The conformational diastereomers of 7-substituted-(8*Z*)-8-chloro-6,7-dihydro-9-(1,2-dihydronaphthalen-4-yl)-5*H*-benzo[7]annulene derivatives, the question of atropisomerism versus ring inversion

Parviz Rashidi Ranjbar* and Hamid Roshan

School of Chemistry, University of Tehran, Tehran, Iran
E. Mail: ranjbar@khayam.ut.ac.ir

Abstract

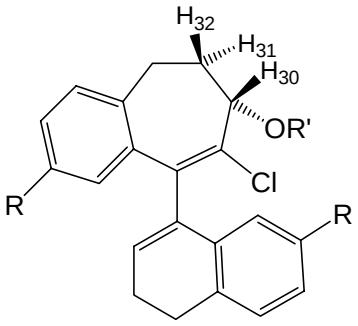
Conformational diastereomers of 7-substituted-(8*Z*)-8-chloro-6,7-dihydro-9-(1,2-dihydro-naphthalen-4-yl)-5*H*-benzo[7]annulene **1** are observed at room temperature in solution. Two conformational processes are possible in **1**, i.e. atropisomerism around the sp^2-sp^2 pivot bond and ring inversion of cycloheptadiene moiety which together provide four minima structures. The ^3J calculation by Haasnoot equation on optimized structures is accordance with the 7-substituents in pseudo equatorial (exo) position in both forms. The barrier to conformational process is determined by dynamic ^{1}H-NMR spectroscopy to be $\Delta G^{\neq}_{(365K)}$=74.5±0.5 kJ/mol. Solvent dependent populations of the two forms are studied in DMSO-d_6 and $CDCl_3$, the population ratio is not sensitive to solvent polarity.

Keywords: Conformational analysis, atropisomer, cycloheptadiene, ring inversion

Introduction

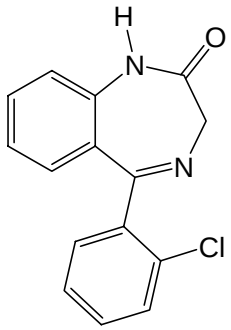
Atropisomeric compounds are of considerable interest due to their presence in a number of biologically active natural and synthetic products[1] and as directing groups in asymmetric synthesis.[2] The condition for existence of atropisomerism has been defined as one where stereoisomers can be isolated and have a half-life of at least 1000 seconds.[3] The most extensively studied class of atropisomerism is biaryls,[4] especially with respect to the substitution required for restricted rotation. In previous papers,[5,6] observation of atropisomerism in solution at room temperature were reported for mono and doubly bridged biphenyls. Reported examples of other classes of atropisomeric molecules include substituted styrenes,[7] axially chiral amides and anilides[8], n-arylimides,[9] *O*-substituted arylcarbinols of the Ar-C(OH)R_2 type,[10] 5,6-disubstituted-3,4-dihydro-1H-pyridin-2-ones,[11] *O*-substituted N-aryl-4alkyl-thiazoline-2-thiones,[12] hindered naphthyl ketones,[13] hindered naphthyl sulfoxides,[14] arylimines,[15] 9-arylfluorenes and related xanthene,[16] triptycenes and triptycene-type compounds,[3,17] and substituted porphyrines.[18]

In the benzocycloheptadienes corresponding to the title compound, the conformation of cycloheptadiene ring is twist boat with low barrier for ring inversion.[19] In this conformation the C-7 substituents can be oriented in pseudo equatorial and pseudo axial positions.[20] The seven-membered ring in 1,4-benzodiazepin-2-ones, which are closely related to benzocycloheptene, except the partial double bond character of the amid bond, has boat-like structure much like the one found in several X-ray analysis.[21] In these compounds most studies have been carried out that show a nonplanar rapidly inverting boat-like structure of the seven membered ring on the NMR time scale.[22] The barrier to ring inversion in 5-(2-chlorophenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **2** (Scheme 1) is reported to be 43.6 kJ/mol.[22d] In this paper, conformational analysis of the 7-substituted-(8Z)-8-chloro-6,7-dihydro-9-(1,2-dihydro-naphthalen-4-yl)5H-benzo[7] annulene **1** (Scheme 1) is discussed.



1

	OR'	R
1a	OMe	H
1b	OEt	H
1c	OPr	H
1d	OBu	H
1e	OMe	Me
1f	OEt	Me
1g	OPr	Me
1h	OBu	Me



