Supporting Information: Is Ring Breaking Feasible in Relative Binding Free Energy Calculations?

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Abstract

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This provides an overview of the Supporting Information supplementary files for the associated paper, and details of testing the real bond length changes.

1 Supporting information about λ spacing

In the absolute calculations, λ_{chg} = [0.0 0.25 0.5 0.75 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0], λ_{bd} = [0.0 0.05 0.10 0.15 0.21 0.26 0.32 0.37 0.42 0.47 0.53 0.58 0.63 0.68 0.74 0.79 0.84 0.89 0.95 1.0] and λ_{LJ} = [0.0 0.00 0.0 0.00 0.0 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.65 0.7 0.75 0.8 0.85 0.9 0.95 1.0]. In GROMACS, a thermodynamic state is specified by a corresponding vector in λ space – in our case, the values of each of these three λ values. Here, in our relative calculations, partial charges are first turned off and then LJ interactions are turned off after the charge modification is complete; strain is added throughout this process. In the absolute case, state 0 corresponds to the molecule in water with no strain, while state 1 corresponds to the molecule "bound" (that is, in the gas phase with internal strain induced by the special bond).

For the relative calculations we found that the free energy difference between λ_3 and λ_4 is large. So four additional λ values were added, resulting in λ_{chg}= [0.0 0.25 0.5 0.75 0.80 0.85 0.90 0.95 1.0 1.00 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0] , λ_{bd}= [0.0 0.00 0.0 0.00 0.0 0.0 0.0 0.0 0.0 0.0 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.65 0.7 0.75 0.8 0.85 0.9 0.95 1.0], and λ_{LJ} = [0.0 0.00 0.0 0.00 0.0 0.0 0.0 0.0 0.0 0.0 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.65 0.7 0.75 0.8 0.85 0.9 0.95 1.0].

2 Supporting Figures

3 Supporting Tables

4 Files

Additional supporting files in the form of topology and coordinate files as well as a README file are available online via ACS. Additionally, trajectory files for the real protein-ligand systems

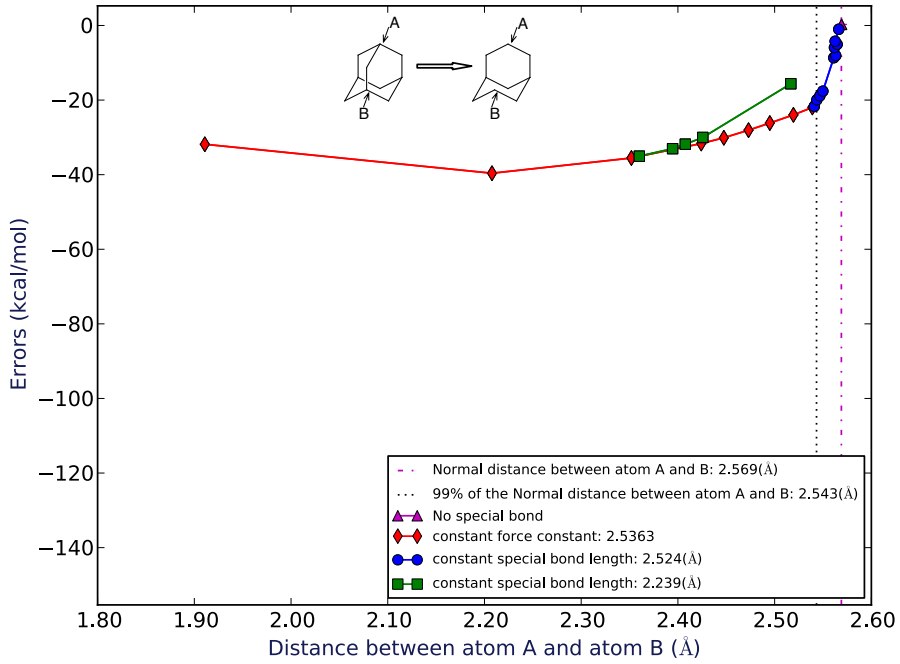

Figure S1: Errors for mutating adamantane to bicyclo[3.3.1]nonane as a function of the average distance between the shared atoms observed in the simulations. This error is for the system of adamantane-bicyclononane without NDE. The ”original” distance is the distance between atom A and atom B in the relative free energy calculation from adamantane to bicyclo[3.3.1]nonane in vacuum without any special bond restrains. Spots in different colors represent different force constants/bond length groups of the special bond.

examined are available via the web at www.escholarship.org/uc/item/27d9s5j9.

