameters from kinetic data obtained from line-shape analysis.[6] The difficulty arises because the line shape is determined by two factors: the rate of exchange (k) and the line width in the absence of exchange as determined by the effective T_2. We believe that the special characteristics of our system allow for an accurate determination of activation parameters. The combination of the high-field spectrometer (500 MHz) and the highly anisotropic environment provided by the naphthalene ring gives rise to a large chemical shift separation for the γ protons ($\Delta\nu = 116.7$ Hz, $J_{AB} = 13.7$ Hz). Line-shape changes, therefore, occur over a very large temperature range—visible broadening of the γ protons is apparent from 220 to 310 K. In accord with the guidelines established by Binsch and Kessler,[6] we have ignored the early and late regions of the coalescence and have considered only spectra for which the line width is at least 6 times greater than the line width under slow exchange conditions. This ensures that essentially all the broadening observed is due to exchange rather than relaxation effects. Normally, adherence to this restriction so severely limits the temperature range amenable to study that meaningful activation parameters cannot be obtained.[6] However, because of the large value of $\Delta\nu$ for **1**, we can study a quite satisfactory temperature range. Another problem frequently encountered in line-shape analysis is a variation in effective T_2 due to field inhomogeneity at lower temperatures. However, in **2** we have an ideal probe for such effects in the θ protons, which are unaffected by the jump rope reaction and thus remain a sharp singlet throughout. Any broadening due to field inhomogeneity or changes in molecular tumbling rates will be manifest in the θ protons, and the T_2 values of Figure 2 were obtained from these protons. As can be seen, only very slight variations occur. Similar conclusions were reached by monitoring solvent peaks ($CHDCl_2$).

The most striking result of the DNMR study of **2** is the *large, negative entropy of activation.* This result is consistent with the above analysis involving a conformationally mobile ground state and a freezing-out of this mobility in an extended conformation so the jump rope reaction can occur. Further studies to quantify the factors that contribute to $\Delta S^{\ddagger}$ are underway, as are studies on **1a**, **1b**, and **1d**, which exhibit similar DNMR phenomena. The synthesis of **1** and substituted derivatives is quite straightforward.[7] Thus, our findings for **2** open the way for a study of the effects of substituents and solvents on an important aspect of the conformational dynamics of polymethylene chains.

Acknowledgment. We gratefully acknowledge the partial support of this work provided by a Young Faculty Grant from the 3M Corp. and the use of the Southern California Regional NMR Facility (NSF Grant 79-16324).

Registry No. 1c, 85851-49-6; **2**, 85851-50-9.

(4) **1c** (1,17-dioxa-[17]-(1,5)-naphthalenophane): mp 68–69 °C; ^{13}C NMR ($CDCl_3$) δ 154.15, 127.44, 124.78, 114.31, 106.25, 67.33, 29.25, 28.40, 28.27, 27.62, 26.97, 24.63; MS (relative intensity), 369 (19), 368 (67), 161 (13), 160 (100), 131 (11). Anal. Calcd for $C_{25}H_{36}O_2$: C, H.

(5) The program DNMR3 (Kleier, D. A.; Binsch, G. *QCPE* **1979**, *11*, 165) was used.

(6) Binsch, G.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 411–428.

(7) (a) Dalla Cort, A.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1980**, *45*, 3923–3925. Mandolini, L.; Masci, B.; Roelens, S. *Ibid.* **1977**, *42*, 3733–3736. (b) Structure **1** with $n = 10$ was reported previously: Lüttringhaus, A.; *Justus Liebigs Ann. Chem.* **1937**, *528*, 181–210.