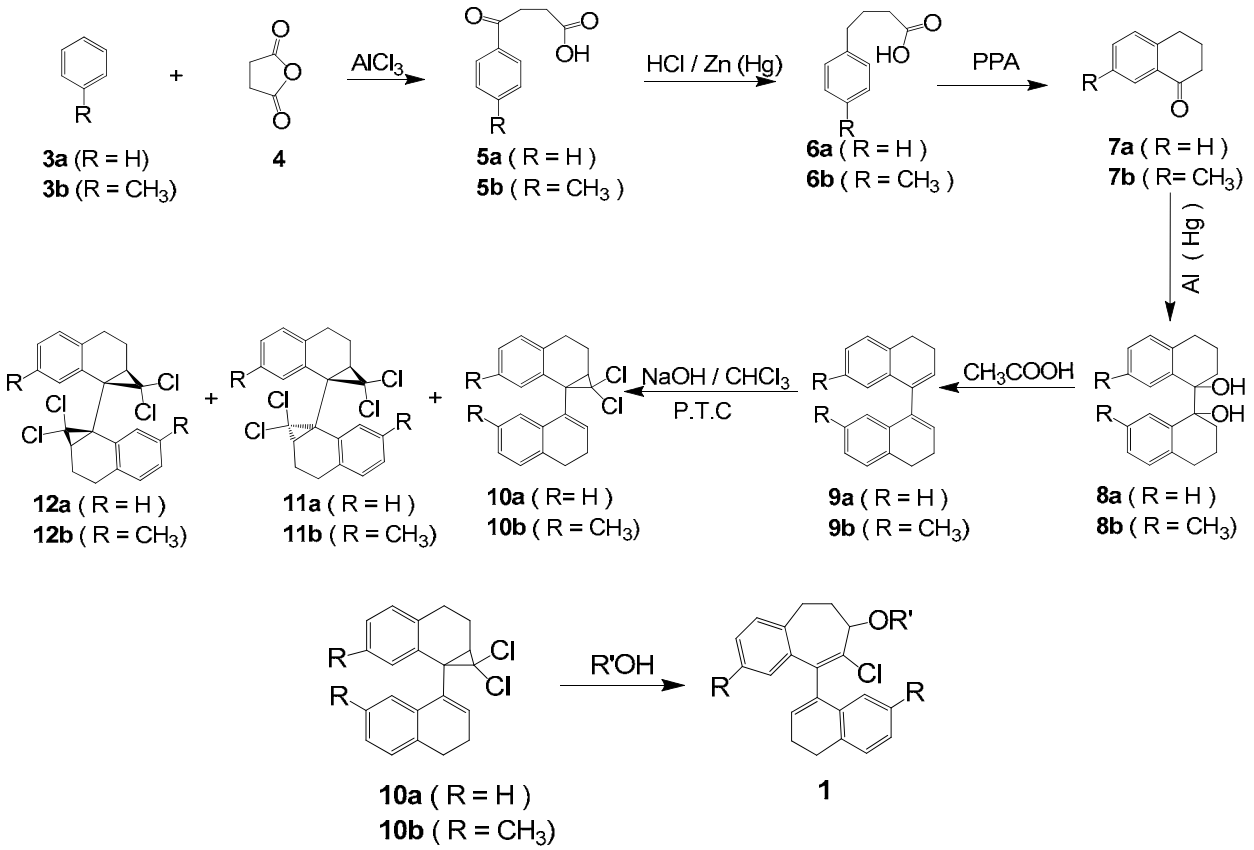
2

Scheme 1

Results and Discussion

Synthesis of **1** is shown in Scheme 2. In brief, 4-oxo-4-substituted butanoic acid **5a**, **5b** were prepared by Friedel-Crafts reaction of succinic anhydride with both benzene[23] and toluene[24]. Clemmensen reduction of the resultants were conducted as described to afford the 4-substituted butanoic acid **6a**, **6b**.[25] Cyclization of **6** by treatment of polyphosphoric acid (PPA) gave[26] 7-substituted 3,4-dihydronaphthalen-1(2H)-one **7a**, **7b** that were converted to the pinacol **8** (1,2,3,4-tetrahydro-1-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-1-yl)naphthalen-1-ol **8a** and its derivative **8b**) with amalgamated aluminum foil in alcohol-benzene according to the procedure described by Newman.[27] The pinacol **8** was isolated as a mixture of crystals. By refluxing for two hours in about seven times its weight of glacial acetic acid, **8** was converted to the substituted **9** (1,2-dihydro-4-(1,2-dihydronaphthalen-4-yl)naphthalene **9a** and its derivative **9b**). The dichlorocarbene monoadduct **10** (substituted 1,1-dichloro-1a,2,3,7b-tetrahydro-7b-(1,2-dihydronaphthalen-4-yl)-1H-cyclopropa[a]naphthalene **10a**, **10b**) was readily obtained as major product when the reaction carried out at 0˚C for approximately 12 hours. **10** was purified by

column chromatography over silicagel using hexane as eluent, then dissolved in suitable alcohol and heated at 180°C in sealed tube for at least 12 hours. After evaporation of solvent under vacuum, the solvolysis products **1** were separated and purified by alumina PLC using hexane-ether (96/4) as the mobile phase.



Scheme 2

AM1 semi-empirical quantum mechanic calculations indicate that the conformation of cycloheptadiene ring in **1** is a twist boat form and any derivative like **1e** adopts four different conformations A, B, C and D (Figure 1). Two conformational processes are possible in **1.** Single bond rotation around the sp^2-sp^2 pivot bond equilibrate atropisomers, and ring inversion of cycloheptadiene moiety which interconvert the e'-a' (exo-endo) positions. The relative energies of these forms estimated by AM1 are given in Table 1. The AM1 calculations show that B, the next local energy minimum which is an atropisomer of A, is 1.8 kJ/mol higher in energy than A (Table 1).

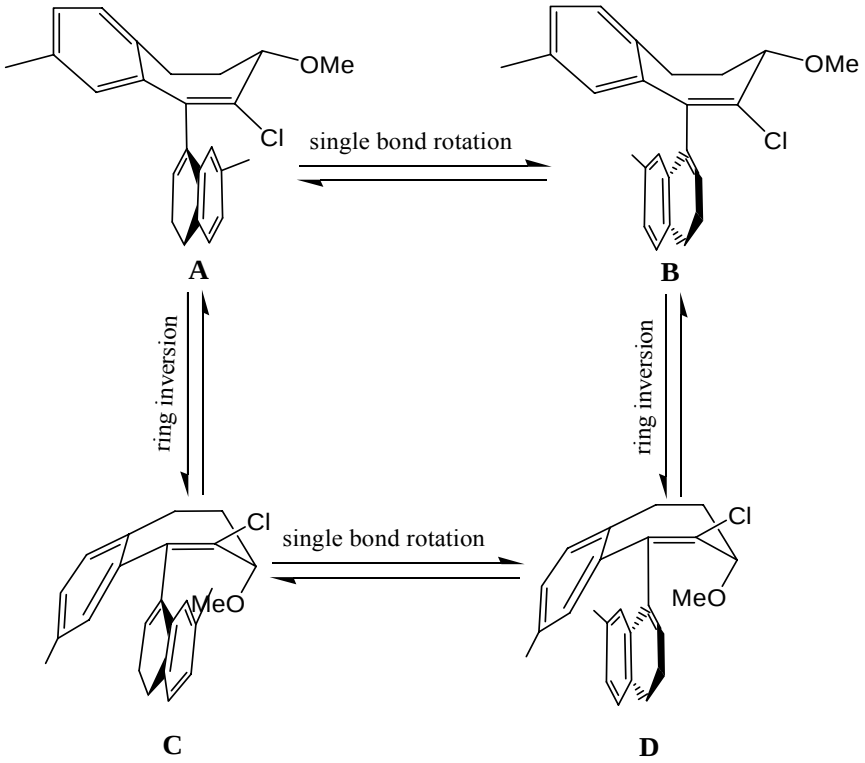


Figure 1. The ring inversion of cycloheptadiene moiety and single bond rotation around the sp^2-sp^2 bond in **1e**.