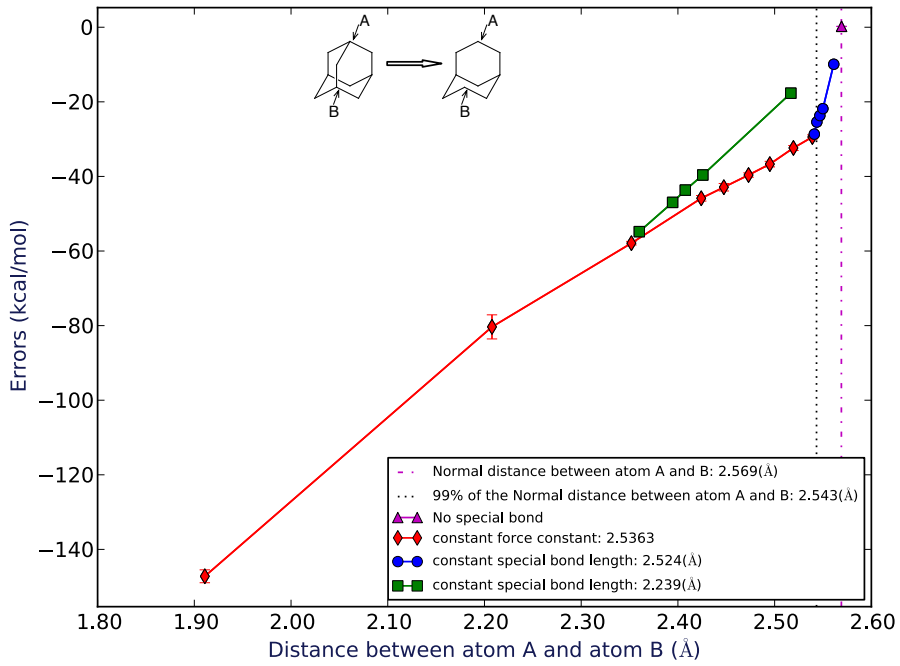

Figure S2: Errors for mutating adamantane to bicyclo[3.3.1]nonane as a function of the average distance between the shared atoms observed in the simulations. This error is for the system of adamantane-bicyclononane with NDE. The ”original” distance is the distance between atom A and atom B in the relative free energy calculation from adamantane to bicyclo[3.3.1]nonane in vacuum without any special bond restrains. Spots in different colors represent different force constants/bond length groups of the special bond.