Table 1. The relative energies for conformations of **1e**, estimated by AM1

Conformation	Relative energy (kJ.mol^{-1})
A	0.0 kJ.mol^{-1}
B	1.8 kJ.mol^{-1}
C	6.7 kJ.mol^{-1}
D	4.8 kJ.mol^{-1}

The ^{1}H-NMR spectra of **1** at room temperature is consistent with the existence of two conformations (Figure 2). The allylic proton is split into doublet of doublet with adjacent protons. The $^3J_{HH}$ between allylic proton and adjacent protons, that were extracted from the ^{1}H-NMR spectra, have been presented in Table 2. Estimation of the $^3J_{HH}$ coupling constants between allylic proton and adjacent protons in A, B, C and D were carried out by Haasnoot equation[28] and presented in Table 3. Comparison of the calculated $^3J_{HH}$ with the experimental ones supports strongly the idea that A and B should be the preferred conformations in solution.

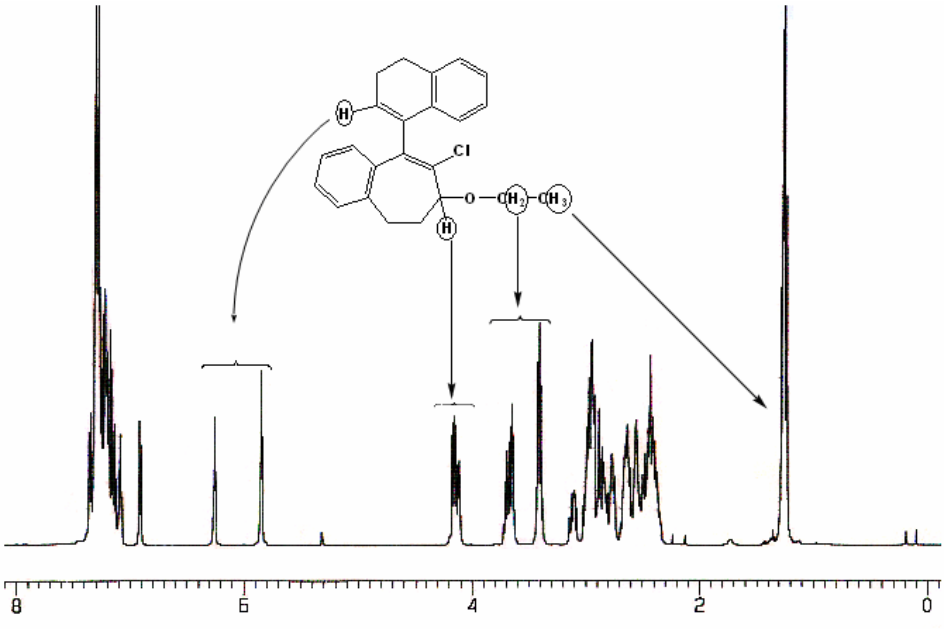


Figure 2. The 500 MHz ^{1}H-NMR of **1b** in $CDCl_3$ at room temperature.

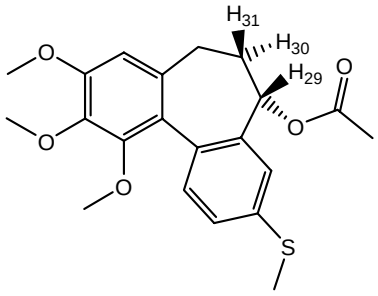
Table 2. The experimental $^{3}J_{HH}$, extracted from ^{1}H-NMR spectrum of **1e** between allylic proton and adjacent protons

Conformation	$^{3}J_{HH}$ (Hz)
Major	10.2
	6.8
Minor	10.0
	6.8

Table 3. Comparison of the calculated $^{3}J_{HH}$ between allylic proton and adjacent protons with the experimental ones for **1e**

Conformer	Dihedral angle	Calc. $^{3}J_{HH}$ (Hz)	Observed $^{3}J_{HH}$ (Hz)
A	H_{30}-C_9-C_{10}-H_{31} = 164.7	11.3	10.2
	H_{30}-C_9-C_{10}-H_{32} = 48.4	6.1	6.8
B	H_{30}-C_9-C_{10}-H_{31} = 164.7	11.3	10.0
	H_{30}-C_9-C_{10}-H_{32} = 48.3	6.1	6.8
C	H_{30}-C_9-C_{10}-H_{31} = 96.1	0.2	
	H_{30}-C_9-C_{10}-H_{32} = -20.1	9.0	
D	H_{30}-C_9-C_{10}-H_{31} = 95.5	0.2	
	H_{30}-C_9-C_{10}-H_{32} = -20.6	8.9	

The accuracy of the $^3J_{HH}$ analysis was checked by calculation of $^3J_{HH}$ in Allothiocolchicinoid derivative **13** (Figure 3).[20a] The agreement between the experimental $^3J_{HH}$ values with the calculated ones (Table 4) are excellent, supporting the above conclusion.



13

Figure 3. O-acyl substituted of Allothiocolchicinoid.

Table 4. The experimental and calculated coupling constants for Allothiocolchicinoid **13**

Configuration	Dihedral angle	Exp. $^3J_{HH}$ (Hz)	Calc. $^3J_{HH}$ (Hz)
aS, 7S	H_{29}-C_9-C_{10}-H_{30} = 166.7	10.8	11.6
	H_{29}-C_9-C_{10}-H_{31} = 49.1	7	6.0
aR, 7S	H_{29}-C_9-C_{10}-H_{30} = 87.9	~ 0	0.3
	H_{29}-C_9-C_{10}-H_{31} = -28.6	5	7.5

The differences in chemical shifts of allylic protons in the two forms of **1** with different substituents are about 0.04 to 0.06 ppm (Table 5) which supports the idea of pseudo axial position for allylic proton in both forms. The differences in the chemical shifts of vinylic protons are expected to be large, as the environments of vinylic protons in two forms are quit different.

Table 5. The chemical shift of allylic and vinylic protons and the difference in the chemical shifts for two conformational diastereomers of substituted **1** in $CDCl_3$

Compound	δ (allylic proton)		$\Delta\delta$ (allylic proton)	δ (vinylic proton)		$\Delta\delta$ (vinylic proton)
	Major form	Minor form		Major form	Minor form	
1a	4.09	4.04	0.05	5.87	6.24	0.37
1b	4.18	4.14	0.04	5.86	6.27	0.41
1c	4.16	4.12	0.04	5.87	6.25	0.38
1d	4.14	4.10	0.04	5.85	6.23	0.38
1e	4.05	3.99	0.06	5.79	6.17	0.38
1f	4.16	4.11	0.05	5.80	6.20	0.40
1g	4.15	4.10	0.05	5.81	6.19	0.38
1h	4.20	4.14	0.05	5.86	6.25	0.39

The ring inversion of cycloheptadiene moiety exchanges the allylic proton position from pseudo equatorial to pseudo axial. It is expected that the difference in the chemical shift of pseudo equatorial and pseudo axial protons to be about 0.4 to 0.7 ppm as reported previously.[5,6]

The ratio of the two forms in $CDCl_3$ and DMSO-d_6 could be derived directly from the ^{1}H-NMR spectra. The free energy between the two conformers ($\Delta G°$) is calculated by using the equilibrium constant taken as the ratio of the major/minor (Table 6). The dipole moments of the four stereomers A, B, C and D are calculated and the differences in the dipole moments are presented in Table 7; large differences are found between A/C and B/D and small differences between A/B and C/D. The small effect of the polarity of the NMR solvents on the population of the two forms supports the idea that the single bond rotation (A/B) and not axial-equatorial changes (A/C) are responsible for the observed changes in population of the two forms.

Table 6. The ratio of the two forms of substituted **1** in $CDCl_3$ and DMSO-d_6, derived directly from the ^{1}H-NMR spectra

Compound	Major		Minor		$\Delta G°$(kJ.mol^{-1}) ($CDCl_3$)	$\Delta G°$(kJ.mol^{-1}) (DMSO)
	p_{exp}(%) ($CDCl_3$)	p_{exp}(%) (DMSO)	p_{exp}(%) ($CDCl_3$)	p_{exp}(%) (DMSO)		
1a	60.36	51.03	39.64	48.97	-1.05	-0.12
1b	59.65	50.92	40.35	49.08	-0.96	-0.08
1c	54.45	50.82	45.55	49.18	-0.46	-0.08
1d	54.86	51.61	45.14	48.39	-0.50	-0.17
1e	60.52	51.90	39.48	48.10	-1.09	-0.21
1f	59.45	51.76	40.55	48.24	-0.96	-0.17
1g	61.33	50.06	38.67	49.94	-1.17	-0.004
1h	61.72	53.37	38.28	46.62	-1.21	-0.34

Table7. The differences in the dipole moments of the four stereomers A, B, C and D

Stereomers equilibrium	Difference in dipole moment (debye)
A⟺B	0.5
C⟺D	0.3
A⟺C	1.1
B⟺D	0.9

The barrier to conformational diastereomerism was studied by dynamic ^{1}H-NMR spectroscopy in **1e**. The spectra were simulated (Figure 4) by line-shape analysis performed by DNMR-3 program.[29] The free energy of activation for the observed dynamic process for the conversion of major to minor form was found $\Delta G^{\neq}_{(365K)}$= 74.5±0.5 kJ/mol.

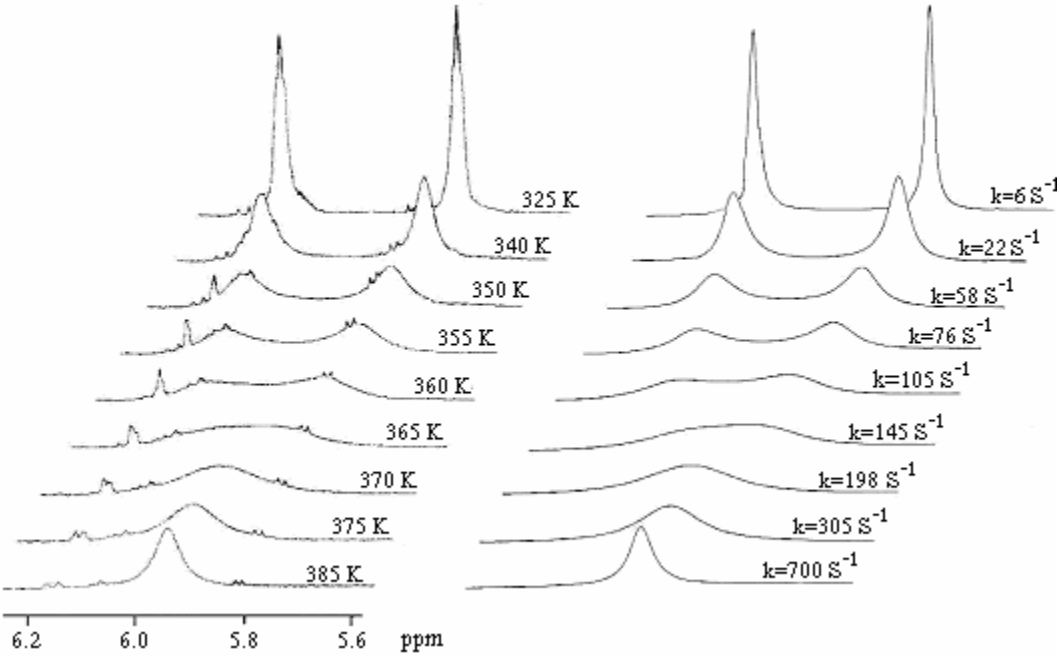


Figure 4. Experimental ^{1}H NMR (500 MHz in DMSO) signals of the vinylic region of **1e** as a function of temperature (left) with the simulations obtained using the rate constants indicated (right).

Conclusions

Two conformational diastereomers of **1** are observed at room temperature in solution with two possible conformational processes. The ^{3}J calculation by Haasnoot equation on optimized structures support that the 7- substituent's are in pseudo equatorial (exo) postion in both conformations, and atropisomerism around the sp^2-sp^2 pivot bond is suggested to be the preferred conformational process.

Experimental Section

General. All the materials were received from Merck and used without further purification. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer.

Initial estimates of the geometry of structures for semi-empirical calculations were obtained by the MMX molecular mechanics method implemented in PCMODEL software.[30] The semi-empirical AM1 Hamiltonian,[31] implemented in the MOPAC 6.0 program,[32] was used for full minimization.