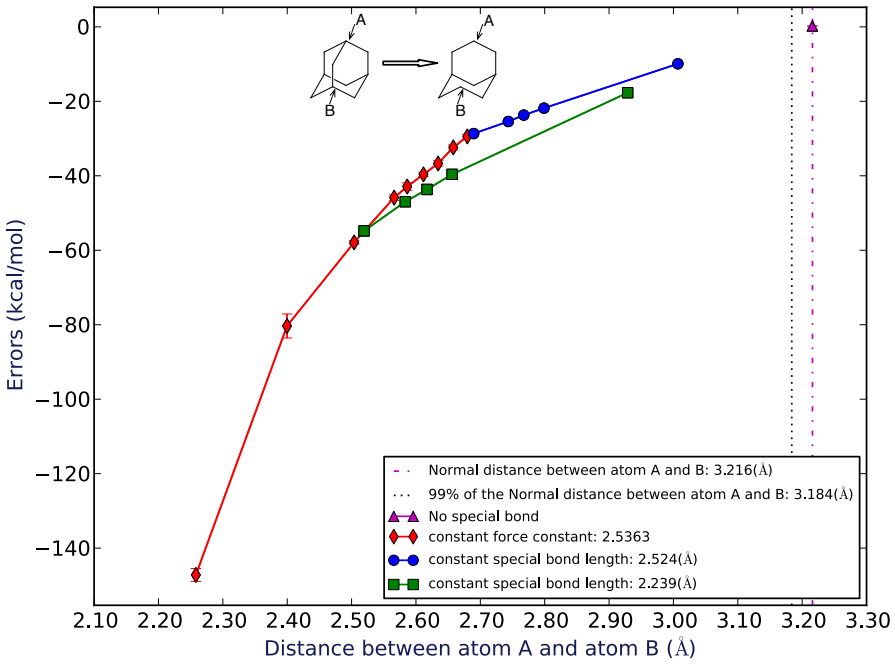

Figure S3: Errors for mutating adamantane to bicyclo[3.3.1]nonane as a function of the average distance between the shared atoms observed in the simulations. This error is for the system of adamantane-bicyclononane with NDE. The ”original” distance is the distance between atom A and atom B in the absolute free energy calculation of bicyclo[3.3.1]nonane without any special bond restrains. Spots in different colors represent different force constants/bond length groups of the special bond.

Table S1: Errors as a function of bond length (strain) for adamantane-bicyclononane, using distances observed in the relative vacuum simulation starting from adamantane for measuring the bond length. The corresponding error figure for this table is S1

ID	Special bond length (Å)	Force constant($kJmol^{-1}nm^{-2}$)	Distance between atom A and B in simulation(Å)	Errors($kcal/mol$)
original	none	none	2.569(1)	0.29 $\pm$ 0.03
0	2.524	2.5363	2.5390(8)	-21.98 $\pm$ 0.10
1	2.494	2.5363	2.5194(8)	-23.97 $\pm$ 0.10
2	2.456	2.5363	2.4950(8)	-26.16 $\pm$ 0.10
3	2.421	2.5363	2.4730(8)	-28.07 $\pm$ 0.10
4	2.383	2.5363	2.4475(8)	-30.11 $\pm$ 0.10
5	2.347	2.5363	2.4241(8)	-31.65 $\pm$ 0.10
6	2.239	2.5363	2.3519(8)	-35.54 $\pm$ 0.10
7	2.019	2.5363	2.2078(8)	-39.61 $\pm$ 0.10
8	1.585	2.5363	1.9109(8)	-31.85 $\pm$ 0.10
11	2.524	2.2827	2.5410(8)	-21.69 $\pm$ 0.08
12	2.524	1.5218	2.5437(9)	-19.93 $\pm$ 0.05
13	2.524	1.2682	2.547(1)	-18.88 $\pm$ 0.05
14	2.524	1.0145	2.550(1)	-17.61 $\pm$ 0.04
15	2.524	0.2536	2.561(1)	-8.65 $\pm$ 0.03
21	2.239	2.2827	2.3601(9)	-35.04 $\pm$ 0.08
22	2.239	1.5218	2.394(1)	-33.02 $\pm$ 0.05
23	2.239	1.2682	2.408(1)	-31.82 $\pm$ 0.05
24	2.239	1.0145	2.426(1)	-30.03 $\pm$ 0.04
25	2.239	0.2536	2.517(1)	-15.63 $\pm$ 0.03

Table S2: Errors as a function of bond length (strain) for system adamantane-bicyclononane with NDE, using distances observed in the relative vacuum simulation starting from adamantane for measuring the bond length. The corresponding error figure for this table is S2

ID	Special bond length (Å)	Force constant($kJmol^{-1}nm^{-2}$)	Distance between atom A and B in simulation(Å)	Errors($kcal/mol$)
original	none	none	2.569(1)	0.23 $\pm$ 0.03
0	2.524	2.5363	2.5390(8)	-29.44 $\pm$ 0.58
1	2.494	2.5363	2.5194(8)	-32.37 $\pm$ 0.67
2	2.456	2.5363	2.4950(8)	-36.70 $\pm$ 0.75
3	2.421	2.5363	2.4730(8)	-39.63 $\pm$ 0.59
4	2.383	2.5363	2.4475(8)	-42.89 $\pm$ 1.01
5	2.347	2.5363	2.4241(8)	-45.86 $\pm$ 0.74
6	2.239	2.5363	2.3519(8)	-57.90 $\pm$ 0.49
7	2.019	2.5363	2.2078(8)	-80.34 $\pm$ 3.23
8	1.585	2.5363	1.9109(8)	-147.21 $\pm$ 1.73
11	2.524	2.2827	2.5410(8)	-28.66 $\pm$ 0.36
12	2.524	1.5218	2.5437(9)	-25.41 $\pm$ 0.08
13	2.524	1.2682	2.547(1)	-23.70 $\pm$ 0.06
14	2.524	1.0145	2.550(1)	-21.83 $\pm$ 0.05
15	2.524	0.2536	2.561(1)	-9.92 $\pm$ 0.03
21	2.239	2.2827	2.3601(9)	-54.80 $\pm$ 0.36
22	2.239	1.5218	2.394(1)	-46.97 $\pm$ 0.08
23	2.239	1.2682	2.408(1)	-43.67 $\pm$ 0.06
24	2.239	1.0145	2.426(1)	-39.62 $\pm$ 0.05
25	2.239	0.2536	2.517(1)	-17.68 $\pm$ 0.03