The variable temperature NMR spectra of **1e** were recorded in DMSO-d_6. The exchange-broadened spectra of the allylic protons were simulated by DNMR-3 program.[29] Evaluation of

the transverse relaxation times (T_2) and free energy of activation was performed as described in the literature.[33] The errors in the computed free-energy barriers are mainly due to errors in temperature measurements and are estimated to be less than ±0.5 kJ/mol. The temperature was calibrated by using an ethylene glycol sample provided by Bruker Company.

General method for the preparation of 1a-1h

The pathways for the synthesis of **1a-1h** were described in the first paragraph of the results and discussion as depicted in Scheme 2.

(8*Z*)-8-Chloro-6,7-dihydro-9-(1,2-dihydronaphthalen-4-yl)-7-methoxy-5*H*-benzo[7]annulene (1a). Colorless oil.

Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.41 (m, 1H), 2.46 (m, 1H), 2.66 (m, 1H),2.76 (m, 2H), 2.87 (m, 1H), 2.94 (m, 2H), 3.39 (s, 3H), 4.09 (dd, J = 9.80 and 6.40 Hz, 1H), 5.87 (t, J = 4.70 Hz, 1H), 7.09-7.37 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 23.83, 28.42, 30.92, 40.90, 58.32, 80.29, 124.45, 127.07, 127.10, 127.56, 128.07, 128.22, 128.29, 128.82, 129.16, 130.78, 134.34, 134.48, 136.65, 140.68, 140.85.

Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.41 (m, 1H), 2.46 (m, 1H), 2.54 (m, 2H), 2.82 (m, 1H), 2.94 (m, 2H), 2.98 (m, 1H), 3.42 (s, 3H), 4.04 (dd, J = 10.24 and 6.62 Hz, 1H), 6.24 (t, J = 4.62, 1H), 6.94 (d, J = 7.66 Hz, 1H), 7.09-7.37 (m, 7H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 23.93, 28.51, 31.08, 40.80, 58.52, 80.32, 124.61, 126.92, 127.00, 127.46, 128.47, 129.31, 129.68, 131.32, 134.13, 134.69, 136.40, 136.86, 137.81, 137.93, 138.68, 140.78.

(8*Z*)-8-Chloro-7-ethoxy-6,7-dihydro-9-(1,2-dihydronaphthalen-4-yl)-5*H*-benzo[7]annulene (1b). Colorless oil.

Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, J=6.98 Hz, 3H), 2.43 (m, 2H), 2.66 (m, 2H), 2.78 (m, 1H), 2.90 (m, 1H), 2.98 (m, 2H), 3.43 (m, 1H), 3.67 (m, 1H), 4.18 (dd, J = 10.53 and 6.47 Hz, 1H), 5.86 (t, J = 4.4 Hz, 1H), 7.09-7.36 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 15.68, 23.85, 28.46, 30.94, 41.10, 66.25, 78.21, 124.44, 127.04,127.14, 127.57, 128.25(2C), 128.68, 129.18, 130.83, 134.62, 135.07, 136.44, 136.88, 137.69, 139.77, 140.93.

Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, J= 6.99 Hz, 3H), 2.43 (m, 2H), 2.57 (m, 2H), 2.84 (m, 1H), 2.98 (m, 2H), 3.12 (m, 1H), 3.43 (m, 1H), 3.70 (m, 1H), 4.14 (dd, J = 10.79 and 6.54 Hz, 1H), 6.27 (t, J = 4.64 Hz, 1H), 6.92 (d, J = 7.46 Hz, 1H), 7.10 (t, J=7.35 Hz, 1H), 7.17-7.36 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 15.68, 23.95, 28.55, 31.17, 41.02, 66.34, 78.23, 124.64, 126.94, 126.98, 127.47, 128.03, 128.10, 128.46, 129.78, 131.37, 134.15, 135.54, 135.85, 137.57, 138.64, 140.88.

(8*Z*)-8-Chloro-6,7-dihydro-9-(1,2-dihydronaphthalen-4-yl)-7-propoxy-5*H*-benzo[7]annulene (1c). Colorless oil.

Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, J=7.44 Hz, 3H), 1.65 (m, 2H), 2.43 (m, 2H), 2.65 (m, 2H), 2.79 (m, 1H), 2.90 (m, 1H), 2.95 (m, 2H), 3.30 (m, 1H), 3.58 (m, 1H), 4.16 (dd, J = 10.02 and 6.40 Hz, 1H), 5.87 (t, J =5.04 Hz, 1H), 7.08-7.32 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125

MHz) δ 11.2, 23.40, 23.84, 28.44, 30.99, 41.07, 72.55, 78.66, 124.48, 126.92, 126.97, 127.08, 128.18, 128.19, 128.62, 129.14, 130.69, 134.33, 135.17, 135.98, 136.45, 139.71, 140.80, 140.96.
Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, *J*=7.16 Hz, 3H), 1.65 (m, 2H), 2.43 (m, 2H), 2.56 (m, 2H), 2.85 (m, 1H), 2.95 (m, 2H), 3.10 (m, 1H), 3.30 (m, 1H), 3.63 (m, 1H), 4.12 (dd, *J* = 10.34 and 6.54 Hz, 1H), 6.25 (t, *J*=4.34 Hz, 1H), 6.94 (d, *J* = 7.42 Hz, 1H), 7.08-7.32 (m, 7H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 11.08, 23.45, 23.93, 28.53, 31.16, 41.00, 72.68, 78.66, 124.64, 127.43, 128.05, 128.07, 128.37, 127.53(2C), 129.68, 131.27, 134.17, 135.55, 136.86, 137.53, 136.85, 138.79, 140.89.

(8Z)-7-Butoxy-8-chloro-6,7-dihydro-9-(1,2-dihydronaphthalen-4-yl)-5H-benzo[7]annulene (1d). Colorless oil.
Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, *J*=7.46 Hz, 3H), 1.40 (m, 2H), 1.60 (m, 2H), 2.43 (m, 2H), 2.63 (m, 2H), 2.79 (m, 1H), 2.89 (m, 1H), 2.93 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 4.14 (dd, *J* = 10.08 and 6.43 Hz, 1H), 5.85 (t, *J* =4.65 Hz, 1H), 7.08-7.38 (m, 8H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.37, 19.77, 23.83, 28.42, 30.98, 32.25, 41.05, 70.69, 78.67, 124.47, 126.89, 127.05, 127.51, 128.16(2C), 128.63, 129.13, 130.70, 134.56, 135.20, 135.93, 136.44, 139.70, 140.80, 140.96.
Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, *J*=7.56 Hz, 3H), 1.40 (m, 2H), 1.60 (m, 2H), 2.43 (m, 2H), 2.55 (m, 2H), 2.83 (m, 1H), 2.93 (m, 2H), 3.08 (m, 1H), 3.32 (m, 1H), 3.65 (m, 1H), 4.10 (dd, *J* = 10.36 and 6.50 Hz, 1H), 6.23 (t, *J*=4.48 Hz, 1H), 6.94 (d, *J* = 7.44 Hz, 1H), 7.08-7.32 (m, 7H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.43, 19.89, 23.92, 28.52, 31.15, 32.34, 40.10, 70.48, 78.67, 124.63, 126.94(2C), 127.41, 128.05(2C), 128.34, 129.66, 131.27, 134.17, 135.54, 136.85, 137.49, 137.84, 138.78, 140.89.

(8*Z*)-8-Chloro-6,7-dihydro-9-(1,2-dihydro-6-methylnaphthalen-4-yl)-7-methoxy-2-methyl-5*H*-benzo[7]annulene (1e). Colorless oil.
Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 3H), 2.35 (s, 3H), 2.41 (m, 2H), 2.59 (m, 2H), 2.71 (m, 1H), 2.83(m, 1H), 2.89 (m, 2H), 3.38 (s, 3H), 4.05 (dd, *J* = 10.15 and 6.76 Hz, 1H), 5.79 (t, *J* = 4.65 Hz, 1H), 6.96 (s, 1H), 7.03-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 21.60, 22.02, 24.14, 28.13, 30.53, 40.97, 58.32, 80.28, 125.4, 128.14, 128.18, 129.24, 129.40, 130.88, 133.49, 134.26, 134.55, 136.39, 136.54, 136.65, 138.08, 139.94, 140.80.
Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 3H), 2.30 (s, 3H), 2.40 (m, 2H), 2.53 (m, 2H), 2.80 (m, 1H), 2.89 (m, 2H), 2.98 (m, 1H), 3.40 (s, 3H), 3.99 (dd, *J* = 9.98 and 6.82 Hz, 1H), 6.17 (t, *J* = 3.90 Hz, 1H), 6.76 (s, 1H), 7.03-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 21.69, 21.88, 24.24, 28.22, 30.60, 40.92, 58.56, 80.41, 125.59, 128.00, 129.11, 129.59, 131.09, 133.90, 134.15, 134.63, 136.19, 136.46, 136.51, 137.81, 138.05, 138.22, 138.57.

(8*Z*)-8-Chloro-7-ethoxy-6,7-dihydro-9-(1,2-dihydro-6-methylnaphthalen-4-yl)-2-methyl-5*H*-benzo[7]annulene (1f). Colorless oil.
Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.26 (t, *J*=6.98 Hz, 3H), 2.32 (s, 3H), 2.39 (s, 3H), 2.42 (m, 2H), 2.60 (m, 2H), 2.72 (m, 1H), 2.85(m, 1H), 2.92 (m, 2H), 3.43 (m, 1H), 3.64 (m, 1H), 4.16 (dd, *J* = 10.83 and 6.49 Hz, 1H), 5.80 (t, *J* = 3.98 Hz, 1H), 6.98 (s, 1H), 7.04-7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 15.64, 21.47, 21.89, 14.02, 28.01, 30.43, 41.00, 66.17, 78.12,

125.32, 128.01, 128.69, 128.98, 129.04, 129.50, 130.80, 133.42, 134.58, 134.90, 136.30, 136.53, 137.80, 138.08, 139.91, 140.92 .

Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, J=6.96 Hz, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 2.42 (m, 2H), 2.55 (m, 2H), 2.82 (m, 1H), 2.92 (m, 2H), 3.08 (m, 1H), 3.43 (m, 1H), 3.68 (m, 1H), 4.11 (dd, J = 10.85 and 6.54 Hz, 1H), 6.20 (t, J = 4.46 Hz, 1H), 6.75 (s, 1H), 7.04-7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 15.64, 21.58, 21.72, 24.12, 28.11, 30.54, 40.96, 66.24, 78.21, 125.52, 125.76, 127.84, 128.56, 129.21, 129.32, 129.51, 130.97, 133.84, 134.05, 135.34, 135.86, 136.12, 137.72, 138.30, 138.42.

(8*Z*)-8-Chloro-6,7-dihydro-9-(1,2-dihydro-6-methylnaphthalen-4-yl)-2-methyl-7-propoxy-5*H*-benzo[7]annulene (1g). Colorless oil.

Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, J=7.46 Hz, 3H), 1.66 (m, 2H), 2.32 (s, 3H), 2.39 (s, 3H), 2.41 (m. 2H), 2.60 (m, 2H), 2.72 (m, 1H), 2.85 (m, 1H), 2.89 (m, 2H), 3.31 (m, 1H), 3.55 (m, 1H), 4.15 (dd, J = 10.66 and 6.46 Hz, 1H), 5.81(dd, J = 4.76 and 3.99 Hz, 1H), 6.98 (s, 1H), 7.04-7.24 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 11.18, 21.6, 22.00, 23.53, 24.17, 28.15, 30.61, 41.09, 72.75, 78.64, 125.50, 128.15(2C), 129.15(2C), 129.46, 130.87, 133.52, 134.66, 135.14, 136.11, 13634, 136.58, 138.26, 140.03, 140.98.

Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, J=7.44 Hz, 3H), 1.66 (m, 2H), 2.25 (s, 3H), 2.31 (s, 3H), 2.41 (m. 2H), 2.54 (m, 2H), 2.82 (m, 1H), 2.89 (m, 2H),3.05 (m, 1H), 3.28 (m, 1H), 3.61 (m, 1H), 4.10 (dd, J =10.82 and 6.58 Hz, 1H), 6.19 (t, J = 4.46 Hz, 1H), 6.79 (s, 1H), 7.04-7.24 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 11.20, 21.70, 21.86, 23.60, 24.26, 28.26, 30.69, 41.13, 72.70, 78.82, 125.65, 128.00, 128.72, 129.28, 129.59, 131.03, 133.92, 134.22, 135.46, 136.46, 136.19, 136.37, 137.83, 137.94, 138.16, 138.74.