Table S3: Errors as a function of bond length (strain) for system adamantane-bicyclononane with NDE, using distances observed in the absolute simulation of bicyclo[3.3.1]nonane for measuring the bond length. The corresponding error figure for this table is S3

ID	Special bond length (Å)	Force constant($kJmol^{-1}nm^{-2}$)	Distance between atom A and B in simulation(Å)	Errors($kcal/mol$)
original	none	none	3.22(7)	0.23 ± 0.03
0	2.524	2.5363	2.68(3)	-29.44 ± 0.58
1	2.494	2.5363	2.66(3)	-32.37 ± 0.67
2	2.456	2.5363	2.63(2)	-36.70 ± 0.75
3	2.421	2.5363	2.61(3)	-39.63 ± 0.59
4	2.383	2.5363	2.59(3)	-42.89 ± 1.01
5	2.347	2.5363	2.57(2)	-45.86 ± 0.74
6	2.239	2.5363	2.50(2)	-57.90 ± 0.49
7	2.019	2.5363	2.40(2)	-80.34 ± 3.23
8	1.585	2.5363	2.26(2)	-147.21 ± 1.73
11	2.524	2.2827	2.69(3)	-28.66 ± 0.36
12	2.524	1.5218	2.74(3)	-25.41 ± 0.08
13	2.524	1.2682	2.77(4)	-23.70 ± 0.06
14	2.524	1.0145	2.80(4)	-21.83 ± 0.05
15	2.524	0.2536	3.01(5)	-9.92 ± 0.03
21	2.239	2.2827	2.52(2)	-54.80 ± 0.36
22	2.239	1.5218	2.58(3)	-46.97 ± 0.08
23	2.239	1.2682	2.62(3)	-43.67 ± 0.06
24	2.239	1.0145	2.66(3)	-39.62 ± 0.05
25	2.239	0.2536	2.93(5)	-17.68 ± 0.03

Table S4: Bond length changes for benzamidine bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C1	C3	$1.3874(4)$	$1.3871(4)$	0.6	0.0
C6	C7	$1.4729(4)$	$1.4729(4)$	0.0	0.0
C4	C6	$1.3891(4)$	$1.3879(4)$	2.4	0.1
C3	C5	$1.3879(4)$	$1.3876(4)$	0.6	0.0
C2	C4	$1.3867(4)$	$1.3877(4)$	2.0	0.1
C5	C6	$1.3870(4)$	$1.3874(4)$	0.8	0.0
C7	N2	$1.3923(4)$	$1.3927(4)$	0.7	0.0
C7	N1	$1.3922(4)$	$1.3928(4)$	1.1	0.0
C1	C2	$1.3874(4)$	$1.3881(4)$	1.3	0.1

Table S5: Bond length changes for p-isopropylbenzamidine bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C1	C3	1.3874(4)	1.3876(4)	0.4	0.0
C4	C6	1.3880(4)	1.3880(5)	0.0	0.0
C2	C5	1.3871(4)	1.3870(4)	0.2	0.0
C2	C4	1.3873(4)	1.3878(4)	1.0	0.0
C10	C9	1.5363(5)	1.5369(5)	0.9	0.0
C10	C8	1.5364(5)	1.5363(5)	0.2	0.0
C5	C7	1.4722(4)	1.4728(4)	1.0	0.0
C1	C5	1.3876(4)	1.3873(4)	0.6	0.0
C7	N2	1.3920(4)	1.3930(4)	1.8	0.1
C3	C6	1.3875(4)	1.3878(4)	0.5	0.0
C7	N1	1.3927(4)	1.3919(4)	1.5	0.1
C10	C6	1.5140(4)	1.5140(4)	0.0	0.0