(8*Z*)-7-Butoxy-8-chloro-6,7-dihydro-9-(1,2-dihydro-6-methylnaphthalen-4-yl)-2-methyl-5*H*-benzo[7]annulene (1h). Colorless oil.

Major. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.01 (m, 3H), 1.43 (m, 2H), 1.68 (m, 2H), 2.37 (s, 3H), 2.44 (s, 3H), 2.47 (m. 2H), 2.65 (m, 2H), 2.76 (m, 1H), 2.95 (m, 2H), 3.41 (m, 1H), 3.65 (m, 1H), 4.20 (dd, J = 10.72 and 6.46 Hz, 1H), 5.86(dd, J = 5.04 and 3.82 Hz, 1H), 7.04 (s, 1H), 7.08-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.43, 19.84, 21.55, 21.96, 24.09, 28.07, 30.51, 32.28, 40.99, 70.85, 78.51, 125.40, 128.09(2C), 129.08, 129.10, 129.45, 130.96, 133.45, 134.58, 135.02, 135.97, 136.33, 138.19, 139.93, 140.94.

Minor. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.01 (m, 3H), 1.43 (m, 2H), 1.68 (m, 2H), 2.29 (s, 3H), 2.35 (s, 3H), 2.47 (m. 2H), 2.58 (m, 2H), 2.86 (m, 1H), 2.95 (m, 2H),3.12 (m, 1H), 3.37 (m, 1H), 3.70 (m, 1H), 4.14 (dd, J =10.41 and 6.53 Hz, 1H), 6.25 (t, J = 4.50 Hz, 1H), 6.84 (s, 1H), 7.08-7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 14.54, 19.87, 21.66, 21.82, 24.18, 28.18, 30.60, 32.43, 41.05, 70.85, 78.73, 125.57, 127.94, 128.06, 128.65, 129.22, 129.53, 131.07, 133.87, 134.13, 135.34, 136.17, 136.55, 137.73, 137.85, 138.00, 138.61.

Acknowledgements

Financial support by the research council of University of Tehran is highly acknowledged.

References

1. (a) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F. *J. Am. Chem. Soc*. **1873**, *95,* 1335. (b) Govindachari, T. R.; Nagarajan, K.; Parthasarathy, P. C.; Rajagopalan, T. G.; Desai, H. K.; Kartha, G.;Chen, S. L.; Nakanishi, K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1413. (c) Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973. (d) Uchida, I.; Ezaki, M.; Shigematsu, N.; Hashimoto, M. *J. Org. Chem*. **1985**, *50*, 1341. (e) Rajamoorthi, K.; Williams, D. H. *J. Org. Chem*. **1987**, *52*, 5435.
2. (a) Lipshutz, B. H.; Liu, Z. P; Kayser, F. *Tetrahedron Lett*. **1994**, *35*, 5567. (b) Nelson, T. D.; Meyers, A. I. *J. Org. Chem*. **1994,** *59,* 2577. (c) Dai, W. M.; Yeung, K. K.Y.; Liu, J. T.; Zhang, Y.; Williams, I. D. *Org. Lett.* **2002**, *4,* 1615.
3. Oki, M. *Top. Stereochem*. **1983**, *14,* 1.
4. (a) Tudor, M. D.; Becker, J. J.; White, P. S.; Gagne, M. R. *Organometallics* **2000,** *19,* 4376. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (c) Reichert, S.; Breit, B. *Org. Lett*. **2007**, *9*, 899.
5. Rashidi-Ranjbar, P.; Taghvaei-Ganjali, S.; Wang, S. L.; Liao, F. L.; Heydari, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1255.
6. Rashidi-Ranjbar, P.; Kianmehr, E.; Wang, S. L.; Liao, F. L. *J. Chem. Soc., Perkin Trans. 2* **2002**, 545.
7. Anderson, J. E.; Barkel, D. J. D.; Cooksey, C. J. *Tetrahedron Lett*. **1983**, *24*, 1077.
8. (a) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett*. **2000**, *41*, 3279. (b) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem*. **2000**, 65, 7033. (c) Clayden, J.; Lai, L. W. *Tetrahedron Lett*. **2001**, *42,* 3163. (d) Ates, A.; Curran, D. P. *J. Am. Chem. Soc*. **2001**, *123*, 5130. (e) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc*. **2002**, *124*, 5266. (f) Honda, A.; Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Chirality* **2003**, *15*, 615. (g) Chan, V.; Kim, J. G.; Jimeno, C.; Carrol, P. J.; Walsh, P. J. *Org. Lett*. **2004**, *6*, 2051. (h) Dai, W. M.; Zhang, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 525. (i) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc*. **2005**, *127*, 3676. (j) Brandes, S.; Bella, M.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 1147.
9. (a) Curran, D. P.; Qi, H.; Greib, S. J.; DeMello, N. C . *J. Am. Chem. Soc*. **1994**, *116*, 3131. (b) Kitagava, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T. *J. Org. Chem*. **1998**, *63*, 2634. (c) Chen, Y.; Smith, M. D.; Shimzu, K. D. *Tetrahedron Lett*. **2001**, *42*, 7185.
10. (a) Lomas, J. S.; Dubois, J. E. *J. Org. Chem*. **1976**, *41*, 3033. (b) Lomas, J. S.; Luong, P. K.; Dubois, J. E. *J. Org. Chem*. **1977**, *42*, 3394. (c) Lomas, J. S.; Anderson, J. E. *J. Org. Chem*. **1995**, *60*, 3246. (d) Lomas, J. S.; Vissermann, J. *J. Chem. Soc. Perkin Trans. 2* **1998**, 1777. (e) Coluccini, C.; Lunazzi, L. ; Mazzanti, A. *J. Org. Chem*. **2005**, *70*, 5098.
11. (a) Jabin, I.; Monnier-Benoit, N.; Gac, S. L.; Netchitailo, P. *Tetrahedron Lett*. **2003**, *44*, 611. (b) Gac, S. L.; Monnier-Benoit, N.; Metoul, L. D.; Petit, S.; Jabin, I. *Tetrahedron: Asymmetry* **2004**, *15*, 139.

12. (a) Bouchekara, M.; Djafri, A.; Vanthuyne, N.; Roussel, C. *Arkivoc* **2002** *(x)* 72. (b) Vanthuyne, N.; Andreoli, F.; Fernandez, S.; Roman, M.; Roussel, C. *Lett. Org. Chem*. **2005**, *2*, 433. (c) Roussel, C.; Vanthuyne, N.; Bouchekara, M.; Djafri, A.; Elguero, J.; Alkorta, I. *J. Org. Chem.* **2008**, *73*, 403.
13. Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521.
14. (a) Casarini, D.; Foresti, E.; Gasparrini, F.; Lunanzzi, L.; Macciantelli, D.; Misti, D.; Villani, C. *J. Org. Chem*. **1993**, *58*, 5674. (b) Baker, R. W.; Kyasoor, R. V.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 2* **1998**, 133.
15. (a) Boyd, D. R.; Al-Showiman, S.; Jennings W. B. *J. Org. Chem*. **1978**, *43*, 3335. (b) Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1363.
16. Ford, W. T.; Thompson, T. B.; Snoble, K. A. J.; Timko, J. M. *J. Am. Chem. Soc*. **1975**, 97, 95.
17. (a) Oki, M. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 87. (b) Oki, M. *Acc. Chem. Res*. **1990**, *23*, 351.
18. (a) Dirks, J. W.; Underwood, G.; Matheson, J. C.; Gust, D. *J. Org. Chem*. **1979**, *44*, 2551. (b) Crossley, M. J.; Field, L. D.; Forster, A. J.; Harding, M. M.; Sternhell, S. *J. Am. Chem. Soc*. **1987**, *109*, 341. (c) Konishi, K.; Miyazaki, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc*. **1990**, *112*, 5639. (d) Collman, J. P.; Garner, J. M.; Hembre, R. T.; Ha, Y. *J. Am. Chem. Soc.* **1992,** *114,* 1292. (e) Ogoshi, H.; Mizutani, T. *Acc. Chem. Res*. **1998**, *31*, 81. (f) Arai, T.; Tsukuni, A.; Kawazu, K.; Aoi, H.; Hamada, T.; Nishino, N. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1381. (g) Zhang, X. X.; Lippard, S. J. *J. Org. Chem*. **2000**, *65*, 5298. (h) Plieger, P. G.; Burrell, A. K.; Jameson, G. B.; Officer, D. L. *Dalton Trans*. **2004**, 319.
19. McCague, R.; Kuroda, R.; Leclercq, G.; Stoessel, S. *J. Med. Chem*. **1986**, *29*, 2053.
20. (a) Shi, Q.; Chen, K.; Chen, X.; Brossi, A.; Verdier-Pinard, P.; Hamel, E.; McPhail, A. T.; Tropsha, A.; Lee, K. H. *J. Org. Chem*. **1998**, *63*, 4018. (b) Vorogushin, A.V.; Wullf, W. D.; Hansen, H. J. *J. Org. Chem*. **2003**, *68*, 9618.
21. (*a*) Camerman, A.; Camerman, N. *J. Am. Chem. Soc*. **1972**, *94*, 268. (b) Sternbach, L. H.; Sancilio, F. D.; Blount, J. F. *J. Med. Chem*. **1974**, *17*, 374. (c) Bandoli, G.; Clemente, D. A. *J. Chem. Soc., Perkins Trans. 2* **1976**, 413. (d) Gilli, G.; Bertolasi, V.; Sacerdoti, M.; Borea, P. A. *Acta Crystallogr*. **1977**, *B33*, 2664. (e) Galdecki, Z.; Glowka, M. L. *Acta Crystallogr*. **1980**, *B36*, 3044. (f) Chananort, P.; Hamor, T. H.; Martin, I. L. *Acta Crystallogr*. **1981**, *B37*, 1371.
22. (a) Linscheid, P.; Lehn, J. M. *Bull. Soc. Chim. Fr*. **1967**, *3*, 992. (b) Bley, W.; Nuhn, P.; Benndorf, G. *Arch. Pharm*. **1968**, *301*, 494. (c) Sadee, W. *Arch. Pharm., (Weinheim)* **1969**, *302*, 49. (d) Sarrazin, M.; Bourdeaux-Pontier, M.; Briand, C.; Vincent, E. J. *Org. Magn. Reson*. **1975**, *7*, 89. (e) Raban, M.; Carlson, E. H.; Szmuszkovicz, J.; Slomp, G.; Chidester, C. G.; Duchamp, D. J. *Tetrahedron Lett*. **1975**, *16*, 139. (f) Romeo, G.; Aversa, M. C.; Gianetto, P.; Vigorits, M. G.; Ficarra, P. *Org. Magn. Reson*. **1979**, *12*, 593. (g) Haran, R.; Tuchagnes, J. P. *J. Heterocycl. Chem*. **1980**, *17*, 1483.

23. Haworth, R. D. *J. Chem. Soc*. **1932**, 1125.
24. Fieser, L. F.; Dunn, J. T. *J. Am. Chem. Soc*. **1936**, *58*, 572.
25. Martine, E. L. *J. Am. Chem. Soc*. **1936**, *58*, 1438.
26. Eisenbraun, E.J.; Hinman, C.W.; Springer, J. M.; Burnham, J. W.; Chou, T. S.; Flanagan, P. W. K.; Hamming, M. C. *J. Org. Chem*. **1971**, *36*, 2480.
27. Newman, M. S. *J. Am. Chem. Soc*. **1940**, *62*, 1683.
28. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
29. Binsch, G.; Klier, D. A. *J. Magn. Reson*. **1970**, *3*, 146.
30. Serena Software, PO Box 3076, Bloomington, IN.
31. Deware, M. J. S.; Zeobish, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc*. **1985**, *107*, 3902.
32. Stewart, J. J. P. *QCPE 581*, Department of Chemistry, Indiana University, Bloomington, IN.
33. Sandstrom, J. *Dynamic NMR Spectroscopy*, Academic Press: London, 1982, pp 88 and 96.