Table S6: Bond length for benzylammonium bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C1	C3	1.3874(4)	1.3877(4)	0.6	0.0
C6	C7	1.5147(5)	1.5139(4)	1.3	0.1
C4	C6	1.3885(4)	1.3878(4)	1.4	0.1
C3	C5	1.3881(4)	1.3881(4)	0.0	0.0
C2	C4	1.3876(4)	1.3880(4)	0.8	0.0
C5	C6	1.3885(4)	1.3883(4)	0.4	0.0
C7	N1	1.5000(5)	1.5000(5)	0.0	0.0
C1	C2	1.3873(4)	1.3874(4)	0.2	0.0

Table S7: Bond length changes for 3-phenylpropylammonium bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C1	C3	1.3882(4)	1.3878(4)	0.7	0.0
C6	C7	1.5137(4)	1.5145(5)	1.2	0.1
C4	C6	1.3878(4)	1.3876(4)	0.4	0.0
C9	N1	1.5007(5)	1.5000(5)	1.1	0.0
C3	C5	1.3876(4)	1.3878(4)	0.4	0.0
C2	C4	1.3877(4)	1.3875(4)	0.4	0.0
C8	C9	1.5355(5)	1.5356(5)	0.2	0.0
C5	C6	1.3876(4)	1.3877(4)	0.2	0.0
C7	C8	1.5362(5)	1.5357(5)	0.8	0.0
C1	C2	1.3865(4)	1.3880(4)	2.9	0.1

Table S8: Bond length changes for n221 bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C3	N1	1.3330(4)	1.3335(4)	1.0	0.0
C6	C7	1.3788(4)	1.3786(4)	0.4	0.0
C8	O1	1.2142(3)	1.2149(3)	1.5	0.1
C8	O2	1.2145(3)	1.2146(3)	0.2	0.0
C7	C8	1.4627(4)	1.4636(4)	1.5	0.1
C3	N2	1.3462(4)	1.3459(4)	0.5	0.0
C2	N2	1.3627(4)	1.3619(4)	1.5	0.1
C5	C7	1.4399(4)	1.4394(4)	0.9	0.0
C1	N1	1.3925(4)	1.3924(4)	0.2	0.0
C1	C2	1.3817(4)	1.3819(4)	0.4	0.0
C4	C5	1.3731(4)	1.3727(4)	0.8	0.0
C6	N2	1.3698(4)	1.3697(4)	0.2	0.0
C3	C4	1.4197(4)	1.4205(4)	1.5	0.1

Table S9: Bond length changes for n340 bound to trypsin.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C10	N2	1.3646(4)	1.3643(4)	0.6	0.0
C6	C9	1.3868(4)	1.3870(4)	0.4	0.0
C9	N1	1.3512(4)	1.3510(4)	0.4	0.0
C4	C9	1.3867(4)	1.3867(4)	0.0	0.0
C2	C3	1.4250(4)	1.4254(4)	0.8	0.0
C3	C8	1.3708(4)	1.3701(3)	1.4	0.1
C1	C4	1.3880(4)	1.3872(4)	1.6	0.1
C1	C5	1.3884(4)	1.3879(4)	1.0	0.0
C10	C5	1.3892(4)	1.3885(4)	1.4	0.1
C8	N1	1.3742(4)	1.3748(4)	1.1	0.0
C7	N1	1.3748(4)	1.3750(4)	0.4	0.0
C2	C7	1.3705(4)	1.3706(4)	0.2	0.0
C10	C6	1.3880(4)	1.3881(4)	0.2	0.0

Table S10: Bond length for Vertex molecule 000001 bound to DNA gyrase.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C10	C11	1.387(1)	1.381(8)	0.7	0.4
C3	O2	1.2140(9)	1.208(4)	1.4	0.5
C16	C17	1.391(1)	1.396(7)	0.8	0.4
C5	C6	1.384(1)	1.389(7)	0.7	0.4
C14	C15	1.388(1)	1.379(9)	1.1	0.7
O1	C3	1.344(1)	1.34(1)	0.0	0.0
C17	C18	1.382(1)	1.376(8)	0.8	0.5
C8	C9	1.340(1)	1.34(1)	0.3	0.2
C11	C12	1.388(1)	1.40(1)	0.7	0.6
N1	C4	1.380(1)	1.376(7)	0.6	0.3
C7	C16	1.398(1)	1.407(8)	1.3	0.7
C18	N3	1.335(1)	1.345(7)	1.5	0.7
C13	C14	1.387(1)	1.393(5)	1.0	0.4
C1	C2	1.536(1)	1.545(9)	1.0	0.6
C6	C7	1.394(1)	1.385(8)	1.0	0.6
C2	O1	1.441(2)	1.433(8)	0.9	0.5
C13	O3	1.359(1)	1.360(7)	0.1	0.0
C9	C10	1.473(1)	1.469(7)	0.5	0.2
C3	N1	1.345(1)	1.336(9)	1.0	0.7
C4	N3	1.389(1)	1.39(1)	0.1	0.1
C5	C18	1.359(1)	1.348(6)	1.9	0.8
C7	C8	1.470(1)	1.472(9)	0.2	0.1
C12	C13	1.388(1)	1.388(7)	0.1	0.1
C4	N2	1.359(1)	1.347(7)	1.9	0.9
N2	C5	1.338(1)	1.348(8)	1.3	0.8
C10	C15	1.386(1)	1.394(9)	0.8	0.5

Table S11: Bond length changes for Vertex molecule 000163 bound to DNA gyrase.

atom ID 1	atom ID 2	bond length in water(Å)	bond length in complex (Å)	z score	percentage
C5	C10	1.359(1)	1.362(7)	0.4	0.2
C17	N7	1.341(1)	1.342(9)	0.2	0.1
C19	C20	1.391(1)	1.395(7)	0.6	0.3
N1	C3	1.348(1)	1.348(7)	0.0	0.0
C7	C8	1.396(1)	1.388(6)	1.2	0.5
C17	C21	1.356(1)	1.344(6)	2.1	0.9
N2	C4	1.382(1)	1.376(9)	0.7	0.4
N3	C5	1.338(1)	1.331(3)	2.0	0.5
C14	C15	1.500(1)	1.507(9)	0.7	0.4
C11	C12	1.387(1)	1.382(8)	0.6	0.3
C3	O1	1.214(1)	1.221(6)	1.2	0.6
C18	C19	1.397(1)	1.399(7)	0.3	0.2
C2	N1	1.462(1)	1.46(1)	0.1	0.0
C12	C17	1.426(1)	1.417(9)	1.0	0.6
N5	C21	1.348(1)	1.33(1)	1.9	1.4
C4	N4	1.386(1)	1.391(6)	0.8	0.3
C13	N6	1.346(1)	1.347(7)	0.1	0.1
C6	C7	1.391(1)	1.39(1)	0.2	0.1
C14	C16	1.498(1)	1.503(8)	0.5	0.3
N7	C18	1.354(1)	1.343(6)	1.6	0.8
C9	C10	1.385(1)	1.385(8)	0.0	0.0
C8	C9	1.390(1)	1.402(7)	1.7	0.9
C15	C16	1.502(1)	1.497(8)	0.5	0.3
C4	N3	1.358(1)	1.364(5)	1.3	0.5
C20	C21	1.378(1)	1.39(1)	1.2	0.9
C5	C6	1.383(1)	1.39(1)	1.0	0.7
C1	C2	1.536(1)	1.54(1)	0.2	0.2
C13	O2	1.214(1)	1.201(9)	1.5	1.1
C7	N5	1.353(1)	1.354(8)	0.2	0.1
N5	C11	1.390(1)	1.39(1)	0.2	0.1
C12	C13	1.463(1)	1.46(1)	0.2	0.1
C3	N2	1.345(1)	1.34(1)	0.6	0.5
N6	C14	1.442(1)	1.439(8)	0.3	0.2
C10	N4	1.334(1)	1.322(6)	1.8	0.9